Failure of non-sedation strategy in critically ill, mechanically ventilated patients

a retrospective, post-hoc analysis of the NONSEDA trial

Nedergaard, Helene Korvenius; Korkmaz, Serkan; Olsen, Hanne Tanghus; Jensen, Hanne Irene; Strøm, Thomas; Toft, Palle

Published in:
Journal of Critical Care

DOI:
10.1016/j.jcrc.2021.12.001

Publication date:
2022

Document version:
Final published version

Journal of Critical Care 68 (2022) 66–71

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Failure of non-sedation strategy in critically ill, mechanically ventilated patients - a retrospective, post-hoc analysis of the NONSEDA trial

Helene Korvenius Nedergaard [a,b,*], Serkan Korkmaz [c], Hanne Tanghus Olsen [d], Hanne Irene Jensen [a,b], Thomas Strøm [d,e], Palle Toft [d]

[a] Department of Anesthesiology and Intensive care, University Hospital of Southern Denmark, Kolding. Sygehusvej 24, DK-6000 Kolding, Denmark
[b] Department of Regional Health Research, University of Southern Denmark, Winsløwsparken 19, 3., DK-5000 Odense C, Denmark
[c] Department of Business and Economics, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark
[d] Department of Anesthesiology and Intensive Care, Odense University Hospital, J.B. Winsløwsvej 4, DK-5000 Odense C, Denmark
[e] Department of Anesthesiology and Intensive Care, Hospital of Southern Denmark, Kresten Philipsens vej 15, DK-6200 Aabenraa, Denmark

ARTICLE INFO

Available online xxxx

Keywords:
Adult intensive care
Sedation
Mechanical ventilation

ABSTRACT

Purpose: There is a growing awareness on minimizing sedation in ICUs. In the NONSEDA trial 700 critically ill patients were randomized to light sedation or non-sedation during mechanical ventilation. Approximately 40% of patients randomized to non-sedation needed sedation. The aim of this study is to obtain knowledge on patients, who experienced failure of non-sedation.
Materials and methods: This study is a retrospective post-hoc analysis of the NONSEDA trial. Patients, who were randomized to non-sedation are sub-divided into those who did not require sedation during mechanical ventilation ("non-sedation success"), and those who needed continuous sedation at least once ("non-sedation failure").
Results: 348 patients were randomized to non-sedation, 199 experienced non-sedation success, whereas 149 experienced non-sedation failure. Patients in the two groups were comparable with regards to age, BMI, disease severity scores and admission diagnoses. Patients with non-sedation failure were more often male. Propofol was mainly used as rescue sedation. Patients with non-sedation failure had less days alive without sedation, coma, delirium, organ support, mechanical ventilation, ICU- and hospital admission. Mortality and long-term outcomes did not differ between groups.
Conclusion: Patients with non-sedation success had better in-hospital outcomes, but mortality and long-term outcomes were not affected by success or failure of non-sedation.

1. Introduction

Within the past decades, there has been a growing awareness on minimizing the use of sedation in intensive care units (ICU). Studies have reported on benefits of avoiding especially heavy sedation [1,2] and guidelines encourage the use of less sedation [3]. In 2020 we published results from the NONSEDA trial; a clinical trial in which 700 critically ill patients in eight Scandinavian ICUs were randomized to either light sedation or non-sedation during mechanical ventilation [4]. In the NONSEDA trial we found more days free of coma or delirium and less thromboembolic events in the non-sedated group. We found no difference between groups regarding length of mechanical ventilation, ICU-admission or 90 days mortality. Sub-studies reported a beneficial effect of non-sedation on physical function at extubation and ICU discharge, however no difference three months later [5], and no difference between groups regarding cognitive function or psychological health (posttraumatic stress, anxiety, depression) [6,7]. For most patients who were randomized to the non-sedation strategy, this was a tolerable treatment modality during mechanical ventilation with oral intubation, and they did not require sedation. However, within critical care there is no "one size fits all", and neither does non-sedation. We found that approximately 40% of patients in the NONSEDA trial who were randomized to non-sedation needed (and were given) sedation at some point during their admission, with the main reason being agitated delirium [4]. We call this "failure of non-sedation".

The aim of this post-hoc study of the NONSEDA trial is to obtain knowledge on the critically ill, mechanically ventilated patients, who

* Corresponding author at: Department of Anesthesiology and Intensive care, University Hospital of Southern Denmark, Kolding. Sygehusvej 24, DK-6000 Kolding, Denmark.
E-mail addresses: helene.korvenius.nedergaard@rsyd.dk (H.K. Nedergaard), hanne.tanghus.olsen@rsyd.dk (H.T. Olsen), hanne.irene.jensen@rsyd.dk (H.I. Jensen), thomas.stroem@rsyd.dk (T. Strøm), palle.toft@rsyd.dk (P. Toft).

https://doi.org/10.1016/j.jcrc.2021.12.001
0883-9441/

experienced failure of non-sedation. No previous study has investigated which factors are associated with failure of non-sedation and the effects on clinical outcomes.

2. Material and methods

This study is a retrospective post-hoc analysis of data from the NONSEDA trial. In brief, the NONSEDA trial included 700 adult ICU-patients who were endotracheally intubated and expected to receive mechanical ventilation for more than 24 h. Patients with a medical reason for sedation were excluded (severe head trauma, therapeutic hypothermia, status epilepticus, severe respiratory failure with a need for prone position, not-medically induced coma at admission). Patients were randomized to non-sedation or to light sedation (a Richmond Agitation and Sedation Score (RASS) [8] of −2 to −3) with daily interruption of sedatives (sedation group). The patients randomized to non-sedation did not receive sedatives during mechanical ventilation but, if needed, received bolus doses of morphine for analgesia, as deemed necessary by the treating team. If patients became anxious or agitated, nonpharmacologic measures and analgesic treatment was used, but if this was insufficient, the patient was given sedatives as in the sedation group. The patients in the sedation group received a continuous infusion of sedatives, with propofol used in the first 48 h and thereafter midazolam, with a daily interruption of sedatives, a "daily wake-up call". More details can be found in the trial protocol [9] and main publication [4].

In this study, we analyze data from the patients who were randomized to non-sedation, and sub-divide them into two groups, 1) those who were randomized to non-sedation, and did not require continuous sedation during mechanical ventilation ("non-sedation success"), and 2) those who were randomized to non-sedation, but needed continuous sedation at least once during mechanical ventilation ("non-sedation failure"). Whether a patient, randomized to non-sedation, had needed continuous sedation in the previous 24 h was evaluated daily by dedicated clinical investigators (ICU nurse or physician) at each site. Single bolus doses of sedatives given during mechanical ventilation in the context of for example clinical procedures, were not deemed "failure of non-sedation", however, continuous infusion of sedatives was (propofol or midazolam, as these were the sedatives used in the NONSEDA trial). Patients were assessed for delirium at least twice a day with the use of the Confusion Assessment Method for the ICU (CAM-ICU [10]).

Data on baseline characteristics, use of medication during admission as well as clinical and follow-up outcomes are analyzed. All patients in the NONSEDA trial were followed up by postal mail three months after ICU discharge and answered questions on health-related quality of life (HRQOL) (using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36 [11]) and degree of independence in activities of daily living (ADL activities) (using the Barthel Index (BI [12]) 3 months post-ICU discharge [13]. A pre-addressed and prepaid return envelope was included in the letter. To limit missing data, reminders were sent out after 2 weeks. If unsuccessful, we tried to reach the patient by telephone in order to perform a telephone interview. If none of this was successful, the participant was considered lost to follow up. All data were attempted obtained from the participating patients themselves and having a relative fill out the questionnaires at home was discouraged. Outcome assessors were blinded to randomization group. Survival status at 90 days was established through the civil registration numbers in the respective participating countries. Patients with no available data were not included in the analysis.

The SF-36 was used to evaluate the participants' HRQOL. It measures eight different health-related domains, which are summarized into two component scores, the mental and the physical component score (PCS), standardized with mean 50 and standard deviation 10 [11]. The SF-36 has been widely used and is validated in ICU populations [14]. The Barthel Index evaluates degree of independence in activities of daily living (ADL) [12]. We used the Barthel Index-20 version, with higher scores indicating a higher degree of independence. In the NONSEDA trial, the intervention was not blinded due to its nature. Assessment of the follow-up outcomes was performed blinded to the participants' primary allocation.

2.1. Ethics

The NONSEDA trial was approved by the local scientific research ethics committees and registered at clinicaltrials.gov (NCT 01967680). Informed consent was obtained from all participating patients in the study, preferably from the patient themselves, but in case of impaired consciousness, from the patient's closest relative and general practitioner.

2.2. Statistics

Descriptive statistics were determined for all primary variables (age, sex, etc.). The data were expressed as mean ± SD except if the distribution was skewed, then data were presented as medians and interquartile range. Fisher's exact test, Wilcoxon ranksum test and Student's *t*-test were performed as appropriate, and $p < 0.05$ was considered statistically significant. No separate sample size or power analysis was done for this sub-study.

3. Results

349 patients were randomized to non-sedation in the NONSEDA trial; however, one patient had no available data (the patient died unexpectedly while being randomized) and was thus excluded from the post-hoc analysis, leaving 348 patients. Of these, 199 patients experienced non-sedation success, and were not sedated during mechanical ventilation, whereas 149 patients experienced non-sedation failure.

59 patients (40%) with non-sedation failure had a tracheostomy performed during their ICU stay, whereas the numbers for non-sedation success was 34 patients (17%).

Table 1 shows that patients in the two groups, non-sedation success and -failure, were comparable with regards to age, BMI, premorbid history of COPD, alcohol and benzodiazepine intake. Patients with non-sedation failure were more often male. Disease severity scores, type of admissions and diagnoses were alike in the two groups as well.

Table 2 shows that if the non-sedation protocol failed, propofol was mainly used as rescue sedation, as patients in the non-sedation failure group received more propofol than patients in the non-sedation success group, whereas doses of midazolam in both groups were very small and did not differ between groups. More morphine was used in the non-sedation failure group. Doses of other psychoactive drugs, haloperidol and clonidine (no other drugs were used in the NONSEDA trial), were small, however doses were higher in the non-sedation failure group.

Table 3 shows that patients with non-sedation failure had less days alive without sedation, less coma and delirium-free days, less days without mechanical ventilation, less days without ICU- and hospital admission, and less days without organ support. There was no significant difference between groups with regard to mortality or three months follow-up data (health-related quality of life and ADL-function).

In Fig. 1 the clinical level of sedation is depicted by daily RASS-scores in the two groups. Patients in the non-sedation failure group were sedated to a level of −1.5 to −1 in the first week, whereas patients in the non-sedation success group had a RASS-score of −1 to −0.5 in the same period. (See Fig. 2.)

In supplement table A, data from the two groups, non-sedation success and -failure, on baseline characteristics, use of medication and outcomes, can be seen alongside data from the patients, who were originally randomized to standard care of sedation with a daily wake-up trial in the NONSEDA trial.

Table 1
Baseline data for patients randomized to non-sedation, divided in "non-sedation failure" and "non-sedation success".

	Non-sedation failure $n = 149$	Non-sedation succes $n = 199$	p-value
Age median (IQR)	72 (64–79.3)	73 (63.5–80)	0.6[a]
Female n (%)	41 (27.5%)	95 (47.7%)	0.0005[b]
Male n (%)	108 (72.5%)	104 (52.3%)	
BMI median (IQR)	26.5 (23.2–30)	25.4 (22.4–29.3)	0.07[a]
History of COPD n (%)	40 (26.85%)	70 (35.18%)	0.09[a]
History of benzodiazepine use n (%)	13 (8.72%)	14 (7.04%)	0.6[a]
History of alcohol abuse n (%)	19 (12.75%)	22 (11.06%)	0.7[a]
Admission data:			
APACHE II median (IQR)	25 (21−30)	26 (22−30)	0.5[a]
SAPS II median (IQR)	49.5 (38–60)	48 (39–60)	0.9[a]
SOFA 1st day median (IQR)	8 (5–11)	7 (5–11)	0.1[a]
Type of admission, medical, n (%)	96 (64.4%)	147 (73.9%)	0.14[b]
Type of admission, surgical, n (%)	48 (32.2%)	45 (22.6%)	
Admission diagnosis:			
Sepsis n (%)	32 (21.5%)	51 (25.6%)	0.2[b]
Pneumonia/ARDS n (%)	61 (41%)	83 (41.7%)	
Excacerbation of COPD n (%)	5 (3.4%)	18 (9%)	
Postoperative complications, n (%)	17 (11.4%)	18 (9%)	
Trauma n (%)	6 (4%)	5 (2.5%)	
Gastrointestinal hemorrhage, n (%)	5 (3.4%)	5 (2.5%)	
Cardiac failure n (%)	1 (0.7%)	4 (2%)	
Pancreatitis n (%)	4 (2.7%)	2 (1%)	

IQR: interquartile range. BMI: body mass index. APACHEII: acute physiology and chronic health evaluation, version II. SOFA: sequential organ failure assessment. SAPSII: simplified acute physiology score, version II. ARDS: acute respiratory distress syndrome. COPD: chronic obstructive pulmonary disease. ARDS: adult respiratory distress syndrome.
[a] Wilcoxon ranksum test.
[b] Pearsons chi^2 test.

4. Discussion

With this study we found that patients with non-sedation success and non-sedation failure had similar baseline characteristics (age, BMI, disease severity scores). However, patients with non-sedation success had more days alive without sedation, more days alive without mechanical ventilation, more coma and delirium free days and more organ support free days. We found no difference between groups with regard to mortality or health-related quality of life or ADL-function.

This study illustrates the difficulties for clinicians in the ICU to predict if a strategy of non-sedation will be successful or not for each patient. In the present post hoc analysis there is no indication of non-sedation being more likely to fail in a specific age-group, disease category or disease severity. Non-sedation is a complex treatment modality, and all patients could potentially experience success of non-sedation, so as with all other treatments in the ICU, individual evaluations are necessary. The difficulties in predicting whether or not non-sedation will be a success calls for daily evaluation of each patient in the ICU. Each patient's condition change on a daily basis, for example regarding disease severity, pain, withdrawal symptoms or delirium. Also, sometimes it is possible to alter the surroundings around the patient, for example having a relative present or move the patient to a single-bed ICU-room. All these factors might lead to non-sedation becoming a successful strategy.

We found that men were more likely than women to experience failure of non-sedation. The reasons behind this need to be explored in further, qualitative studies, but gender could be one of the factors to consider when making individual assessments of need for sedation.

We found that more patients with non-sedation failure had a tracheostomy performed during their ICU stay compared to patients with non-sedation success (40% vs 17%). The tracheostomies can have been performed in an effort to increase the comfort and perhaps thereby make non-sedation acceptable, or they can have been performed because patients with non-sedation failure had longer ICU stays. Relatively few patients who experienced non-sedation success had a tracheostomy (17%), so a tracheostomy is obviously not mandatory for non-sedation to be successful.

In the present post-hoc analysis we find that patients, who experience failure of non-sedation has less days free from coma and delirium. However, the interplay between sedation/non-sedation and delirium is complex, and it is difficult to determine exactly which is the chicken and which is the hen. Sometimes sedation can cause delirium (especially when benzodiazepines are used) and sometimes non-sedation can be impossible due to delirium. This study is a post-hoc analysis and data cannot be used to conclude on causality, as data does not allow us to evaluate the exact time course and relation between sedation and delirium. However, the less days free from coma and delirium in the non-sedation failure group along with the worsened outcomes in this group, strengthens the perception that any cerebral dysfunction, it being coma, delirium or need for sedation, is an indication of a more severe outcome for the patient.

Overall, fairly small amounts of sedatives were used (propofol and/or midazolam, no other sedatives were used in the NONSEDA trial)

Table 2
Medication used within the first 7 or 28 days from randomization.

	Non-sedation failure Mean (±SD) $n = 149$	Non-sedation succes Mean (±SD) $n = 199$	P-value
Propofol. mg/kg/h, first 28 days, all patients	0.09 (±0.24)	0.01 (±0.046)	<0.01[a]
Propofol. mg/kg/h, first 7 days, all patients	0.16 (±0.348)	0.01 (±0.045)	<0.01[a]
Patients, who received propofol, first 7 days, n (%)	137 (92%)	97 (49%)	NA
Propofol, mg/kg/h, Excluding those patients, who did not receive propofol, first 7 days	0.29 (± 0.34)	0.08 (±0.09)	NA
Midazolam. mg/kg/h, first 28 days, all patients.	0.0009 (±0.006)	0.0007 (±0.009)	0.84[a]
Midazolam. mg/kg/h, first 7 days, all patients.	0.003 (±0.0162)	0.0007 (±0.0085)	0.11[a]
Patients, who received midazolam, first 7 days, n (%)	52 (35%)	33 (17%)	NA
Midazolam, mg/kg/h, Excluding those patients, who did not receive midazolam, first 7 days	0.01 (±0.02)	0.00 (±0.02)	NA
Morphine. mg/kg/h 28 days.	0.015 (±0.03)	0.01 (±0.03)	0.17[a]
Morphine. mg/kg/h first 7 days.	0.02 (±0.03)	0.01 (±0.03)	<0.01[a]
Patients, who received morphine, first 7 days, n (%)	147 (99%)	182 (91%)	NA
Morphine, mg/kg/h Excluding those patients, who did not receive midazolam, first 7 days	0.02 (±0.03)	0.01 (±0.03)	NA
Haloperidol. mg/kg/h 28 days.	0.0006 (±0.001)	0.0002 (±0.0009)	0.01[a]
Clonidine. microg/kg/h 28 days.	0.047 (±0.01)	0.022(±0.06)	0.01[a]

All medication was given intravenously. Within the NONSEDA trial the use of propofol, midazolam and morphine was standard. In rare cases of allergy towards morphine, fentanyl was used instead, and doses then converted to morphine equivalents (100 microg fentanyl equaling 10 mg morphine iv). No other benzodiazepines were used.
SD: standard deviation. Mg/k/h: milligrams per kilogram per hour. Microg: micrograms.
[a] Student's t-test.

Table 3
Clinical outcomes in each group.

	Non-sedation failure n = 149	Non-sedation success n = 199	P-value
Days alive without ICU in the first 28 days Mean (±SD)	9.4 (±10.6)	14.1 (±10.8)	<0.01[a]
Days alive without coma and delirium, in the first 28 days (days after discharge from ICU = no delirium) Mean (±SD)	26.6 (±2.3)	27.6 (±1.5)	<0.01[a]
Days alive without coma and delirium, in the first 7 days (days after discharge from ICU = no delirium) Mean (±SD)	5.6 (±2.0)	6.7 (±1.1)	<0.01[a]
Patients, who experienced delirium, n (%)	141 (95%)	141 (71%)	<0.01[a]
Days with delirium, in the first 28 days (days after discharge from ICU = no delirium) Mean (±SD)	8.8 (±7.0)	3.8 (±5.2)	<0.01[a]
Days alive without mechanical ventilation in the first 28 days Mean (±SD)	14.1 (±14.6)	18.3 (±15.5)	<0.01[a]
Days alive without sedation in the first 28 days Mean (±SD)	18.9 (±9.5)	22.3 (±9.6)	<0.01[a]
Days alive without hospital in the first 28 daysMean (±SD)	4.4 (±7.7)	7.5 (±8.8)	<0.01[a]
Days alive without organ support (mechanical vent, CRRT/dialysis, vasoactive drugs) in the first 28 days Mean (±SD)	21.6 (±7.0)	24.8 (±4.9)	<0.01[a]
Mortality:			
All-cause mortality at 90 days after randomization no. (%)	82 (41.2%)	67 (45%)	0.48[a]
Follow-up assessment:	*n* = 58 (39%)	*n* = 98 (49%)	
HR-QoL 3 months after ICU-discharge. Mental component score, SF-36 Median (IQR)	45 (36–54.75)	48 (36–58)	0.35[a]
HR-QoL 3 months after ICU-discharge. Physical component score, SF-36 Median (IQR)	37.5 (29.25–44.75)	37.5 (31–45.75)	0.66[a]
ADL-function Barthel score (0 to 20) Median (IQR)	19.5 (17–20)	20 (16–20)	0.93[a]

ICU: intensive care unit. SD: standard deviation. IQR: interquartile range. CRRT: continuous renal replacement therapy. HR-QoL: health related quality of life. SF-36: Medical Outcomes Study 36-Item Short Form Health Survey. ADL: activities of daily living.
[a] Student's t-test.

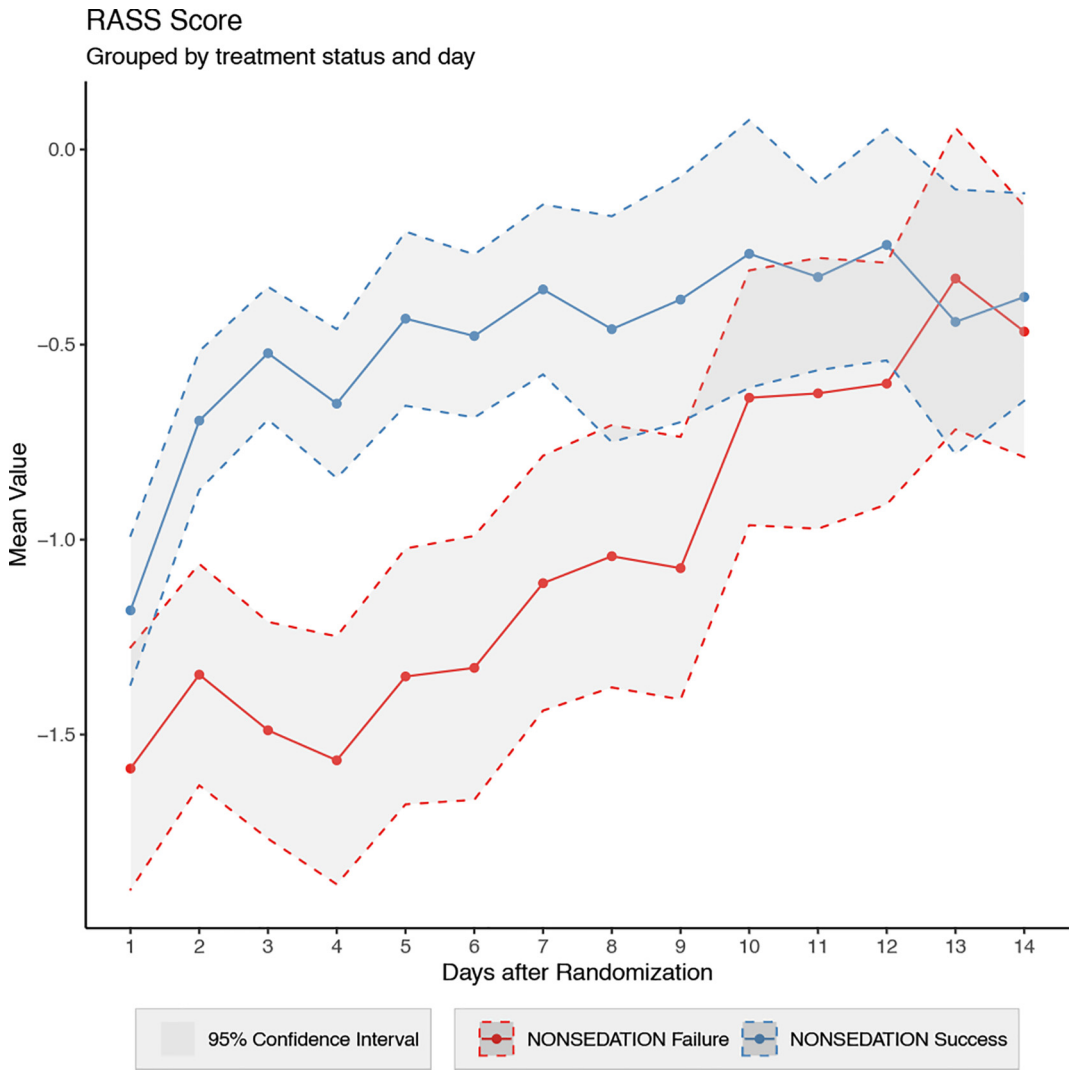

Fig. 1. RASS-score, grouped by treatment status (non-sedation success or -failure) and days after randomization.

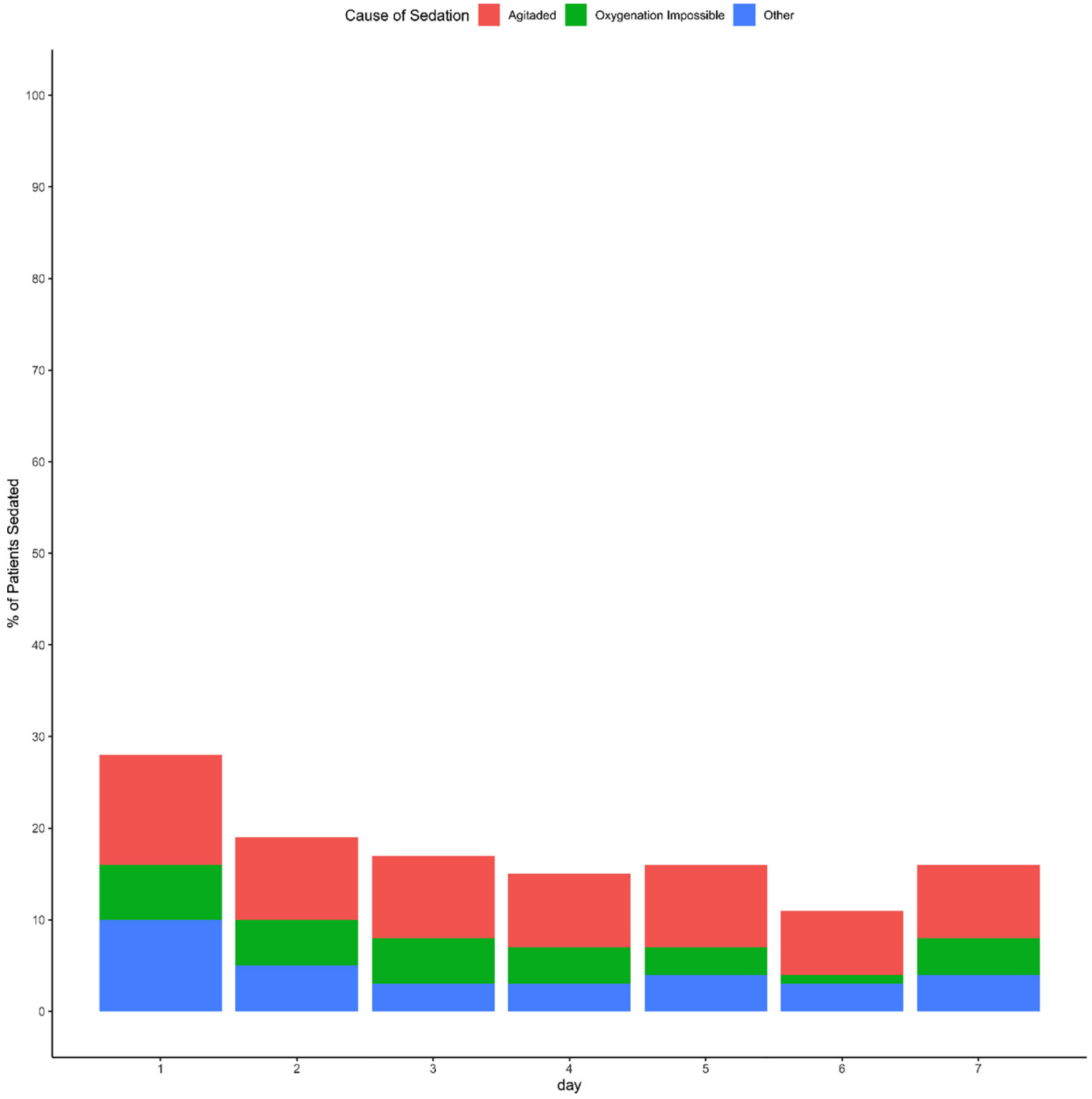

Fig. 2. Reasons for the use of sedation.
Reason for the use of sedation in patients, who were randomized to non-sedation and experienced failure of non-sedation. First seven days from inclusion in the NONSEDA trial. Red: Agitation. Green: Difficulties oxygenating the patient. Blue: Other.

(Table 2). Further, the RASS-scores shown in Fig. 1 indicate that even though the protocol of strict non-sedation had failed, the patients were still lightly sedated. We found that patients in the non-sedation failure group had received more morphine, haloperidol and clonidine, which was probably administered in an attempt to handle pain, withdrawal symptoms and delirium without sedatives. Based on the available data, we are not able to ascertain the exact timing of medication given in relation to failure of non-sedation. Failure of non-sedation can (and often does) happen intermittingly; a patient can need sedation on day 2, 5 and 6 for example, and in between be comfortable on non-sedation.

Patients, who experienced non-sedation failure, received a little less sedative medication than patients, who were originally randomized to sedation in the NONSEDA trial; their clinical outcomes were comparable with patients randomized to sedation (supplement table A).

The very small doses of propofol and midazolam found in the non-sedation success group can be explained by occasional procedural sedation (for example transesophageal echocardiography) or doses given in the first hours after intubation, before inclusion and randomization in the NONSEDA-trial (which happened within 24 h from intubation).

The definition of "failure of non-sedation" used in this study is relatively conservative (failure defined as the use of continuous sedation

just once or more), which we find reasonable and robust. Another definition of non-sedation failure could for example have been use of sedation at least three times during ICU admission or use of sedation at least three days in a row. The clinical outcomes found in this study are therefore probably in the lower end on a spectrum of the effect of "failure" versus "success" of non-sedation.

Currently, we might experience a post-COVID19 caregiver-fatigue following the pandemic. Further, many COVID19-patients in ICUs have been deeply sedated to facilitate ventilation/oxygenation and prone position. There is a risk that this can lead to a general rise in the use of sedation in ICUs. However, current guidelines still recommend light sedation with a daily wake-up call, and our results show that for the majority of non-COVID19 patients in a general ICU, non-sedation or very light sedation are viable options.

This study has limitations. It is a post-hoc analysis, that we had not preplanned, but conceived while analysing the NONSEDA data, as we found that the complex clinical situation of non-sedation failure warranted further investigation. Based on our current data, we are unable to conclude on causality. As mentioned above, we unfortunately did not collect data in a manner that enables us to analyze the timing of medication given before versus after failure of non-sedation (morphine, haloperidol, clonidine). Further, our current data are insufficient to make detailed analyses on individual levels of the relation between failure of non-sedation and delirium. Less that half of the patients answered the follow-up questionnaires. Unfortunately, in the NONSEDA trial we did not collect data on withdrawal symptoms, pharyngeal reflexes or pre-morbid anxiety. These data might have been useful in the understanding of why non-sedation failed. Neither did we collect data on communication difficulties. When talking to patients at the follow-up assessments, more of them mentioned frustrations with communication, especially those, who had not been able to write notes for their relatives and treating staff. Data on these challenges could also have been useful.

This study also has strengths. We analyze data from a large sample, 348 mechanically ventilated, critically ill patients from eight ICUs in three Scandinavian countries, providing a high external validity. The included patients were all randomized to a detailed clinical protocol of non-sedation, thus heightening the internal validity. Our study is the first to attempt to gather knowledge on failure of non-sedation and its consequences.

5. Conclusion

For those patients where non-sedation is successful, it is a good treatment modality, preferable to sedation, as it seems to have a positive effect on clinical in-hospital outcomes. However, those patients who cannot tolerate non-sedation, for example due to agitated delirium, should be offered treatment and sedation in accordance with the current guidelines (preferably light sedation and with a daily sedation interruption) [3]. It is difficult to predict if non-sedation will be a success for a particular patient, so individual assessments must be made on a daily basis.

Authors' contributions

HKN, HTO, TS and PT designed the main NONSEDA trial and this posthoc analysis. HIJ participated in the design of this sub-study, SK participated in planning the statistical analysis plan. HKN, SK, TS, PT, HTO and HIJ analyzed and interpreted the data. HKN drafted the manuscript. All authors approved the submitted version, and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Declaration of Competing Interest

All authors declare that we have no conflicts of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.12.001.

References

[1] Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375:475–80. https://doi.org/10.1016/S0140-6736(09)62072-9.
[2] Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371:126–34.
[3] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU, 46; 2018. https://doi.org/10.1097/CCM.0000000000003299.
[4] Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian K-A, Ytrebø LM, et al. Nonsedation or light sedation in critically ill, mechanically ventilated patients. N Engl J Med. 2020;382:1103–11. https://doi.org/10.1056/nejmoa1906759.
[5] Nedergaard HK, Jensen HI, Olsen HT, Strøm T, Lauridsen JT, Sjøgaard G, et al. Effect of non-sedation on physical function in survivors of critical illness - a substudy of the NONSEDA randomized trial. J Crit Care. 2021;62:58–64. https://doi.org/10.1016/j.jcrc.2020.11.017.
[6] Nedergaard HK, Jensen HI, Stylsvig M, Olsen HT, Strøm T, Toft P. Effect of non-sedation on post-traumatic stress and psychological health in survivors of critical illness—a substudy of the NONSEDA randomized trial. Acta Anaesthesiol Scand. 2020;64:1136–43. https://doi.org/10.1111/aas.13648.
[7] Nedergaard HK, Jensen HI, Stylsvig M, Olsen HT, Korkmaz S, Strøm T, et al. Effect of nonsedation on cognitive function in survivors of critical illness. Crit Care Med. 2020;48:1790–8. https://doi.org/10.1097/CCM.0000000000004573.
[8] Sessler CN, Gosnell MS, Grap MJ, Brophy GM, Neal PVO, Keane KA, et al. The Richmond agitation – sedation scale validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338–44. https://doi.org/10.1164/rccm.2107138.
[9] Toft P, Olsen HT, Jorgensen HK, Strom T, Nibro HL, Oxlund J, et al. Non-sedation versus sedation with a daily wake-up trial in critically ill patients receiving mechanical ventilation (NONSEDA Trial): study protocol for a randomised controlled trial. Trials. 2014;15:499. https://doi.org/10.1186/1745-6215-15-499.
[10] Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in Mechanically Ventilated Patients. Validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), 286; 2001; 2703–10.
[11] Ware J, Kosinski M. SF-36 physical and mental health summary scales: A manual for users of version 1. 2nd ed.. Lincoln, RI Qual Inc; 2001.
[12] Mahoney F, Barthel D. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61–5.
[13] Olsen HT, Nedergaard HK, Hough CL, Korkmaz S, Jensen HI, Strøm T, et al. Non-sedation—does it improve health-related quality of life after critical illness? A 3-month follow-up sub-study of the NONSEDA trial. Acta Anaesthesiol Scand. 2021;65:481–8. https://doi.org/10.1111/aas.13775.
[14] Chrispin PS, Scotton H, Rogers J, Lloyd D, Ridley SA. Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. Anaesthesia. 1997;52:15–23.