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Original article

Association between first-week propofol administration and long-term outcomes of critically ill mechanically ventilated patients: A retrospective cohort study

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SUMMARY

Background & aim: Propofol is commonly used in ICUs, but its long-term effects have not been thoroughly studied. In vitro studies suggest it may harm mitochondrial function, potentially affecting clinical outcomes. This study aimed to investigate the association between substantial propofol sedation and clinical outcomes in critically ill patients.

Methods: We conducted a single-centre cohort study of critically ill, mechanically ventilated (≥7 days) adults to compare patients who received a substantial dose of propofol (cumulative >500 mg) during the first week of ICU admission with those who did not. The primary outcome was the association between substantial propofol administration and 6-month mortality, adjusted for relevant covariates. Subanalyses were performed for administration in the early (day 1–3) and late (day 4–7) acute phases of critical illness due to the metabolic changes in this period. Secondary outcomes included tracheostomy need and duration, length of ICU and hospital stay (LOS), discharge destinations, ICU, hospital, and 3-month mortality.

Results: A total of 839 patients were enrolled, with 73.7 % receiving substantial propofol administration (substantial propofol dose group). Six-month all-cause mortality was 32.4 %. After adjusting for relevant variables, we found no statistically significant difference in 6-month mortality between both groups. There were also no significant differences in secondary outcomes.

Conclusion: Our study suggests that substantial propofol administration during the first week of ICU stay in the least sick critically ill, mechanically ventilated adult patients is safe, with no significant associations found with 6-month mortality, ICU or hospital LOS, differences in discharge destinations or need for tracheostomy.

1. Introduction

Propofol (2,6-diisopropyl phenol) is an intravenously administered sedative-hypnotic agent, that also can be considered as parenteral nutrition as it is dissolved in a high-caloric lipid emulsion. Due to its favourable pharmacological properties, including a fast onset and offset of action, it is frequently used in critically ill patients admitted to the Intensive Care Unit (ICU) to reduce anxiety and agitation, promote tolerance of mechanical ventilation, and prevent auto-extubation [1–5].

However, propofol also has the potential for severe side effects [6]. As such, prolonged or high-dose use of propofol (>4–5 mg/kg*h or >48 h) may lead to a life-threatening condition known as propofol infusion syndrome (PRIS) [7–10]. PRIS can manifest in various ways among patients and ultimately result in multiple organ failure [4,7,8,10–13]. While its exact pathophysiology is not yet understood, several studies suggest that propofol-induced suppression of mitochondrial function plays a pivotal role. This makes patients with pre-existing mitochondrial diseases particularly vulnerable to this syndrome [12–15].

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List of abbreviations

Acetyl-CoA	Acetyl coenzyme A
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
APACHE II	Acute Physiology and Chronic Health Evaluation II
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
95%CI	95 % confidence interval
EN	Enteral nutrition
ETC	Electron transport chain
FAD	Flavin adenine dinucleotide
HR	Hazard ratio
IBW	Ideal body weight
ICU	Intensive Care Unit
ICU-AW	Intensive Care Unit-acquired weakness
IQR	Interquartile range
LOS	Length of stay
NAD	Nicotinamide-adenine dinucleotide
mNUTRIC	Modified Nutrition Risk In Critically ill
OR	Odds ratio
PDMS	Patient Data Management System
PICS	Post-Intensive Care Syndrome
PN	Parenteral nutrition
PRIS	Propofol Infusion Syndrome
RASS	Richmond Agitation Sedation Scale
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
VIF	Variance inflation factor
ZGV	Gelderse Vallei Hospital

1.1. Mitochondrial (dys)function in health and sepsis

Mitochondria, known as the cell powerhouses, primarily produce energy through the oxidative phosphorylation process (see Fig. 1). In health, acetyl coenzyme A (Acetyl-CoA), derived from glycolysis as pyruvate and the beta-oxidation of fatty acids, is oxidised in the citric acid cycle to carbon dioxide and water. This process generates an electrochemical gradient that is used to phosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) by moving electrons across the mitochondrial electron transport chain (ETC) at the inner mitochondrial membrane [13,16–19].

During the early stages of sepsis, a general dysfunction of mitochondria has been observed [18–23]. Persistent mitochondrial dysfunction during critical illness has been associated with ICU-acquired weakness (ICU-AW) and prolonged muscle weakness after ICU discharge [24,25].

1.2. Propofol-induced mitochondrial dysfunction

Propofol may adversely affect mitochondrial functioning. Studies in animal models and human skeletal muscle cells suggest a disruptive effect on the oxidative phosphorylation process described above [10,12,15,26–30]. Furthermore, propofol-induced apoptosis has been demonstrated in patients with pre-existing mitochondrial dysfunction or using biguanide drugs such as metformin [9]. Altogether this may worsen sepsis-induced bioenergetic downregulation, aggravating multiple organ failure and thus influencing clinical outcomes [16–18,31–34].

1.3. Additional effects of propofol influencing outcomes

In addition, an increased risk of healthcare-related infections due to the lipophilic nature of propofol formulations has been reported, favouring bacterial growth at room temperature [35].

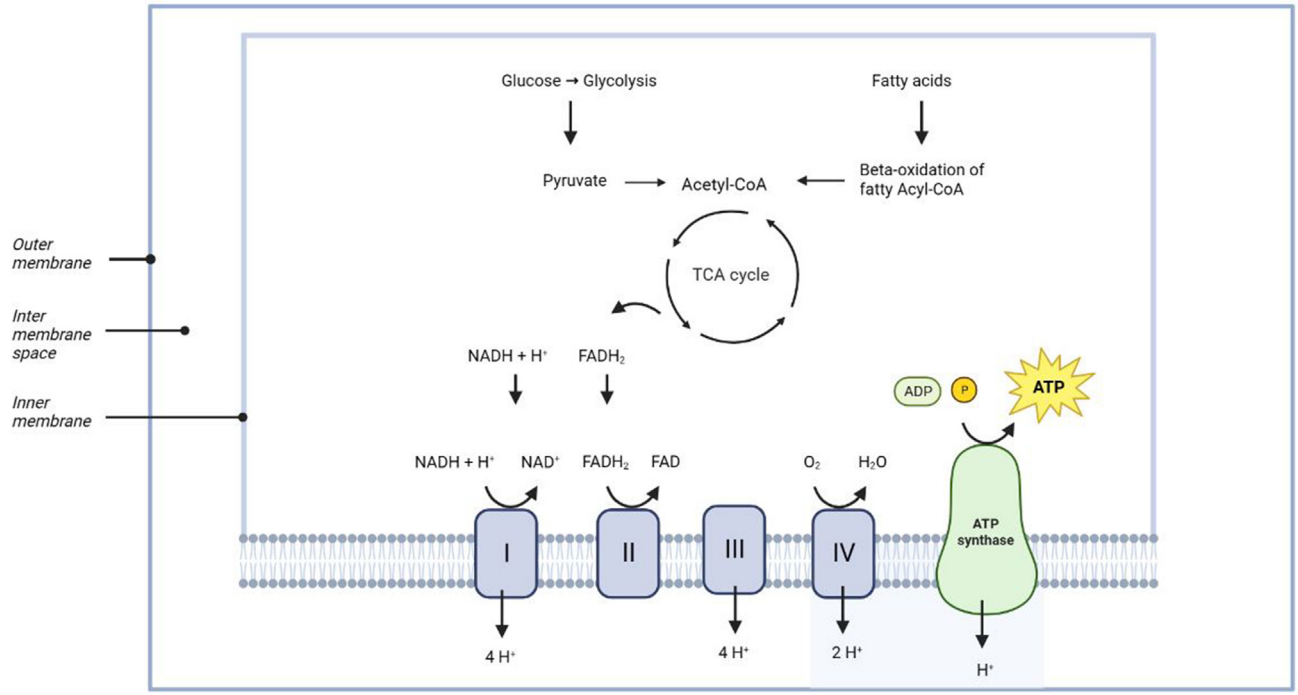

Fig. 1. Title: Simplified schematic overview of ATP production in a mitochondrion via the process of oxidative phosphorylation. Legend: Acetyl-CoA = acetyl coenzyme A; ADP = adenosine diphosphate; ATP = adenosine triphosphate; FADH = flavin adenine dinucleotide (FAD) + hydrogen (H); NADH = nicotinamide-adenine dinucleotide (NAD) + hydrogen (H); TCA = tricarboxylic acid cycle. Created with Biorender.com for this publication.

However, propofol's beneficial immunomodulating effects have also been observed, such as anti-inflammatory and antioxidant properties [36–38].

1.4. Long-term effects of propofol

Despite its routine use in the ICU, the long-term effects of propofol used for sedation in critically ill patients have not been studied well. Very recently, Kotani and coworkers conducted a meta-analysis of randomised controlled trials (RCTs) studying all-cause mortality in postoperative and critically ill patients receiving propofol versus any other sedative agent [5]. No significant difference in mortality was observed in the ICU patient group (52/252 of studies, 21 %).

To address the lack of knowledge regarding the long-term effects of substantial propofol use, this study aimed to investigate its potential negative impact on clinical outcomes. Although mitochondrial function could not be measured in this retrospective study, the hypothesis was that propofol's adverse effects on mitochondria could worsen clinical outcomes, such as mortality and ICU-AW, as well as discharge destination. The study analysed the association between 6-month mortality and patients who received a substantial dose of propofol for an extended period (>500 mg cumulative dose) during the first week of ICU admission and those who did not. The cut-off value of 500 mg was intentionally chosen to distinguish patients who received a substantial dose of propofol from patients who received no propofol or only a small dose periprocedural considering that such a small dose would likely not affect clinical endpoints. The no substantial propofol dose group included patients who received a small dose of propofol for intubation or other short procedures only. In the group who received a substantial dose of propofol, subanalyses were performed for administration in the early (day 1–3) and late (day 4–7) acute phases of critical illness due to the metabolic changes in this period (endogenous energy production, bio-energetic downregulation) The study's secondary outcomes were ICU and hospital LOS, duration of mechanical ventilation, the need for a tracheostomy to wean from mechanical ventilation, discharge destinations, and ICU, hospital, and 3-month mortality.

2. Materials and methods

2.1. Study design & participants

We conducted a retrospective observational single-centre cohort study on adult patients (aged ≥18 years) who were mechanically ventilated for ≥7 days and admitted between January 1st 2011, and May 31st 2021, to the mixed medical-surgical ICU of Gelderse Vallei Hospital (ZGV, Ede, The Netherlands).

Patients with neuromuscular or mitochondrial diseases or a pre-existent need for dialysis were excluded, as were patients with incomplete sedative or nutritional provision data, contraindications to full nutrition, or who started mechanical ventilation more than 48 h after ICU admission. Patients who were transferred from another hospital were also excluded. Only the first admission was evaluated for patients with ICU readmission within six months after discharge.

2.2. Sedation protocol

All patients were sedated using either propofol and/or midazolam and received concomitant analgesia (remifentanil or fentanyl) as per our local ICU protocol. The sedative medication was titrated using the Richmond Agitation Sedation Scale (RASS; target −2 to 0) and interrupted daily whenever possible through a wake-up call.

2.3. Substantial propofol doses versus no substantial propofol doses study groups

To assess the long-term effects of substantial propofol use, all eligible patients were divided into two groups: patients who received a substantial dose of propofol (hereafter: 'substantial propofol dose group') were compared to patients who did not. Substantial propofol administration was defined as a cumulative propofol dose of >500 mg during the first week of ICU stay. This cut-off value was chosen intentionally (being about 2.5 vials of 200 mg propofol) to distinguish patients who received a substantial dose of propofol from patients who received no propofol or only small doses periprocedural; these latter patients were analysed in the no substantial propofol dose group.

2.4. Study endpoints

The primary outcome was 6-month mortality. In the substantial propofol group, we also examined the association between the primary outcome and propofol administration given during the early and late acute phases, respectively, due to the metabolic changes expected in these periods. In the acute phase of critical illness there is an enormous endogenous energy production, and, at the same time, demands are lower as the body's metabolism is downregulated. It is thought that mitochondria are more vulnerable and cannot utilise substrates in this phase [22]. Secondary study parameters included duration of mechanical ventilation, need for a tracheostomy to wean from mechanical ventilation, ICU and hospital LOS, discharge destinations, and ICU, in-hospital, and 3-month mortality.

2.5. Data collection

Data collection from the electronic Patient Data Management System (PDMS) included patient characteristics (gender, age, anthropometry, comorbidities), admission type, several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), modified Nutrition Risk In Critically ill (mNUTRIC), Charlson Comorbidity Index (CCI)), laboratory values, (non-)nutritional intake (including enteral/parenteral nutrition (EN/PN)), outcome parameters such as duration of mechanical ventilation, length of ICU and hospital stay, discharge destination, and readmission rates. Data regarding propofol use was collected from the precise and automated recording of all individual non-nutritional calorie infusions from glucose, citrate and propofol for the first seven days after ICU admission. The amount of non-nutritional calories from propofol was used to calculate the exact daily and cumulative dosages of propofol (one millilitre (10 mg/mL) propofol contains 1.1 kilocalories). Moreover, the use of sedative and neuromuscular blocking agents was recorded. Finally, data collection included nutritional intake and achievement of energy and protein targets, as it has been demonstrated that macronutrient intake impacts clinical outcomes, particularly protein intake [39–45].

Data extraction was performed using queries searching the ICU PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (NeoZis; MI Consultancy, Katwijk, The Netherlands). The National Population Register was consulted for death records. Data verification was conducted manually. All parameters of interest had been routinely collected during standard clinical care and therefore imposed no burden or risk to patients.

2.6. Nutritional support

All patients in our ICU received nutritional support according to our local ICU protocol (as proposed by Van Zanten et al. [46]). Energy and protein targets were calculated by the dieticians using the Food and Agricultural Organization and World Health Organization (FAO/WHO/UNU) formulas, adapted for specific patient groups according to the local hospital protocol (see Supplement 1) [47]. The amount of intake (energy and proteins) was used to calculate the percentage of reached energy and protein targets (hereafter indicated with "adequacy").

Bodyweight was adjusted to ideal body weight (IBW) at a Body Mass Index (BMI) of 18.5 or 27 kg/m^2 in case of BMI <18.5 or >27 kg/m^2.

Intake targets on the day of ICU discharge were adjusted for the actual time spent in the ICU that day. Days were defined as calendar days.

2.7. Statistical analysis

To analyse the data, continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on whether the data were parametric or non-parametric, respectively. Normality was examined both numerically and graphically. Discrete variables were reported as proportions.

To compare the baseline characteristics and outcomes between the substantial propofol and no substantial propofol dose groups, the chi-square test, independent samples t-test, and Wilcoxon rank sum test were used where appropriate.

After adjusting for relevant parameters, the primary outcome parameter was evaluated using Kaplan-Meier curves and uni- and multivariable Cox proportional hazards regression models.

As appropriate, Cox, linear, or logistic regression models were used for secondary outcome parameters. Multivariable Cox regression analyses were conducted using the Enter and Forward (Stepwise Wald) methods. Variables were dichotomised based on median values in case of non-linearity (by visual assessment of boxplots).

The variables age, gender, BMI, APACHE II and mNUTRIC scores, CCI, sepsis on admission, administration of parenteral nutrition, and energy and protein adequacies were analysed in regression analyses based on literature and clinical relevance. However, energy and protein adequacies were excluded from the analysis due to their strong correlation with the administration of PN during days 1–7. The variables age, APACHE II, and CCI were also omitted in the final regression models due to their overlap with the mNUTRIC score. BMI and protein adequacy were dichotomised due to their non-linear relationship with the outcome parameters.

The variance inflation factor (VIF) was used to check for multicollinearity. A VIF value less than 2 was considered acceptable. All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, New York, United States of America, 2016). P-values less than 0.05 were considered statistically significant, while p-values less than 0.10 were considered trends.

3. Results

The study included 839 patients who met the eligibility criteria out of 3637 patients admitted to the ICU between January 1st 2011, and May 31st 2021 (see Fig. 2). These eligible patients were mechanically ventilated for seven days or more. Of the initial 1004 patients who met the mechanical ventilation criteria, 165 were excluded based on predefined exclusion criteria.

Table 1 presents the baseline characteristics of the study population. The median duration of mechanical ventilation was 11 days (IQR 8–17). About 16.9 % of the patients received PN during their ICU stay. The mean daily energy and protein intake were 17.8 (SD 5.3) kcal/kg and 0.92 (SD 0.3) g/kg, respectively.

3.1. Substantial versus no substantial dose of propofol

During the first seven days of ICU admission, 73.7 % of the patients (n = 618) received more than 500 mg of propofol, categorising them as the 'substantial propofol dose group'. Compared to the 'no substantial propofol dose group', which received no or

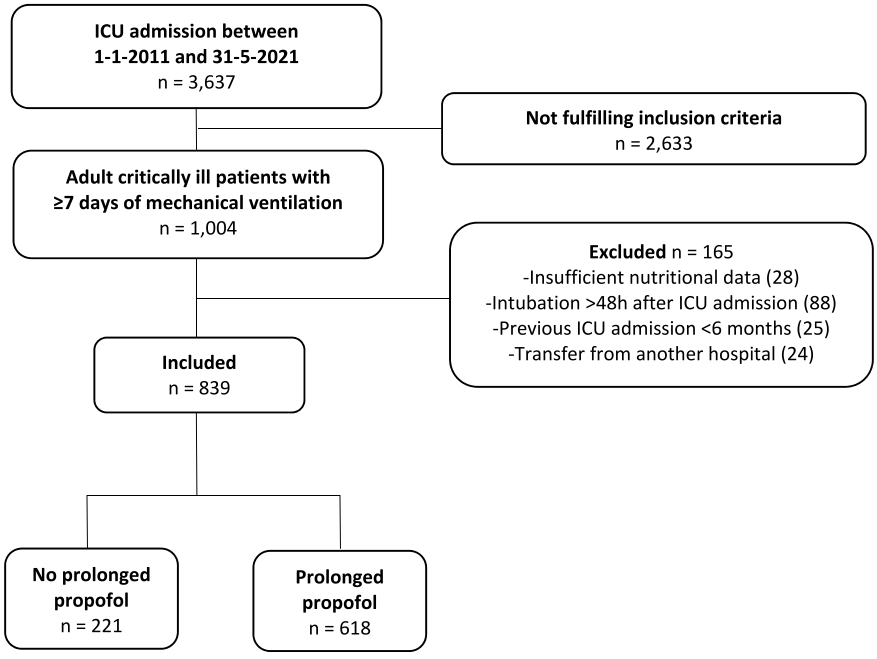

Fig. 2. Title: Study Flowchart. Legend: ICU = Intensive Care Unit; n = number of patients.

Table 1
Baseline characteristics.

		All patients	Cumulative propofol dose day 1–7		p-value[a]
			≤500 mg	>500 mg	
		(n=839)	*(n=221)*	*(n=618)*	
Gender (male)	*n (%)*	525 (62.6)	129 (58.4)	396 (64.1)	0.132
Age (years)	*mean (SD)*	66.4 (13.9)	70.1 (11.7)	65.2 (14.4)	<0.001*
BMI (kg/m^2)	*mean (SD)*	27.8 (5.8)	27.4 (5.8)	27.9 (5.8)	0.279
APACHE II score	*mean (SD)*	23.0 (7.0)	23.9 (7.2)	22.7 (6.9)	0.022*
SOFA score	*mean (SD)*	8.1 (3.1)	8.0 (3.5)	8.2 (2.9)	0.411
mNUTRIC score	*mean (SD)*	5.0 (1.8)	5.3 (2.0)	4.9 (1.8)	0.016*
Charlson Comorbidity Index	*mean (SD)*	3.8 (2.4)	4.5 (2.3)	3.6 (2.3)	<0.001*
Admission type (surgical)	*n (%)*	249 (29.7)	56 (25.3)	193 (31.2)	0.100
Sepsis on admission (yes) [n = 838]	*n (%)*	348 (41.5)	126 (57.0)	222 (35.9)	<0.001*
Propofol administered (yes)	*n (%)*	712 (84.9)	68 (30.8)	618 (100)	<0.001*
Cumulative dose day 1–7 (mg)	*median [IQR]*	3005 [418–9909]	0 [0–145]	5855 [2452–13364]	<0.001*
>200 mg	*n (%)*	657 (78.3)	64 (29)	618 (100)	
>500 mg	*n (%)*	618 (73.7)	0 (0)	618 (100)	
>1000 mg	*n (%)*	566 (67.5)	0 (0)	577 (93.4)	
Cumulative dose day 1–7 (mg/kg IBW)	*median [IQR]*	4.1 [0.5–13.4]	0 [0–0.2]	7.8 [3.3–17.1]	<0.001*
Muscle relaxants administered (yes)	*n (%)*	355 (42.3)	87 (39.4)	268 (43.4)	0.302
Number of days	*median [IQR]*	2 [1–4]	2 [1–4]	2 [1–4]	0.779

APACHE II = Acute Physiology and Chronic Health Evaluation II (on ICU admission); BMI = Body Mass Index (on ICU admission); IBW = ideal body weight; ICU = Intensive Care Unit; IQR = interquartile range; n = number of patients; mNUTRIC = modified Nutrition Risk in Critically Ill (on ICU admission); SD = standard deviation; SOFA = Sequential Organ Failure Assessment (on ICU admission).
* p-value <0.05.
[a] p-values were calculated using the chi-square test, independent samples t-test or Wilcoxon rank sum test where appropriate.

≤500 mg of propofol, the substantial dose group was younger (65.2 (SD 14.4) vs. 70.1 (SD 11.7) years, p < 0.001), had fewer comorbidities (CCI 3.6 (SD 2.3) vs. 4.5 (SD 2.3), p < 0.001), and were diagnosed with sepsis on admission less frequently (35.9 vs. 57.0 % of cases, p < 0.001). Additionally, the substantial propofol dose group had lower APACHE II (22.7 (SD 6.9) vs. 23.9 (SD 7.2), p = 0.022) and mNUTRIC scores (4.9 (SD 1.8) vs. 5.3 (SD 2.0), p = 0.016) on ICU admission. However, no significant differences in muscle relaxants or chronic steroid use were observed (p > 0.05).

3.2. Sedative administration and nutritional assessment

The substantial propofol dose group received a median dose of 5855 [IQR 2452-13,364] mg of propofol during the first seven days of ICU admission, equivalent to 7.8 [3.3–17.1] mg/kg IBW (Table 1). Energy targets and intake were comparable between groups, but the substantial propofol dose group had a significantly higher load of non-nutritional kilocalories (median 2.6 [IQR 1.5–4.4] kcal/kg IBW*day versus median 1.1 [0.6–2.2] kcal/kg IBW*day in the no substantial propofol dose group, p < 0.001) (Supplement 2). Although both groups had similar energy adequacies, there was a significant difference in protein intake (mean 0.90 (SD 0.3) versus 0.97 (SD 0.3) g/kg IBW*day, p = 0.007) and day 1–7 protein adequacy (mean 72.0 (SD 23.4) versus 78.3 % (SD 24.0), p = 0.004) between the substantial propofol dose and no substantial propofol dose group, respectively.

3.3. Primary outcome: 6-month mortality

Six-month mortality was observed in 272 patients (32.4 %). Univariable analysis revealed a statistically significant difference in mortality between the substantial propofol dose group and the no substantial propofol dose group (30.3 % versus 38.5 %, respectively; p = 0.025; univariable Cox regression >500 mg propofol: HR 0.753 (95%CI 0.582–0.973), p = 0.030) (Tables 2–3).

3.4. Cox regression

However, in the multivariable Cox regression model, no association between substantial propofol use and 6-month mortality was found. Only BMI (≤27 kg/m^2: HR 1.408, 95%CI 1.107–1.790, p = 0.005) and mNUTRIC score (HR 1.379, 95%CI 1.284–1.481, p < 0.001) remained significantly associated with 6-month mortality (Table 3 and Supplement 4). The variables in this final model had a VIF of <2.

3.5. Substantial propofol dose group: propofol administered during the early (days 1–3) versus late (days 4–7) acute phases of critical illness

The association between the primary outcome of 6-month mortality and substantial propofol administration during the early (days 1–3) and late (days 4–7) acute phases was analysed. In the early acute phase, no significant differences were observed between the substantial dose and no substantial propofol dose groups in uni- and multivariable analyses. In the late acute phase, a survival benefit was observed for the group receiving >500 mg propofol (HR 0.750, 95%CI 0.591–0.952, p = 0.018), but this effect disappeared when corrected for other factors in the multivariable analysis (Supplement 3).

3.6. Secondary outcomes

An overview of the duration of mechanical ventilation and need for a tracheostomy to wean from mechanical ventilation, ICU and hospital LOS, discharge destinations, ICU readmission within six months, and ICU, in-hospital, and 3-month mortality for both substantial and no substantial propofol dose groups are shown in Tables 2 and 4.

Multivariable analyses revealed a statistically significant difference between the two groups regarding discharge destinations. Patients who received >500 mg of propofol during the first seven days of ICU admission were more likely to be discharged home than those who did not (OR 1.675, 95%CI 1.142–2.457, p = 0.008;

Table 2
Clinical outcomes.

		All patients	Cumulative propofol dose day 1–7		p-value[a]
			≤500 mg	>500 mg	
		(n=839)	*(n=221)*	*(n=618)*	
Discharge destination	*n (%)*				0.026*
Transfer to another hospital		75 (8.9)	22 (10.0)	53 (8.6)	
Home		251 (29.9)	49 (22.2)	202 (32.7)	
Nursing home		150 (17.9)	41 (18.6)	109 (17.6)	
Rehabilitation centre		139 (16.6)	42 (19.0)	97 (15.7)	
Hospice		2 (0.2)	2 (0.9)	0 (0)	
Mortuary (in-hospital death)		213 (25.4)	63 (28.5)	150 (24.3)	
Else		9 (1.1)	2 (0.9)	7 (1.1)	
Mortality	*n (%)*				
ICU		145 (17.3)	47 (21.3)	98 (15.6)	0.068
In-hospital		213 (25.4)	63 (28.5)	150 (24.3)	0.214
3-month		258 (30.8)	83 (37.6)	175 (28.3)	0.011*
6-month		272 (32.4)	85 (38.5)	187 (30.3)	0.025*
Duration of MV (days)	*median [IQR]*	11 [8–17]	11 [8–17]	11 [8–17]	0.251
Need for a tracheostomy to wean (yes)	*n (%)*	200 (23.8)	56 (25.3)	144 (23.3)	0.542
Need for CRRT (yes)	*n (%)*	144 (17.2)	56 (25.3)	88 (14.2)	<0.001*
ICU LOS (TDA, days) [n = 694]	*median [IQR]*	16 [11–27]	18 [13–29]	15 [11–27]	0.292
Hospital LOS (TDA, days) [n = 626]	*median [IQR]*	30 [21–46]	32 [23–45]	29 [21–47]	0.409
All-cause readmission <6 months [n = 626]	*n (%)*				
To hospital		260 (41.5)	74 (33.5)	186 (30.1)	0.350
To ICU		38 (6.1)	15 (6.8)	33 (5.3)	0.426

CRRT = continuous renal replacement therapy; ICU = Intensive Care Unit; IQR = interquartile range; LOS = length of stay; MV = mechanical ventilation; n = number of patients; TDA = time to alive discharge.
* p-value <0.05.
[a] p-values were calculated using the chi-square test or Wilcoxon rank sum test where appropriate.

Table 3
Univariable and multivariable COX regressions for the association of substantial propofol administration[a] and 6-month mortality.

Day 1–7	Univariable	p-value	Multivariable	p-value
	HR (95 % CI)		HR (95 % CI)	
Propofol dose day 1–7 (>500 mg)	0.753 (0.582–0.973)	0.030*	0.899 (0.689–1.175)	0.436
Gender (female)	0.905 (0.705–1.161)	0.431	0.891 (0.693–1.146)	0.369
BMI (>27 kg/m^2)	0.733 (0.577–0.930)	0.011*	0.710 (0.559–0.903)	0.005*
mNUTRIC score	1.386 (1.291–1.487)	<0.001*	1.379 (1.284–1.481)	<0.001*
Sepsis on admission (yes)	1.142 (0.899–1.451)	0.276	1.124 (0.8880–1.437)	0.348
Admission type (surgical)	0.996 (0.769–1.291)	0.976	0.909 (0.682–1.211)	0.514
PN administered days 1–7 (yes)	1.355 (1.012–1.815)	0.041*	1.167 (0.844–1.614)	0.350

BMI = Body Mass Index; 95 % CI = 95 % confidence interval; mNUTRIC = modified Nutrition Risk in Critically Ill; PN = parenteral nutrition.
Multivariable Cox regression analyses were conducted using the Enter and Forward (Stepwise Wald) methods.
* p-value <0.05.
[a] substantial propofol administration: >500 mg during the first seven days of ICU admission.

adjusted for death as a competing risk). However, this association was no longer significant when additionally adjusted for days spent in the hospital (p = 0.069). No statistically significant differences were observed between the groups in other secondary endpoints of interest (all p > 0.05).

4. Discussion

The use of propofol is common in critically ill patients requiring mechanical ventilation, but its impact on long-term outcomes has not been extensively studied. In this large retrospective study, we investigated the effects of substantial doses of propofol, defined as cumulative administration of over 500 mg during the first week of ICU admission, on clinical outcomes, including 6-month mortality.

Our findings indicate no significant association between substantial propofol use and 6-month mortality or other secondary outcomes, such as duration of mechanical ventilation and need for a tracheostomy, ICU and hospital length of stay, discharge destinations, and ICU, in-hospital, and 3-month mortality when corrected for other variables relevant for these endpoints.

Our study is consistent with a recent meta-analysis by Kotani et al. studying all-cause mortality in postoperative and critically ill patients receiving propofol versus any other sedative agent [5]. In total, they included 252 RCTs (comprising 30,757 patients). They found that propofol significantly increases mortality in non-ICU patients, as they reported higher mortality rates in the propofol group versus the comparator groups (5.2 % versus 4.3 %; risk ratio = 1.10; 95 % confidence interval 1.01–1.20; p = 0.03), number needed to harm 235). However, they also found no significant difference in mortality among ICU patients receiving propofol (risk ratio = 1.04, 95%CI 0.93–1.16, p = 0.50). Of note, this meta-analysis had limitations, such as not considering the dosage and duration of propofol infusions in the analyses and including studies with varying follow-up times.

In our multivariable analyses, lower BMI and higher mNUTRIC score were significantly associated with 6-month mortality, consistent with previous studies [48–50].

Ho and colleagues conducted a meta-analysis of 16 trials among heterogeneous populations of critically ill patients, including trauma and cardiothoracic surgery, to evaluate the association between propofol versus alternative sedatives on secondary outcomes such as

Table 4
Univariable and multivariable regressions for the association of substantial propofol administration and secondary outcomes.

A. ICU mortality

	Univariable	p-value	Multivariable	p-value
	HR (95 % CI)		HR (95 % CI)	
Propofol dose day 1–7 (>500 mg)	0.726 (0.513–1.028)	0.071	0.932 (0.648–1.340)	0.704
Gender (female)	0.865 (0.613–1.220)	0.407	0.844 (0.596–1.194)	0.338
BMI (>27 kg/m^2)	0.618 (0.443–0.862)	0.005*	0.603 (0.432–0.841)	0.003*
mNUTRIC score	1.389 (1.261–1.530)	<0.001*	1.376 (1.247–1.517)	<0.001*
Sepsis on admission (yes)	1.343 (0.969–1.860)	0.076	1.303 (0.933–1.820)	0.120
Admission type (surgical)	0.914 (0.637–1.312)	0.626	0.724 (0.482–1.087)	0.120
PN administered days 1–7 (yes)	1.726 (1.188–2.508)	0.004*	1.620 (1.063–2.467)	0.025*

B. In-hospital mortality

	Univariable	p-value	Multivariable	p-value
	HR (95 % CI)		HR (95 % CI)	
Propofol dose day 1–7 (>500 mg)	0.824 (0.614–1.106)	0.197	1.021 (0.751–1.387)	0.896
Gender (female)	0.937 (0.708–1.241)	0.651	0.931 (0.702–1.235)	0.62
BMI (>27 kg/m^2)	0.726 (0.554–0.951)	0.020*	0.699 (0.533–0.918)	0.010*
mNUTRIC score	1.444 (1.332–1.566)	<0.001*	1.446 (1.332–1.571)	<0.001*
Sepsis on admission (yes)	1.139 (0.869–1.493)	0.346	1.145 (0.868–1.510)	0.337
Admission type (surgical)	0.969 (0.722–1.300)	0.833	0.891 (0.643–1.235)	0.488
PN administered days 1–7 (yes)	1.316 (0.944–1.833)	0.105	1.130 (0.782–1.633)	0.515

C. Three-month mortality

	Univariable	p-value	Multivariable	p-value
	HR (95 % CI)		HR (95 % CI)	
Propofol dose day 1–7 (>500 mg)	0.725 (0.558–0.941)	0.016*	0.866 (0.659–1.136)	0.299
Gender (female)	0.968 (0.751–1.247)	0.802	0.951 (0.736–1.228)	0.700
BMI (>27 kg/m^2)	0.713 (0.558–0.912)	0.007*	0.690 (0.539–0.884)	0.003*
mNUTRIC score	1.378 (1.282–1.481)	<0.001*	1.371 (1.274–1.475)	<0.001*
Sepsis on admission (yes)	1.144 (0.895–1.462)	0.284	1.115 (0.867–1.433)	0.397
Admission type (surgical)	0.980 (0.751–1.279)	0.882	0.912 (0.678–1.225)	0.540
PN administered days 1–7 (yes)	1.315 (0.972–1.779)	0.076**	1.130 (0.808–1.580)	0.474

D. Duration of mechanical ventilation, length of ICU and hospital stay

	Duration of MV		p-value	ICU LOS, TDA		p-value	HOS LOS, TDA		p-value
	β	SE		β	SE		B	SE	
Propofol dose day 1–7 (>500 mg)	−0.013	0.019	0.510	−0.023	0.023	0.318	−0.008	0.022	0.721
Gender (female)	−0.005	0.017	0.759	−0.038	0.020	0.060	−0.009	0.02	0.661
BMI (>27 kg/m^2)	0.009	0.017	0.608	−0.001	0.019	0.942	0.031	0.019	0.102
mNUTRIC score	0.010	0.004	0.030*	0.015	0.005	0.003*	0.031	0.005	<0.001*
Sepsis on admission (yes)	0.005	0.017	0.793	−0.003	0.020	0.897	0.015	0.020	0.439
Admission type (surgical)	0.015	0.02	0.449	0.021	0.023	0.361	0.066	0.023	0.004*
PN administered days 1–7 (yes)	0.048	0.025	0.058	0.076	0.029	0.010*	0.113	0.029	<0.001*

E. Need for a tracheostomy and discharge destination home

	Tracheostoma needed		p-value	Discharged home alive		p-value	.. corrected for HOS days		p-value
	β	SE		β	SE		β	SE	
Propofol dose day 1–7 (>500 mg)	−0.081	0.209	0.699	0.546	0.206	0.008*	0.215	0.118	0.069
Gender (female)	−0.157	0.188	0.405	0.050	0.176	0.777	0.113	0.108	0.298
BMI (>27 kg/m^2)	−0.457	0.18	0.011*	−0.179	0.168	0.287	−0.016	0.105	0.880
mNUTRIC score	0.091	0.049	0.065	−0.210	0.047	<0.001*	−0.040	0.030	<0.001*
Sepsis on admission (yes)	0.061	0.187	0.744	0.172	0.175	0.325	−0.151	0.110	0.171
Admission type (surgical)	−0.125	0.211	0.554	0.149	0.201	0.458	−0.313	0.123	0.011*
PN administered days 1–7 (yes)	0.107	0.263	0.683	0.357	0.252	0.157	−0.577	0.162	<0.001*

BMI = Body Mass Index; 95%CI = 95 % confidence interval; HOS = hospital; ICU = Intensive Care Unit; mNUTRIC = modified Nutrition Risk in Critically Ill; MV = mechanical ventilation; PN = parenteral nutrition; TDA = time to alive discharge (ICU n = 694; HOS n = 626).
* p-value <0.05.
p-values were assessed using Cox proportional hazards, logistic or log-transformed linear regression models where appropriate.

length of ICU stay and duration of mechanical ventilation [51]. They reported that patients sedated with propofol might have a reduced length of mechanical ventilation and ICU LOS compared to long-acting benzodiazepines (weighted-mean difference in days −0.99, 95%CI -1.51 to −0.47, p = 0.0002). However, this association was lost when the comparison was limited to propofol and midazolam. Garcia et al.'s systematic review and meta-analysis reported similar findings, including seven RCTs evaluating clinical outcomes of critically ill ICU patients who received propofol or midazolam [52]. Conversely, Zhang and coworkers' network meta-analysis, which included 16 studies comparing propofol and midazolam, found a shorter duration of mechanical ventilation in favour of the propofol group. However, the analysis included heterogeneous study populations due to a broad definition of critical illness [53].

Several studies have compared propofol versus dexmedetomidine use with heterogeneous study populations and varying

results. Heybati et al.'s most recent meta-analysis of eight studies showed no differences in the duration of mechanical ventilation, ICU LOS, and mortality in critically ill, non-cardiac surgery patients between both hypnotic agents [54]. However, no studies have investigated the associations between propofol administration and clinical outcomes that reflect ICU-AW, such as the need for a tracheostomy to wean from mechanical ventilation and discharge destinations.

Our study's findings suggest that the effect of substantial doses of propofol on mitochondrial function is limited and does not significantly affect muscle function or ICU-acquired weakness and therefore does not impact clinical outcomes. Of note, this is probably only true for the least sick patients, as we would expect clinical staff to use alternative sedatives in unstable patients. This is reflected in the baseline data: patients in the no substantial propofol dose group had higher APACHE II scores and higher mortality.

Another possible explanation is that propofol's early pharmacological suppression of mitochondrial function may facilitate an adaptive process, and discontinuation of propofol may allow for mitochondrial function recovery. However, this is speculative and more basic research is necessary to elucidate the underlying mechanisms involved.

4.1. Strengths

This study is the most extensive to date regarding the clinical outcomes of patients who received propofol during their ICU stay. Strengths of this study include an extended follow-up period of 6 months and evaluation of several outcome parameters, including the need for a tracheostomy to wean from mechanical ventilation and discharge destinations. Additionally, due to the ICU patient data management system, non-nutritional calories could be precisely quantified, and nutritional support could be adapted to prevent overfeeding [55].

4.2. Limitations

First, it is a retrospective observational study, and there were significant baseline differences between the substantial propofol and no substantial propofol dose groups, introducing bias and confounding. In univariable analysis, there appeared to be a survival benefit for the substantial propofol dose group, mainly when administered during the late acute phase of illness, but this effect disappeared in multivariable analyses due to differences in baseline characteristics. Moreover, we might have introduced bias by defining the cut-off value to distinguish patients who were administered a substantial dose of propofol and those who were not. Additionally, the study is limited by its single-centre design and the inclusion of only critically ill patients who were mechanically ventilated for at least seven days. Furthermore, the energy targets used in the ICU were based on the static FAO/WHO/UNU formula, not accounting for individual needs measured with indirect calorimetry.

The study also had some limitations regarding propofol and other medications. Only propofol use during the first seven days was analysed, so propofol administration during more than seven days in 252 patients might have altered outcomes. The cut-off value of 500 mg of propofol was arbitrarily chosen to distinguish patients who received a substantial dose of propofol from patients who received only small doses periprocedurally. The study did not adjust for sedation intensity (depth), as measured by the RASS score. Finally, the possible effects of any other medication administered (except for muscle relaxants or chronic steroids) could not be corrected [56].

4.3. Future directions

Future research should focus on conducting randomised controlled trials to confirm the safety of the administration of substantial doses of propofol in critically ill patients and to investigate its potential association with outcomes such as ICU-acquired weakness and discharge destinations.

5. Conclusion

In conclusion, this retrospective observational study found no significant association between substantial propofol administration (defined as a cumulative dose >500 mg during the first week of ICU admission) and adverse clinical outcomes such as mortality, duration of mechanical ventilation, need for tracheostomy, ICU and hospital length of stay, and discharge destinations. Therefore, sedation with substantial doses of propofol, guided by RASS scores and sedation interruptions, appears safe in the least sick (as evaluated by clinical staff) critically ill adult patients who require mechanical ventilation for at least seven days. It is unlikely that propofol has a significant impact on mitochondrial function translating into negative effects on clinically relevant endpoints in these patients.

Ethics approval

The Gelderse Vallei Hospital ethical approval committee approved the study under protocol number 1901-004. This was a retrospective study with anonymised data, so a waiver was granted for informed consent.

Consent for publication

Not applicable.

Availability of data and material

All data collected and analysed during this study are available upon reasonable request from the corresponding author.

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Authors' contributions

Rianne Slingerland: Conceptualisation, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Dara Curation, Writing – Original Draft, Visualisation.

Maren Kummerow: Conceptualisation, Methodology, Software, Validation, Investigation, Resources, Dara Curation, Writing - Review & Editing.

Sesmu Arbous: Writing - Review & Editing, Supervision.

Arthur van Zanten: Conceptualisation, Methodology, Writing - Review & Editing, Supervision, Project Administration, Funding Acquisition.

Conflict of interest

Professor Van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, AoP Pharma, Baxter, Cardinal Health, Danone-Nutricia, Dim-3, Fresenius Kabi, GE Healthcare, Medcaptain, Mermaid,

Nestle-Novartis, PAION, Lyric, and Rousselot. The other authors have nothing to declare.

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Appendix A. Supplementary data

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