RESEARCH ARTICLE

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High-dose preoperative glucocorticoid for prevention of emergence and postoperative delirium in liver resection: A double-blinded randomized clinical trial substudy

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Abstract

Background: Emergence delirium (ED) and postoperative delirium (POD) are associated with increased morbidity and mortality and occur in up to one-third of patients undergoing major non-cardiac surgery, where the underlying pathogenesis is multifactorial, including increased inflammation. We aimed to assess the effect of preoperative high- versus low-dose glucocorticoid on the occurrence of ED and POD.

Methods: This was a substudy from a randomized, double-blinded clinical trial. Patients ≥18 years, undergoing open liver resection were randomized 1:1 to high-dose (HD, 10 mg/kg methylprednisolone) or low-dose (LD, 8 mg dexamethasone) glucocorticoid and assessed for ED and POD for a maximum of 4 days during hospitalization. The 3-min Diagnostic Interview for CAM-defined delirium (3D-CAM) was used for assessment, 15 and 90 min after arrival in the post-anesthesia care unit (PACU), and subsequently once daily in the ward.

Results: Fifty-three patients were included in this secondary substudy (26 HD-group and 27 LD-group). ED occurred in $n = 5$ HD versus $n = 6$ LD patients 15 min after PACU arrival. At 90 min after PACU arrival, 4 patients had ED, all from LD-group, and resulted in significantly longer PACU admission, 273 versus 178 min in ED versus Non-ED patients. During the first 4 days in the ward, $n = 5$ patients had at least one occurrence of POD, all from LD-group.

Conclusions: The primary finding of the current substudy was a lower occurrence of ED/POD in the PACU 90 min after arrival and during the first four postoperative days in patients receiving high-dose glucocorticoid compared with patients receiving low-dose glucocorticoid. The two study groups were not evenly balanced concerning known explanatory factors, i.e., age and size of surgery, which calls for larger studies to elucidate the matter.

KEYWORDS
emergence, liver resection, postoperative delirium, preoperative glucocorticoid

Editorial Comment

Preoperative glucocorticoids are used to try to reduce or mitigate risk from some perioperative complications, and complications of different types. In this secondary analysis of the results from a published trial, this treatment and postoperative delirium outcomes are explored. This study provide a good example for an approach to studying this question prospectively.

1 | INTRODUCTION

Cognitive impairment after anesthesia and surgery is related to increased risk for morbidity and mortality and can be sub-classified into a time-dependent range of overlapping conditions.[1,2] Inadequate emergence from anesthesia, also called emergence delirium (ED), occurs in the immediate post-anesthetic period before or on arrival at the post-anesthesia care unit (PACU) in the transition from anesthesia-induced unconsciousness to expected complete wakefulness.[1,2] Postoperative delirium (POD) occurs during the first postoperative days, while postoperative cognitive dysfunction (POCD) may last for weeks and months after anesthesia and surgery.[3] The incidence of POD is reported to range between 4% and 65%,[4,5] with a significantly lower occurrence in enhanced recovery (ERAS) versus non-ERAS pathways,[6,7] but incidences also vary according to assessment methodology.[1,8,9] ED and POD present in three subtypes: hyperactive (agitated and combative), hypoactive (decreased alertness, decreased motor activity, and anhedonia), or mixed.[10] Incidences of the different subtypes vary, with the hypoactive form being the most common with reports of up to 74% of all delirium subtypes, but again depending on the assessment method.[11]

The underlying pathophysiology for ED/POD is not yet clarified but suggested to be multifactorial, with increased risk from postoperative pain, poor sleep, opioid administration,[12] surgically induced inflammation,[13] and neuroinflammation.[14,15]

To counter the detrimental effect of surgically induced inflammation and pain, pre-operative glucocorticoid administration has been used in different surgical settings[15] and has been shown to reduce postoperative nausea and vomiting (PONV) and pain.[16] Several studies have shown that the pre-operative administration of glucocorticoids reduces peripheral inflammatory markers in hepatic surgery.[17,18]

Consequently, this substudy investigated the effect of pre-operative high versus low dose (standard PONV prophylaxis) of glucocorticoid in a randomized clinical trial on the occurrence of ED and POD during hospitalization in patients undergoing liver resection. To form the basis for future and larger clinical trials, we hypothesized that the occurrence of ED and POD would be lower among patients receiving a high dose of glucocorticoid.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a predefined substudy from the study on "Pre-operative High Dose Steroids for Liver Resection—Effect on Complications in the Immediate Postoperative Period". The trial was registered at ClinicalTrials.gov (NCT03403517) and EudraCT (2017-002652-81) and monitored by the Good Clinical Practice (GCP) unit at Copenhagen University Hospitals. Prior to initiation of enrolment, the trial was approved by the Danish data protection agency, and the Danish Medicines Agency. The trial was conducted at Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, between December 2017 and September 2020.

2.1.1 | Ethics

Prior to initiation of enrolment, the trial was approved by the local ethics committee (reg. no. H-17025897), The Capital Region of Denmark, Copenhagen, Denmark on October 18, 2017.

2.2 | Participants

Patients were enrolled as in the original study,[19] but only during the first 7 months when dedicated staff for the current sub study was available (January–July 2018) as defined in the study protocol of the original study: All patients at the department of surgical gastroenterology were consecutively screened for study eligibility if >18 years of age and planned for open liver resection. Further inclusion criteria were the ability to understand Danish or English and provide informed oral and written consent. Exclusion criteria were combined surgery on other organs, combined ventral herniotomy with implantation of mesh, two-stage liver resection, insulin-treated diabetes, pregnancy or lactation, epidural anesthesia not feasible, inoperability, allergy toward study medication, and treatment with systemic glucocorticoids and/or immunosuppressive treatment within the last 10 days prior to surgery.

2.3 | Procedure and intervention

All participants in the study followed standard procedures during hospitalization, except for glucocorticoid administration, as this was the study intervention.[20]

The perioperative set-up has been described previously but overall consisted of patients fasting for 6 h for solids and 2 h for fluids before surgery. An epidural analgesia catheter was inserted at thoracic level 8–10 with a 30 mg bolus of 0.5% bupivacaine after anesthesia induction, repeated every hour with 15 mg 0.5% bupivacaine and maintained with a continuous infusion of bupivacaine/morphine (2.5 mg + 50.0 μg ml^{-1}) during surgery.
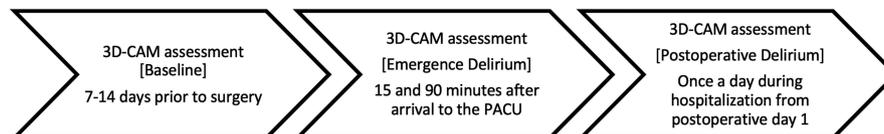
FIGURE 1 3D-CAM Assessment Procedure Flowchart. 3D-CAM: 3-min diagnostic interview for CAM defined delirium. PACU, post anesthesia care unit

Propofol (1.5–2.5 mg kg^{-1}) and remifentanil (0.3–0.8 μg kg^{-1}) were used to induce anesthesia in conjunction with cisatracurium (0.1 mg kg^{-1}) or suxamethonium (1 mg kg^{-1}). Anesthesia was maintained with propofol 0.05–0.15 mg kg^{-1} min^{-1}, remifentanil (0.3–0.8 μg kg^{-1} min^{-1}) and cisatracurium aiming at a train of four (TOF) response of 0%. In cases of major liver resection with future liver remnant close to 30% of total liver volume (standardized liver volume), sevoflurane could replace propofol. Dependent on the level of pain upon PACU arrival, patients were given morphine, oxycodone, or fentanyl as rescue analgesia. The standard regimen for postoperative care consisted of epidural infusion of bupivacaine/morphine (2.5 mg ml^{-1} + 50.0 μg ml^{-1}) until no later than postoperative day 3, slow-release acetaminophen 1330 mg every 8 h started immediately after surgery (individual prescription in the major resection group). Furthermore, administration of 600 mg gabapentin (reduced dose if weight <50 kg, age >65 years or in case of impaired renal function) and 200 mg celecoxib was started from postoperative day 2 (evening) and continued every 12 h (200 mg celecoxib, 300 mg gabapentin in the morning, and 600 mg in the evening) for 1 week.

Patients were randomized 1:1 to either 10 mg/kg methylprednisolone i.v. (Solu-Medrol, Pfizer ApS) (High-Dose group (HD-group)) or 8 mg dexamethasone i.v. (Dexamethasone, Krka) (Low-Dose group (LD-group)) as standard PONV prophylaxis, both infused in 100 ml 0.9% saline. The trial drug was administered immediately after anesthesia induction over a period of 30 min prior to the start of surgery. Patients was randomized according to the expected surgical trauma in two groups: major (resection of ≥3 liver segments) and minor (resection of <3 liver segments). Actual surgery could differ from the planned due to intraoperative findings and surgeon's assessment of optimal procedure for the given patients in accordance with clinical practice and ethics.

2.4 | Outcomes

This secondary exploratory substudy analysis assessed the difference in ED occurrence after 15 and 90 min after arrival at the PACU from the operating room and POD occurrence during the first four postoperative days in the ward between the HD and LD groups. Exploratory outcomes were motor subtype of delirium, PACU, and hospital length of stay (LOS).

Explanatory variables included: demographics, extend of surgery (major vs. minor), inflammation (C-reactive protein (CRP)), pain, and opioids.

2.5 | Assessment method and data collection

The diagnosis of delirium (ED and POD) was assessed by the four diagnostic features in the 3D-CAM, derived from the Confusion Assessment Method (CAM), which is (1) acute change or fluctuating course, characterized as either subjective statements or deviation between assessments, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. The presence of features 1, 2, AND 3 OR 4 was diagnostic for delirium.[21] A baseline 3D-CAM was performed at study inclusion, 7 to 14 days prior to surgery. Emergence delirium (ED) was assessed postoperatively at 15 min and at 90 min (±30 min depending on the clinical situation) after PACU arrival. Postoperative delirium was assessed once daily at noon for up to 4 days (unless the patient was discharged before day 4). A procedure flow chart is presented in Figure 1.

Delirium cases were reported as either hypoactive, hyperactive, or mixed delirium, based on the features registered in the 3D-CAM.[22] All 3D-CAM assessments in the PACU and ward were performed by HNA and KJS.

Other variables included were demographics, pre-operative analgesics, and psychopharmacological medicine, major versus minor liver resections, anesthesia technique, surgery time, intra- and postoperative administration of opioids, analyzed as Oral Morphine Equivalent Equivalents (OMEQ).[23] CRP samples were collected preoperatively and daily until day 3 in major resection procedures only.

Patients were assessed in the operating room and the PACU for vital signs, pain, nausea, and level of sedation by a standardized and implemented post-anesthesia recovery score.[24]

Postoperative complications were registered for all patients at 30 days follow-up and are presented in the main study.[19]

2.6 | Statistical analysis

This study was a predefined exploratory substudy to form the basis for future potential more extensive studies, and as such, there was no separate sample size calculation. All patients included in the main study during the first 7 months (January 2018 to July 2018) were also included in this predefined substudy.[19]

Acknowledging an unbalanced distribution of potential important confounders, we refrained from the planned primary outcome analysis of a chi-square test for differences in the occurrence of ED between intervention groups. Secondary outcomes of PACU LOS were analyzed with the chi-square test for the difference in the occurrence of POD between intervention groups.

Categorical data are presented as numbers with relative percentages. Continuous data are presented as means with 95% confidence intervals (CI) or medians with 25th and 75th interquartile range (IQR), where appropriate. Continuous data for CRP level measurements are presented as means ± standard deviation (SD). Assessment for normal distribution was performed with the Kolmogorov–Smirnov and Shapiro–Wilk tests. The alpha level was set at 0.05 for all analyses. Test for difference and significance between groups were assessed with a two-sample t-test or Wilcoxon rank-sum test depending on the distribution of analyzed data. Missing data (3.7% of delirium variables) was compensated by censoring and unit-imputation. Data were collected and managed using the Research Electronic Data Capture (RedCap) (v.8.10.18) tool. The software MATLAB (MATLAB Release 2020a, The MathWorks, Inc.) was used to import and analyze the data.

3 | RESULTS

In total, 132 patients were assessed for inclusion, with 79 patients excluded during the substudy period, between January 2018 and July 2018, leaving 53 patients for analysis (26 HD-group and 27 LD-group), see Figure 2. Reasons for noneligibility included simultaneous surgery on other organs ($n = 14$), logistical reasons ($n = 9$), patients receiving preoperative glucocorticoid ($n = 7$), refused to participate ($n = 7$), two-stage surgery ($n = 6$), immunosuppressive treatment <10 days ($n = 4$), does not understand Danish or English ($n = 3$), insulin-dependent diabetes mellitus ($n = 3$), simultaneous

hernia repair ($n = 2$), postponed surgery ($n = 2$), and other reasons ($n = 12$). Demographic, intraoperative, and PACU-related variables are presented in Table 1.

The occurrence of ED was not different between groups 15 min after PACU arrival (HD; $n = 5$ (19%) vs. LD; $n = 6$ (22%)). The occurrence of ED at the 90-min PACU assessment was lower in HD ($n = 0$, 0%) versus LD ($n = 4$, 15%).

During the first 4 days in the ward, a lower incidence of POD occurred in the HD-group ($n = 0$, 0%) versus LD ($n = 5$, 19%). All four patients who had ED after 90 min in the PACU subsequently developed POD on at least 1 day during the following four postoperative days. The occurrence of ED and POD is detailed in Table 2.

ED/POD patients differed from non-ED/POD patients on the following parameters: The median age was 74 (IQR 63–77) versus 64 years (IQR 54–71) in ED/POD versus non-ED/POD patients, respectively.

Sixteen patients (36%) underwent major liver resections, $n = 5$ (42%) in ED/POD versus $n = 11$ (27%) in non-ED/POD, and comorbidities were more frequent in ED/POD patients, $n = 10$ (83%) versus $n = 28$ (68%) in non-ED/POD patients. There were no statistically significant differences in postoperative pain trajectories between patients with or without ED/POD.

Opioid administration was similar in patients with or without ED/POD during the last hour of surgery and before arrival to the PACU, where median OMEQ was 50 mg (IQR 40–54) versus 50 (IQR 42–62) in ED/POD versus non-ED/POD, respectively. Median OMEQ administration in the total postoperative period from arriving to the general ward until hospital discharge was 18 mg (IQR 0–32) in the
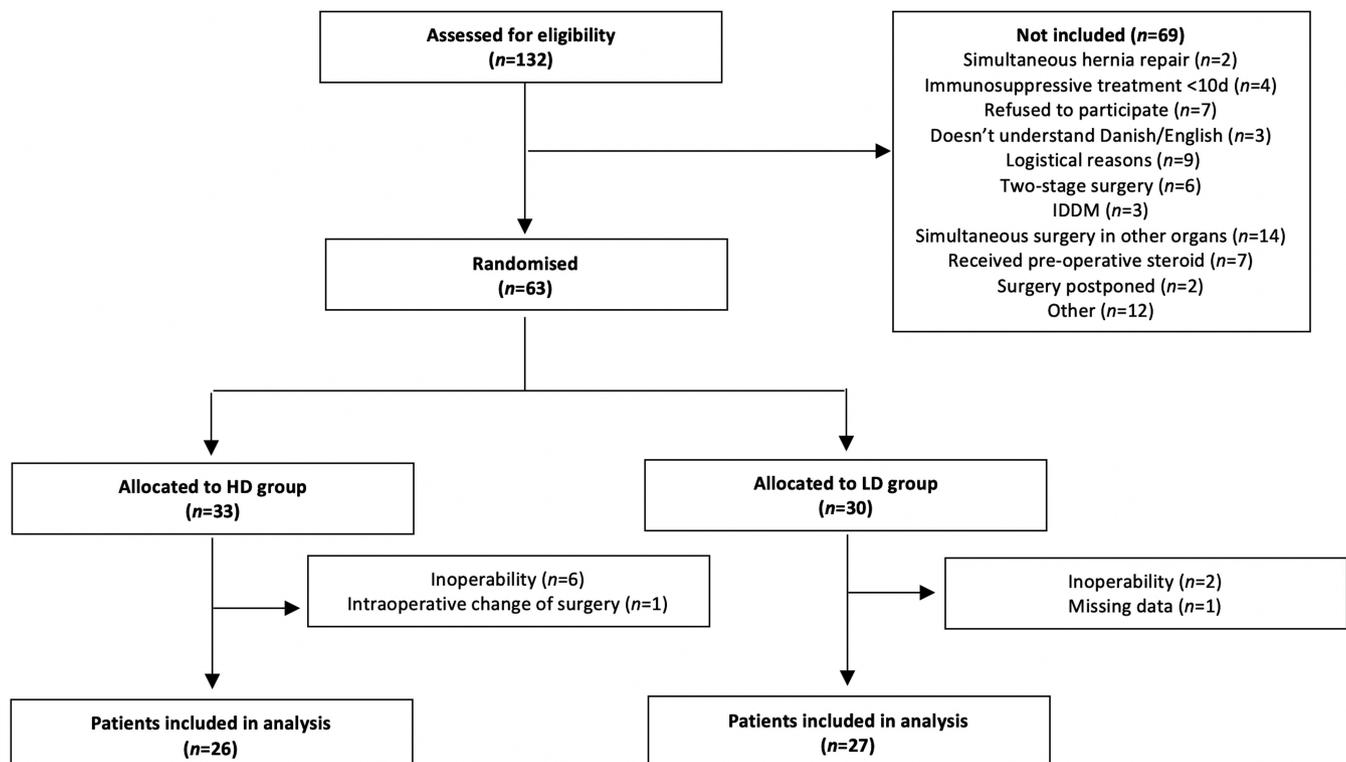

FIGURE 2 Number of patients assessed for eligibility, included in the study, and included in the final analysis. HD, high dose; LD, low dose

TABLE 1 Patient characteristics, peri- and postoperative data

	Non-ED/POD (n = 41)	ED/POD (n = 12)
Pre-operative and demographics		
Age, median (IQR)	64 (54–71)	74 (63–77)
Gender (M/W), n	19/22	6/6
Height, median (IQR)	172 (168–179)	173 [165–181]
Weight, median (IQR)	81 [67–90]	81 [73–84]
Comorbidity [unspecified][a], n (%)	28 (68%)	10 (83%)
ASA score, n (%)		
I	1 (2.5%)	0 (0%)
II	22 (53.5%)	8 (67%)
III	18 (44%)	4 (33%)
Neoadjuvant therapy incl. prednisolone <2 mo. of surgery, n (%)	18 (44%)	5 (42%)
Pre-operative medication, n (%)		
Analgesics	7 (17%)	2 (17%)
Psychiatric medication	1 (2%)	1 (8%)
Peri- and postoperative		
Surgery, n (%)		
Liver resection, major (≥3)	11 (27%)	5 (42%)
Liver resection, minor (<3)	25 (61%)	5 (42%)
Other (Open radio-frequency ablation/Non-anatomically major)	5 (12%)	2 (16%)
Sevoflurane at induction of anaesthesia, n (%)	12 (29%)	3 (25%)
Surgery time [minutes], Median, (IQR)	169 (126–198)	170 (135–209)
Pringle Maneuver	24 (59%)	5 (42%)
Ischemia time [minutes], median (IQR)	30 (15–38)	45 (12–50)
Blood loss [ml], Median (IQR)	670 (434–1079)	673 (368–1010)
Propofol (bolus + infusion) [ml], median (IQR)	265 (233–309)	265 (241–709)
Intraoperative opioid administration		
OMEQ, median (IQR)	50 (40–54)	50 (42–62)
Morphine, n (%)	36 (88%)	11 (92%)
Fentanyl, n (%)	9 (22%)	3 (25%)
NRS pain on transfer to PACU, Median (IQR)	0 (0–4)	0 (0–0)

Abbreviation: OMEQ, oral morphine equivalents.

[a]Comorbidity registered: Hypertension, NIDDM, lung disesase, Heart disease, Cirrhosis, colorectal cancer and metastasis to distant organs.

non-ED/POD group and 24 mg (IQR 0–40) in the ED/POD group. In patients undergoing major liver resection, n = 16, (30%), increased CRP levels in ED/POD versus non-ED/POD group were seen over the first three postoperative days, reaching biggest difference between groups on postoperative day 2, coinciding with the highest occurrence of POD (Table 2). Median CRP level in ED/POD was 86.39 mg/L (IQR 56.3–116.5) versus non-ED/POD 61.99 mg/L (IQR 45.1–78.9).

Complications during the days leading up to POD occurred in one patient with POD (gastrointestinal bleeding from ulceration) and two non-POD patients (fascial disruption and transient ischemic attack), equivalent to complications occurring in one HD and two LD patients.

The subtype pattern of the positive ED cases showed that n = 7 (47%) were hypoactive, n = 3 (20%) hyperactive, and n = 5 (33%) were mixed delirium cases. The subtype pattern of the positive POD cases identified n = 5 (63%) as hypoactive, n = 2 (25%) hyperactive, and n = 1 (12%) as a mixed delirium case.

Median LOS in the PACU was 178 min (IQR 152–233) in the non-ED/POD group and 273 min (IQR 200–338) in the ED/POD group, p = 0.003, with significantly higher levels of sedation seen in n = 5 (42%) ED/POD patients compared with n = 3 (7%) non-ED/POD patients, p = 0.001.

The median total hospital LOS was 121 h (IQR 95–167) in the non-ED/POD group and 120 h (IQR 87–179) in the ED/POD group.

4 | DISCUSSION

The primary finding of the current substudy was a lower occurrence of ED/POD in the PACU 90 min after arrival and during the first four postoperative days in patients receiving high-dose glucocorticoid compared with patients receiving low-dose glucocorticoid, but also a higher median age and incidence of major liver resection in ED/POD patients. Patients receiving low-dose glucocorticoid with subsequent ED had a higher risk for development of POD in the following postoperative days compared with patients receiving high-dose glucocorticoid with subsequent ED. Thus, no patients receiving high-dose glucocorticoid had POD in the postoperative days during hospitalization. The observed 21% occurrence of ED and 9% occurrence of POD during the first four postoperative days for our entire cohort is similar to the overall 5%–30% findings of ED/POD from recent specific studies in liver resection[4]. Our findings are based on a well-implemented ERAS liver resection program[6] but contrast with reports of POD after other ERAS procedures with a low occurrence of less than 3%.[25,26] This can potentially be explained by the use of the more sensitive 3D-CAM assessment tool, especially for hypoactive delirium.

The maximum incidence of POD on postoperative day 2 in the current study is consistent with recent studies,[27,28] including a hip-fracture study where a single pre-operative dose of 125 mg methylprednisolone also reduced the prevalence of POD.[29] The finding also coincided with a statistically significant difference in CRP levels between the two patient groups in the subset undergoing major resections, supporting recent studies with significantly higher levels of CRP and IL-6 in patients with postoperative delirium compared with controls,[27,28] supporting the systemic- and neuroinflammatory

TABLE 2 Occurrence of emergence delirium and postoperative delirium

n (%)	HD glucocorticoid (n = 26)	LD glucocorticoid (n = 27)	Total (n = 53)
ED—postoperative 15-min	5 (19%)	6 (22%)	11 (20%)
ED—postoperative 60/120 min	0	4 (15%)	4 (8%)
POD1	0	2 (7%)	2 (4%)
POD2	0	5 (19%)	5 (9%)
POD3	0	1 (4%)	1 (2%)
POD4	0	1 (4%)	1 (2%)

Abbreviations: ED, emergence delirium; HD, high dose; LD, low dose; POD, postoperative delirium.

component in POD.[30] Although a correlation between peripheral- and central nervous inflammation and subsequent delirium has been suggested,[14,15] there is a gap in knowledge of the relative role of neuroinflammation, especially in relation to other suggested risk factors such as impaired perfusion, pain, sleep, opioids[31] calling for further studies, ideally including biomarkers for neuroinflammation. We did not find an increased incidence of complications leading up to POD to explain the observed difference between patients with and without POD.

The majority of ED and POD cases in our study were hypoactive, which is in line with recent studies.[10,32] Since hypoactive delirium most often goes unrecognized through clinical settings and is associated with the worst outcome,[33] this finding stresses the necessity of applying a sensitive delirium screening tool with good predictive value for all subtypes including hypoactive cases, such as the 3D-CAM[21] used in the present study.

The role of postoperative opioid administration as a risk factor for POD has been discussed in multiple studies.[12,34] However, we found no difference in opioid administration in the perioperative setting and the risk for delirium in the current study. A significantly longer stay in the PACU in ED/POD patients compared with the non-ED/POD group was observed, similar to other studies, and explained by a statistically significantly higher level of sedation. Our results suggest that increased age and male sex might constitute as predisposing factors for POD, in line with recent studies.[1,35]

4.1 | Strength and limitations

The main limitation in the current study is the relatively small sample size, and the reported findings in this subanalysis should form the basis for future larger confirmatory studies, especially regarding controlling for other confounding factors such as pain, sleep, opioids, inflammation, age and extent of the surgical procedure. Reason for not continuing inclusion of patients from the main study and into this substudy was because of logistical reasons. The limited number of patients with major resections in the current study does not allow for assessment of potential complications to explain the increased inflammation on day 2 in this subset of patients, and detailed information on CRP in all patients and concomitant complications must be included in future studies. Thus, we observed obvious differences between patients with and without ED/POD, with patients being older, with more comorbidities, and higher frequency of major resections. Especially age is a

well-known risk factor for delirium, and reducing risk factors, including inflammation, may be particularly important in this high-risk group.[2,6] Although nonsignificant, the age and co-morbidity difference found between patients with and without ED/POD might introduce bias into the interpretation of the results and should be addressed by performing allocation in future intervention studies. Our study was performed in a well-implemented ERAS setting, and we cannot directly transfer the findings to other non-ERAS settings, although a potential effect would also be expected in settings with a higher risk for delirium. Although we cannot rule out-that an assessor carryover effect could be present due to only two assessors performing all 3D-CAM scoring, the randomized, blinded study design should minimize bias related to the intervention modality.

A strength of the current study is the use of the validated 3D-CAM that has shown superior accuracy compared with other delirium assessment tools, due to its feasibility in clinical administration and research, high specificity and sensitivity for delirium, and high (95%) inter-rater agreement, which has been validated in different clinical settings.[21,36] The 3D-CAM is assessed partly by interviews and observations before comparison with previous assessments is made reducing the bias caused by a potential learning effect of the interview questions. Lastly, the randomized and blinded methodology also reduces bias and supports the validity of the findings.

5 | CONCLUSION

The primary finding of the current substudy was a lower occurrence of ED/POD in the PACU 90 min after arrival and during the first four postoperative days in patients receiving high-dose glucocorticoid compared with patients receiving low-dose glucocorticoid. The two study groups were not evenly balanced concerning known explanatory factors, i.e. age and size of surgery, which calls for larger studies to elucidate the matter.

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