Targeted interventions in mechanically ventilated patients

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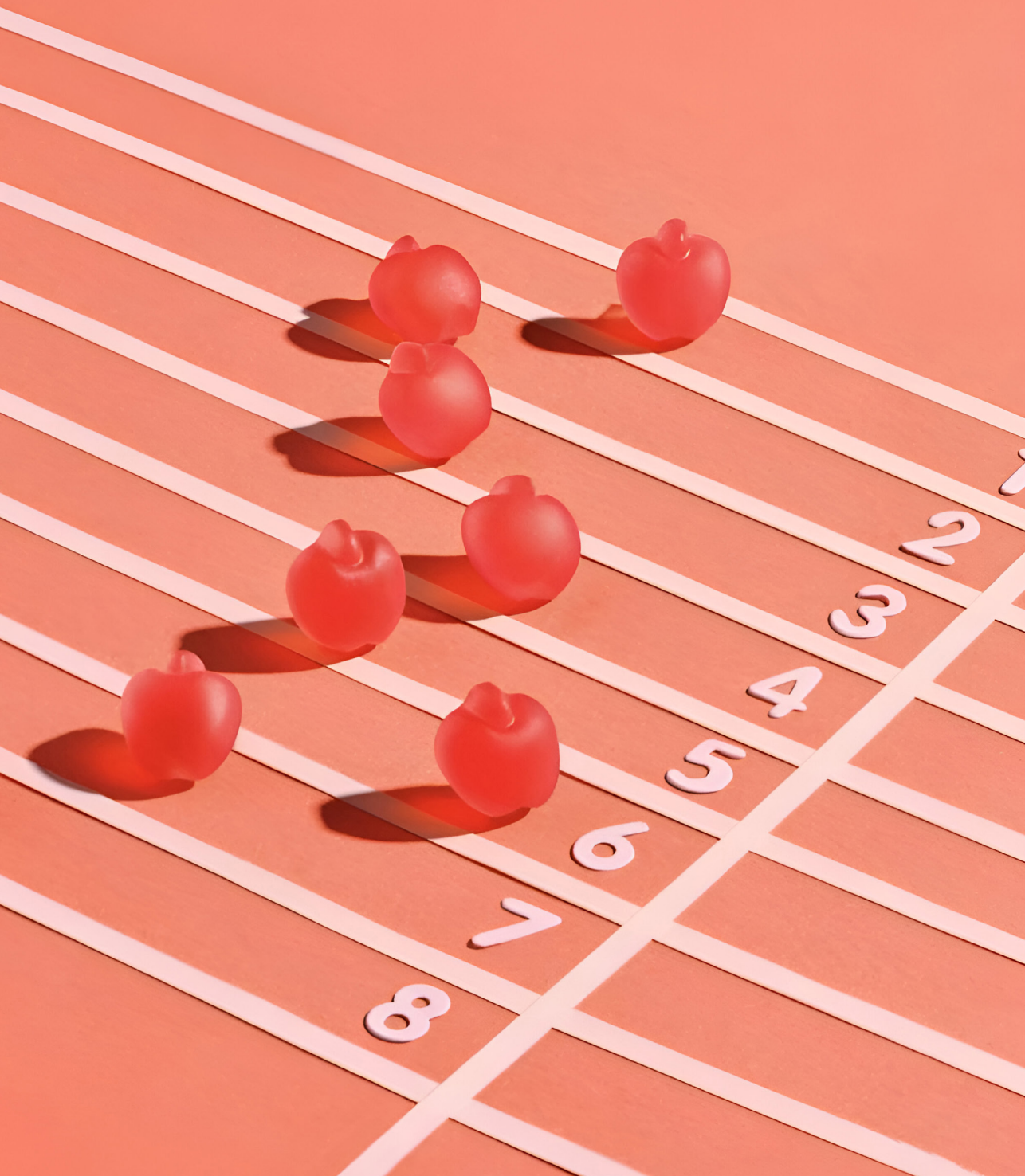
L.I. van der Wal



Targeted Interventions in Mechanically Ventilated Patients

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	Dr. M. Niesters	
	Dr. A.M.E. de Man	Universiteit van Amsterdam

If you cannot explain it simply,
you don't understand it well enough

Albert Einstein

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General introduction and thesis outline

In the Intensive Care Unit (ICU), it is imperative to provide optimal care to improve patients' pathophysiological conditions. This is particularly true for patients requiring mechanical ventilation, as they are in a fragile state and have a limited ability for physiological compensation. Through various treatments and supportive measures, clinicians aim to support the patient in order to improve their health. The use of target ranges during these treatments may offer helpful guidance, helping clinicians to provide the intervention in the most effective way and reduce the risk of complications by staying within specific target ranges. However, finding optimal target ranges for each therapy can be a complex task, since different pathologies, different severeness of pathologies, and use of target ranges in different individuals can all affect what the best target range might be.

In this thesis we aimed to enhance the use of targeted interventions in mechanically ventilated ICU patients in three key areas, namely, oxygenation, anticoagulant treatment, and pain management.

OXYGEN

Oxygen has played an important role in acute care settings for over hundreds of years and has proven to be a lifesaver for critically ill patients at risk for hypoxemia (1). A hypoxic condition, characterized by low levels of oxygen in the blood, can lead to severe tissue damage, organ failure, and even death if not timely assessed. Health care professionals have traditionally responded to this risk by administering supplemental oxygen, at times even aiming for supranormal arterial oxygen levels (2, 3). While this approach has been effective in treating hypoxemic patients, the growing recognition of the potential deleterious effects of oxygen has caused a shift in practice. Adverse outcomes of hyperoxia can include cerebral and coronary vasoconstriction, reduced cardiac output, and various forms of lung and central nervous system damage (4). Confronted with these uncertainties and the potential risks of both hypoxia and hyperoxia, researchers have attempted to establish an oxygen target for safe oxygen administration, however, identifying a safe range has proven to be a challenge.

The initial publication that revealed a link between elevated PaO2 levels and increased mortality rates among ICU patients was published in 2008 (5). Subsequent to this publication, a variety of observational studies were conducted. A meta-analysis aggregating these studies indicated a correlation between hyperoxia and a higher risk of mortality, although the different patient populations and the observational design of the studies necessitated a careful interpretation of these results (6). The first randomized controlled trial (RCT) specifically examining oxygenation strategies in the

ICU was published in 2016, and showed a higher mortality for the higher oxygenation group, seemingly confirming the results found in previous observational studies (7). In 2020, however, a contradictory study was published, demonstrating a higher 90-day mortality in the lower oxygenation group (8). Four RCTs that followed, also comparing low and high oxygenation targets in the ICU, found no differences in patient outcomes (9-12). So far, analyses of both single and combined datasets have been inconclusive, potentially due to different subgroups, utilization of different targets (either SpO2 or PaO2), an absence of statistical power, or insufficient contrast between the achieved oxygenation targets of the two groups (13, 14). In order to provide an overview of the results, we systematically reviewed evidence from all most recent RCT's comparing higher and lower oxygenation strategies in mechanically ventilated ICU patients in chapter 2. In chapter 3, we describe the methodology of our multicenter RCT, the ICONIC trial, where we compare conservative and liberal oxygenation targets in ICU patients. Following this, in chapter 4, we discuss the findings of the ICONIC trial.

Achieving optimal oxygenation in mechanically ventilated patients is a complex process that can be influenced by many factors, such as, ventilator settings, lung function, and the amount of oxygen administered. Research pointing to the potential detrimental effects of oxygen therapy has predominantly relied on indirect markers of oxygen exposure, such as PaO_2 and SpO_2. While these markers are routinely used in clinical settings and hold relevance, they serve as an indirect indicator of the exposure to the potentially toxic effects of oxygen and do not provide a direct reflection of oxygen exposure. Therefore, in chapter 5, we investigate a novel parameter to measure oxygen exposure, examining the volume of oxygen administered during mechanical ventilation as a direct parameter to assess oxygen exposure.

Informed consent is a fundamental ethical principle in medical research (15). However, obtaining informed consent from patients in the ICU proves to be a challenge. Patients in the ICU are often unable to provide informed consent due to their condition and seeking consent from a representative before starting the trial is often not an option due to the time-sensitive nature of initiating trial treatment and the overwhelming impact of the critical situation (16). In the ICONIC trial, an emergency trial requiring to start the intervention within 2 hours after intubation, we used the deferred consent procedure. Despite being an effective strategy that is generally accepted by most patients, this approach continues to generate ethical debates, weighing the necessity of conducting emergency research against the potential violation of patient autonomy. In chapter 6, we explore the retrospective views of ICONIC trial participants on their enrollment prior to giving consent, evaluating how their quality of life post-ICU admission might have influenced their opinions on the consent process.

ANTICOAGULANT TREATMENT

Since its emergence in December 2019, Corona Virus Disease 2019 (COVID-19) has profoundly impacted global public health, resulting in over 750 million infections and almost 7 million deaths (17). Patients with severe progression of the disease often experience intense pulmonary inflammation, necessitating mechanical ventilation and extended ICU stays. A frequently seen complication in these patients is the development of a prothrombotic state, leading to thrombotic complications, predominantly pulmonary embolism, despite the administration of adequate thromboprophylaxis (18).

The distinct pathogenesis of coagulation activation in COVID-19 differs from that seen in disseminated intravascular coagulation (DIC) associated with sepsis, presenting a unique challenge in understanding and managing the disease. Contrary to DIC, COVID-19 patients tend to have high d-dimer levels, normal platelet counts, and coagulation tests, pointing towards a different mechanism of coagulation activation (19). Furthermore, the phenotype of COVID-19 associated pulmonary embolism (PE) appears to differ from non-COVID-19 PE, often manifesting in the peripheral lung segments and being less extensive (20).

Due to the different pathophysiology of coagulation in COVID-19 patients, question were raised whether unfractionated heparin (UFH), or anticoagulation in general, were effective in the attenuation of the procoagulant state. Therefore, we evaluated the effectiveness of UFH treatment in COVID-19 patients in chapter 7. In addition, COVID-19 patients appeared to require higher UFH doses compared to control ICU patients. To verify whether these doses were indeed higher, we compared UFH doses in COVID-19 patients and a historical ICU cohort in chapter 8, and explored factors that could potentially have influenced the UFH dose in COVID-19 patients.

PAIN MANAGEMENT

Ensuring optimal pain management is crucial for mechanically ventilated patients, as inadequate pain management can lead to a cascade of negative physiological responses, such as elevated stress hormones, hypercoagulability and immune system dysfunction (21, 22). The interaction between pain and physiological processes in mechanically ventilated patients necessitates an increased emphasis on pain management. However, assessing pain in sedated mechanically ventilated patients presents significant challenges, as they cannot self-report on their pain levels.

Pain assessment in sedated patients often relies on vital signs. In the ICU additional pain assessment tools incorporating behavioral variables are used (23). Vital signs, however, can be influenced by various physiological conditions, and while tools like the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) are considered valid and reliable, they are subjective and may vary between healthcare professionals. Therefore, there is need for more objective tools that can quantify pain in sedated patients.

In the last few years, the medical field has seen the development of various monitors that objectively measure nociception in sedated patients. Nociception refers to the neural processes involved in identifying, transforming, and transmitting signals of harmful stimuli (24). The Nociception Level (NOL) monitor, produced by Medasense Biometrics Ltd. in Ramat Gan, Israel, is one of these tools. It evaluates pain by integrating various physiological parameters, including heart rate, heart rate variability, photo-plethysmographic amplitude, and skin conductance, and their time derivates. These parameters are aggregating into a single index, ranging from 0 (no nociception) to 100 (maximal nociception) (25). The monitor has been approved for use in the operating room based on multiple studies, and showed a reduction in stress hormones, postoperative pain, and improved hemodynamics (25-32). In chapter 9 we aggregated data from two of these studies in order to verify if the use of NOL reduced pain scores in the post-anesthesia care unit (PACU).

Studies demonstrating the use of NOL within an ICU setting are limited, but have shown that NOL is capable to detect nociceptive stimuli in patients able to self-report. However, further research is needed to assess efficacy of NOL in anesthetized ICU patients. During the COVID-19 pandemic, opioid dosing in ICU patients notably increased, and sometimes tripled compared to historical ICU data (33), raising questions about whether this was due to a genuine need for higher pain relief or if clinicians aimed at a higher level of analgesia. Therefore in chapter 10, we conducted an explorative observational study aiming to evaluate opioid dosing in sedated COVID-19 and control patients, by comparing subjective (CPOT, BPS) and objective measure (NOL) to assess pain in both groups.

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PART I

OXYGEN

Higher versus lower oxygenation strategies in the general intensive care unit population:

a systematic review, meta-analysis and meta-regression of randomized controlled trials

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ABSTRACT

Purpose

Oxygen therapy is vital in adult intensive care unit (ICU) patients, but it is indistinct whether higher or lower oxygen targets are favorable. Our aim was to update the findings of randomized controlled trials (RTCs) comparing higher and lower oxygen strategies.

Materials and Methods

MEDLINE, EMBASE, and Web of Science were searched. RCTs comparing higher (liberal, hyperoxia) and lower (conservative, normoxia) oxygen in adult mechanically ventilated ICU patients were included. The main outcome was 90-day mortality; other outcomes include serious adverse events (SAE), support free days and length of stay (LOS).

Results

No significant difference was observed for 90-day mortality. A lower incidence was found for SAEs, favoring lower oxygenation (OR, 0.86; 95%CI, 0.77-0.96; I^2 13%). No differences were observed in either support free days at day 28 or ICU and hospital LOS.

Conclusions

No difference was found for 90-day mortality, support free days and ICU and hospital LOS. However, a lower incidence of SAEs was found for lower oxygenation. These findings may have clinical implications for practice guidelines, yet it remains of paramount importance to continue conducting clinical trials, comparing groups with a clinically relevant contrast and focusing on the impact of important side effects.

INTRODUCTION

Oxygen therapy has been successfully used in the acute care setting for over a century (1). Most critically ill patients are at risk for hypoxemia which may cause tissue damage, organ failure or even death. Owing to these risks, the professional norm among health care specialists is to attentively avoid and sometimes even overcompensate hypoxemic events by liberally administering oxygen or deliberately inducing supranormal arterial oxygen levels (2, 3). Oxygen has proven to be very effective in the treatment of hypoxemic patients, but may not be beneficial in all patients. The deleterious properties of oxygen are increasingly acknowledged. Harmful effects can include cerebral and coronary vasoconstriction, reduction of cardiac output, absorption atelectasis, acute lung injury and central nervous system toxicity (4). In addition, studies repeatedly showed a negative correlation between hyperoxia and patient centered outcomes (5-7). Accordingly, newer guidelines on oxygen therapy generally recommend a more conservative approach (8). However, not all cautions with regards to hyperoxia have been conclusively justified as observational studies and randomized controlled trials (RCTs) comparing higher versus lower oxygen targets show heterogeneous results.

Few systematic reviews have been conducted in order to provide guidance for administering oxygen in a safe and efficient manner to intensive care unit (ICU) patients. The results were unequivocal (5, 9-12), but new studies have recently been published (13, 14). Furthermore, important data concerning vital secondary outcomes, such as ischemic events and shock, have not been aggregated in detail before. By systematically combining all available evidence from RCTs comparing higher and lower targeted oxygen strategies in mechanically ventilated patients, we aimed to provide conclusive insights into favorable oxygen therapy.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (supplemental table 1) (15). The protocol of this study was registered on PROSPERO (CRD42021286372). Inclusion criteria were as follows: RCTs comparing higher (liberal) and lower (conservative) oxygen therapy strategies in the general adult ICU population of which the majority is mechanically ventilated.

Information sources and search

After consulting a librarian, electronic databases of Medline (1962-2021), EMBASE (1970-2021) and Web of Science (1970-2021) were searched. This search was supplemented

by manually screening reference lists of included studies and other relevant articles. Full search terms and search strategies can be found in supplemental file 1. Main MeSH headings and key words were "oxygen inhalation therapy", "hyperoxia", "hypoxia", "oxygen" and "respiration, artificial". The literature search was last updated August 9th 2022.

Study selection and Data collection process

Two authors (L.I.W, H.J.F.H) independently and in pairs screened articles on title and abstract. Reports considered potential for inclusion were screened in full text. Differences in this process were resolved by consensus. When no consensus was reached, a third co-author would resolve the issue. No language or timeline restrictions were applied. Studies were excluded using the following criteria: patients younger than 18 years, animal studies, extracorporeal life support and perioperative settings. Studies that solely focused on one specific patient group (e.g. myocardial or cerebral infarction) were excluded to improve the comparability of the study population. Duplicates were removed using the method of Bramer et al (9).

Data analysis and outcomes

Data abstraction was done by two content area experts (L.I.W., H.J.F.H) using an a priori created electronical standardized data abstraction sheet. Extractions were reviewed by two review authors independently. Disagreements were resolved by consensus. If no consensus could be reached, a third co-author would resolve the issue. The main outcome of interest was mortality at day 90. Mortality at day 28, day 180 and ICU and hospital mortality were also analyzed. Other outcomes were adverse events, support-free days at day 28 and length of stay (LOS).

Corresponding authors were contacted to clarify important missing data, for further trial details and when outcome data was not available in mean and standard deviation (SD). When no mean and SD could be provided the data was omitted from the analysis. The Grading Of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to grade the certainty of evidence (supplemental table 3) (16). Heterogeneity between studies and between subgroups was assessed by visual inspection of the forest plots by checking the point estimates and the confidence interval (CI) overlap. Additionally, Chi^2 and I^2 statistics were used and presented as p-values and percentages. A low p-value ($p<0.1$) was considered as evidence of heterogeneity of intervention effects. An I^2 of 0 to 40% was considered not important, 30 to 60% was considered moderate, 50 to 90% was considered substantial and 75 to 100% considerable (17). Interventions effects were assessed using a random effects model.

Odd ratios (ORs) with 95% CIs were calculated for dichotomous data, mean difference with CIs for continuous outcomes. Dichotomous data was analyzed using a Mantel and Haenszel (M-H) model; continuous data using an inverse variance model. Pooled estimates are displayed in forest plots. The effects of hyperoxia by achieved oxygenation in the randomized groups were analyzed using a meta-regression framework (16). For this meta-regression analyses we calculated a combined score in order to assess the effects of the achieved difference in PaO_2 (contrast) between the oxygenation groups in combination with the degree of hyperoxia that was achieved in the higher oxygenation group. Hence, the combined score was calculated as: between group difference in achieved PaO_2 plus the achieved PaO_2 in the highest group. The ORs were based on the 90-day mortality. Our hypothesis was that a higher between-group difference and a more severe hyperoxic target in the higher group, increase the effect size for 90-day mortality. All analyses were conducted using RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R version 4.0.3. (R Foundation for Statistical Computing, Vienna, Austria) with RStudio (RStudio, Boston, MA).

In order to assess bias, the Cochrane risk of bias tool for randomized trials was used (18). Reporting bias was displayed in a funnel plot, using standard errors of the intervention effect estimate. Asymmetry was tested by visual inspection.

RESULTS

Study selection and study characteristics

Figure 1 depicts the study flowchart. Our search strategy resulted in 1551 studies considered for inclusion after deleting duplicates. In total, 68 full-text articles were assessed for eligibility after title and abstract screening. The most important exclusion reasons were study types other than RCTs, post hoc analyses or lack of comparison between higher and lower oxygenation. For the final analysis nine studies with 5807 patients were included (table 1) (13, 14, 19-25). Data collection took place between 2010 and 2020; study reports were published between 2015 and 2021. All included studies were RCTs comparing a higher versus a lower oxygenation in mechanically ventilated patients focusing on the general ICU population. Either PaO_2, SpO_2, FiO_2 or a combination of these parameters were used to pursue oxygenation targets. The duration of the interventions ranged from 24 hours to 90 days.

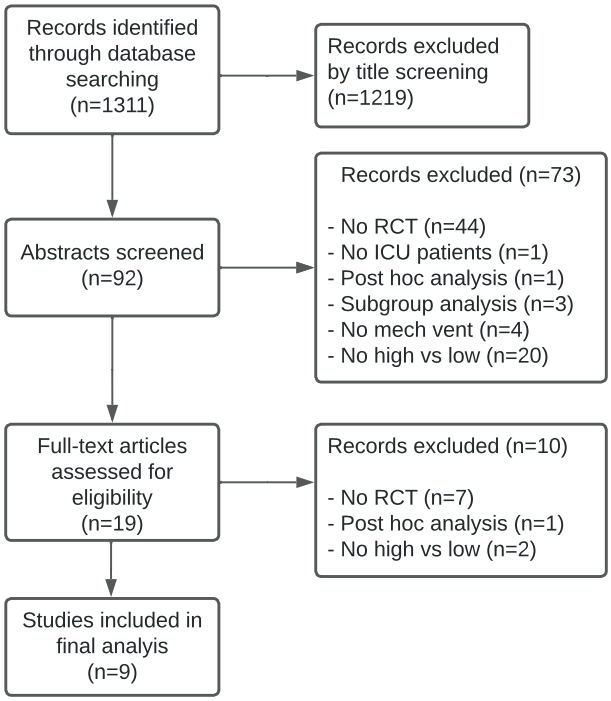

Figure 1. Flowchart of study selection

Risk of bias in studies

Overall, the risk of bias was moderate to low, except for blinding and early stopping bias (supplemental table 2, supplemental figure 1,2). Due to the design of the trials, it was essentially unfeasible to blind clinicians for the assigned treatment group. If clinicians were not blinded but outcome assessors were, the trial was graded low risk of bias for blinding. Visual inspection of the funnel plot suggested no funnel plot asymmetry (supplemental figures 3, 4).

Main outcome

Mortality at day 28, day 90, day 180, in the ICU and in the hospital were assessed separately (figure 2). No effect of different oxygenation strategies was found for mortality at day 90 (OR, 1.01; 95% CI, 0.85-1.20; I^2, 38%). The certainty of evidence, using the GRADE approach, was rated low (supplemental table 3). Also no difference was seen at day 28 (OR, 0.94; 95% CI, 0.63-1.40; I^2, 43%; very low certainty), day 180 (OR, 1.05; 95% CI, 0.81-1.38; low certainty), ICU mortality (OR, 0.90; 95% CI, 0.63-1.28; I^2, 43%; low certainty) or hospital mortality (OR, 0.86; 95% CI, 0.54-1.38; I^2, 50%; very low certainty).

Table 1. Characteristics of included studies

Study	Journal	Year	Country	Sample size	Population	Intervention		Primary endpoint	Duration intervention
						Lower oxygenation	Higher oxygenation		
Asfar (20)	Lancet	2017	France	442	Sepsis	SpO_2 88%-95%	FiO_2 1.0	28 day mortality	24h
Barrot (21)	NEJM	2020	France	205	ARDS	PaO_2 55-70 mm Hg or SpO_2 88-92%	PaO_2 90-105 mm Hg or SpO_2 at least 96%	28 day mortality	7 days
Gelissen (14)	JAMA	2021	Netherlands	400	Total ICU population	PaO_2 8-12 kPa	PaO_2 14-18 kPa	Cumulative daily delta SOFA score from day 1 to day 14	14 days or ICU discharge
Girardis (22)	JAMA	2016	Italy	480	Total ICU population	PaO_2 70-100 mm Hg or SpO_2 94-98%	PaO_2 up to 150 mm Hg or SpO_2 97-100%	ICU mortality	ICU discharge
Mackle (19)	NEJM	2019	New Zealand, Australia	1000	Total ICU population	SpO_2 91-97%, FiO_2 as low as possible	≥ 91% without upper limit	Number of ventilator free days	ICU discharge or day 28
Martin (25)	JICS	2021	England	34	Total ICU population	SpO_2 88-92%	SpO_2 ≥ 96%	Feasibility	Until extubation, tracheostomy, transfer or death
Panwar (23)	AJRCCM	2015	Australia, New Zealand, France	104	Total ICU population	SpO_2 of 88-92%	SpO_2 ≥ 96%	Mean AUC for SpO_2, SaO_2, PaO_2 and FiO_2. % spent off target	Entire duration of mechanical ventilation
Schjørring (13)	NEJM	2021	Denmark, Switzerland, Finland, The Netherlands, Norway, the United Kingdom, Iceland	2928	Total ICU population	PaO_2 60 mm Hg	PaO_2 90 mm Hg	90 day mortality	ICU discharge or day 90
Yang (24)	J Thorac Dis	2019	China	214	Total ICU population	SpO_2 of 90-95%	SpO_2 of 96-100%	28 day mortality	14 days or ICU discharge

Study or Subgroup	Lower targets Events	Total	Higher targets Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Day 28						
Asfar Lancet 2017	77	217	93	217	44.6%	0.73 [0.50, 1.08]
Barrot NEJM 2020	34	99	27	102	27.7%	1.45 [0.79, 2.66]
Yang JTD 2019	26	100	32	114	27.7%	0.90 [0.49, 1.65]
Subtotal (95% CI)		**416**		**433**	**100.0%**	**0.94 [0.63, 1.40]**
Total events	137		152			
Heterogeneity: Tau² = 0.05; Chi² = 3.49, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 0.31 (P = 0.75)						
1.1.2 Day 90						
Asfar Lancet 2017	90	217	104	217	13.3%	0.77 [0.53, 1.13]
Barrot NEJM 2020	44	99	31	102	7.2%	1.83 [1.03, 3.27]
Gelissen JAMA 2021	72	205	67	205	12.1%	1.12 [0.74, 1.68]
Girardis JAMA 2016	58	235	80	243	12.5%	0.67 [0.45, 1.00]
Mackle NEJM 2019	166	479	156	480	19.7%	1.10 [0.84, 1.44]
Martin JICS 2021	8	17	6	17	1.5%	1.63 [0.41, 6.46]
Panwar AJRCCM 2015	21	52	19	51	4.2%	1.14 [0.52, 2.52]
Schjørring NEJM 2021	618	1441	613	1447	29.5%	1.02 [0.88, 1.18]
Subtotal (95% CI)		**2745**		**2762**	**100.0%**	**1.01 [0.85, 1.20]**
Total events	1077		1076			
Heterogeneity: Tau² = 0.02; Chi² = 11.36, df = 7 (P = 0.12); I² = 38%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.1.3 Day 180						
Mackle NEJM 2019	170	476	164	475	100.0%	1.05 [0.81, 1.38]
Subtotal (95% CI)		**476**		**475**	**100.0%**	**1.05 [0.81, 1.38]**
Total events	170		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
1.1.4 ICU						
Barrot NEJM 2020	36	99	27	102	19.0%	1.59 [0.87, 2.90]
Gelissen JAMA 2021	50	205	49	195	24.7%	0.96 [0.61, 1.51]
Girardis JAMA 2016	25	216	44	218	21.5%	0.52 [0.30, 0.88]
Martin JICS 2021	6	17	5	17	5.4%	1.31 [0.31, 5.53]
Panwar AJRCCM 2015	13	52	12	51	11.4%	1.08 [0.44, 2.67]
Yang JTD 2019	21	100	32	114	18.0%	0.68 [0.36, 1.28]
Subtotal (95% CI)		**689**		**697**	**100.0%**	**0.90 [0.63, 1.28]**
Total events	151		169			
Heterogeneity: Tau² = 0.08; Chi² = 8.80, df = 5 (P = 0.12); I² = 43%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.1.5 Hospital						
Gelissen JAMA 2021	66	205	61	195	45.2%	1.04 [0.68, 1.59]
Girardis JAMA 2016	52	216	74	218	45.3%	0.62 [0.41, 0.94]
Martin JICS 2021	7	17	5	17	9.5%	1.68 [0.41, 6.96]
Subtotal (95% CI)		**438**		**430**	**100.0%**	**0.86 [0.54, 1.38]**
Total events	125		140			
Heterogeneity: Tau² = 0.08; Chi² = 3.99, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 0.63 (P = 0.53)						

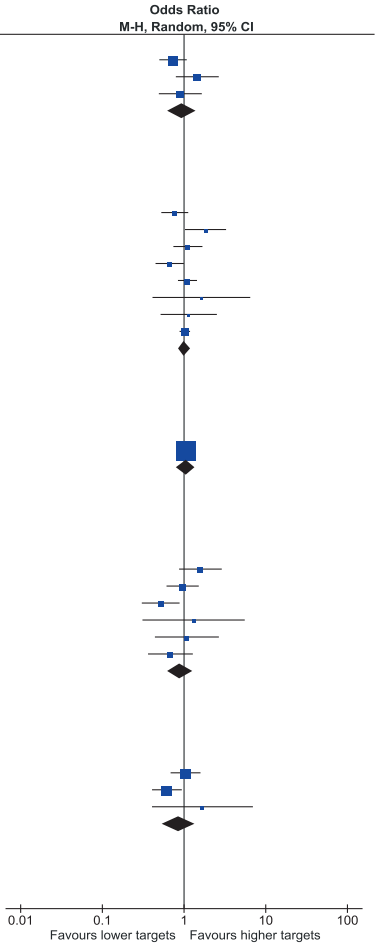

Figure 2. Forest plot mortality

Other outcomes

Adverse events were categorized in the following subgroups: myocardial ischemia, intestinal ischemia, ischemic stroke, respiratory infection, systemic infection, shock, organ failure, renal replacement therapy and arrythmias (figure 3). Regarding the adverse infectious events, respiratory infection (OR, 0.88; 95% CI, 0.63 -1.22; I^2, 0%) showed no significant difference between groups, although lower targets were favorable in cases of systemic infection (OR, 0.51; 95% CI, 0.29-0.88; I^2, 0%). The evidence was graded very low for both outcomes. For ischemia, including myocardial ischemia (OR, 1.29; 95% CI, 0.61-2.73; I^2, 14%; very low certainty), intestinal ischemia (OR, 1.12; 95% CI, 0.43-2.93; I^2, 47%; very low certainty) and ischemic stroke (OR, 0.94; 95% CI, 0.44-2.04; I^2, 12%; very low certainty), an uncertain effect was found considering the wide confidence intervals. Overall, the incidence of adverse events showed a significant OR of 0.86 (95% CI, 0.77-0.96; I^2, 13%) in favor of lower targets. The certainty of evidence was graded very low.

Support-free days were analyzed as ventilator- and vasopressor-free days at day 28 (figure 4). In general, the support-free days did not show a significant difference (mean difference (MD), 0.19; 95% CI, -0.40-0.78; I^2, 24%). The evidence was graded very low.

The analysis of LOS was categorized according to two subgroups (figure 5): hospital LOS (MD, -0.19; 95% CI, -8.43-8.04; I^2, 42%; very low certainty) and ICU LOS (MD, -0.64; 95% CI, -1.75-0.47; I^2, 0%; very low certainty). No significant differences were observed in the different subgroups.

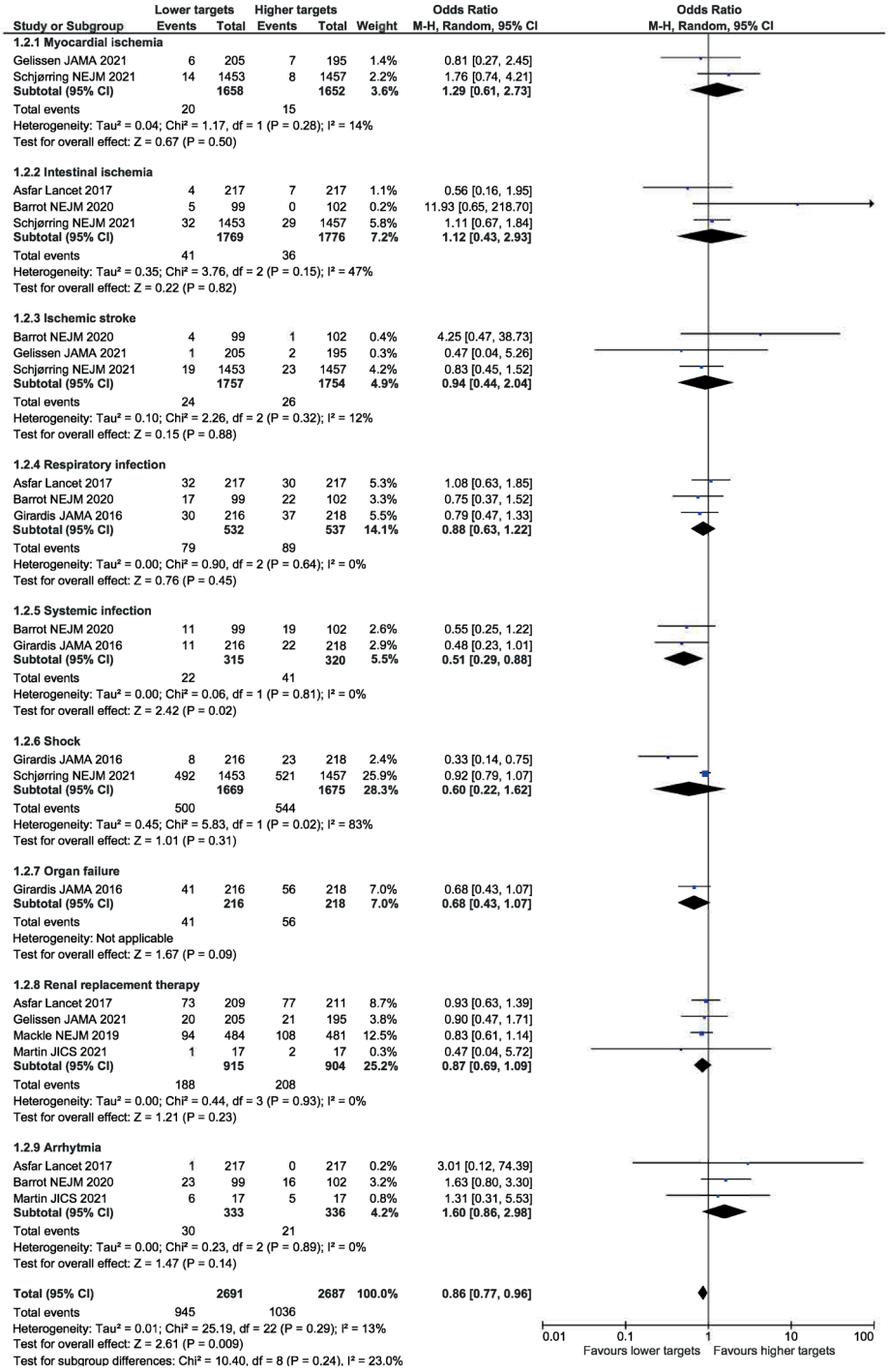

Figure 3. Forest plot serious adverse events. Patients from each study are counted once in the test for overall effect.

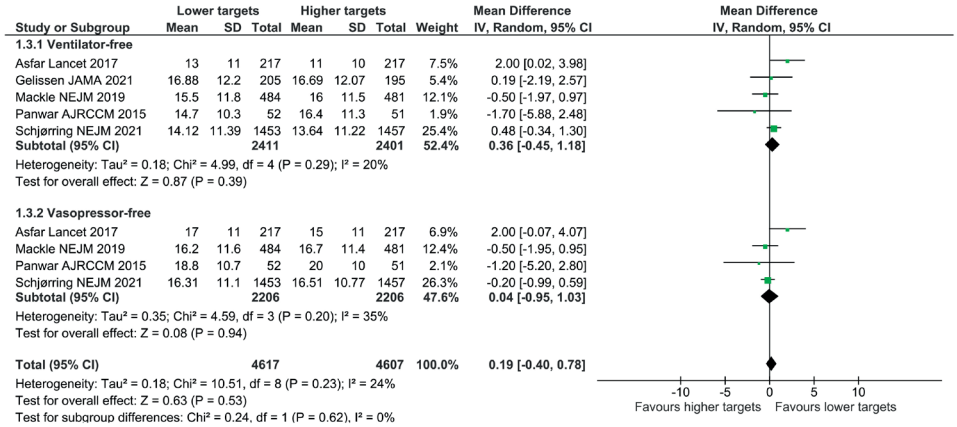

Figure 4. Forest plot support free days at day 28

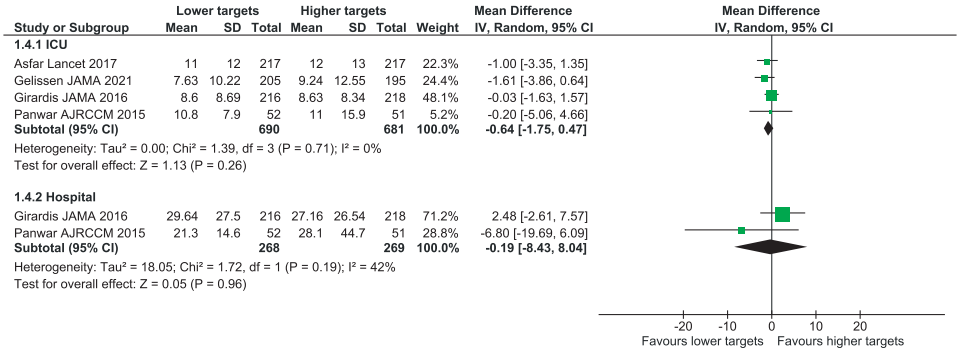

Figure 5. Forest plot hospital and ICU length of stay.

Meta-regression

All included studies in this meta-analysis were assessed using the GRADE approach (16). In most cases, the certainty of evidence was very low to low (supplemental table 3). Due to a variety in the chosen targets of the studies, we performed a meta-regression analysis that compared the odds for lower oxygenation on 90-day mortality for different achieved oxygenation targets. The regression was performed for both the achieved high and low oxygenation groups (supplemental Figures 5, 6) and for the combined score (Figure 6). The combined score is calculated by combining the achieved difference between the high and low oxygenation targets and the achieved higher oxygenation targets (Table 4, supplemental digital content). Figure 6 shows that this combined score is in the same order of magnitude for the majority of the trials (13, 14, 19, 21-23, 25) and the OR of mortality in the lower group approximates 1. One

trial (20) showed a combined score of 260 mm Hg in combination with a lower OR for mortality in the lower group. Taken together, the risk of mortality after 90 days in the lower group may be dependent on the combined score, i.e. the combination of the difference of achieved oxygenation and the severity of achieved hyperoxia in the higher group. However, the beta associated with this meta-regression analysis did not reach statistical significance.

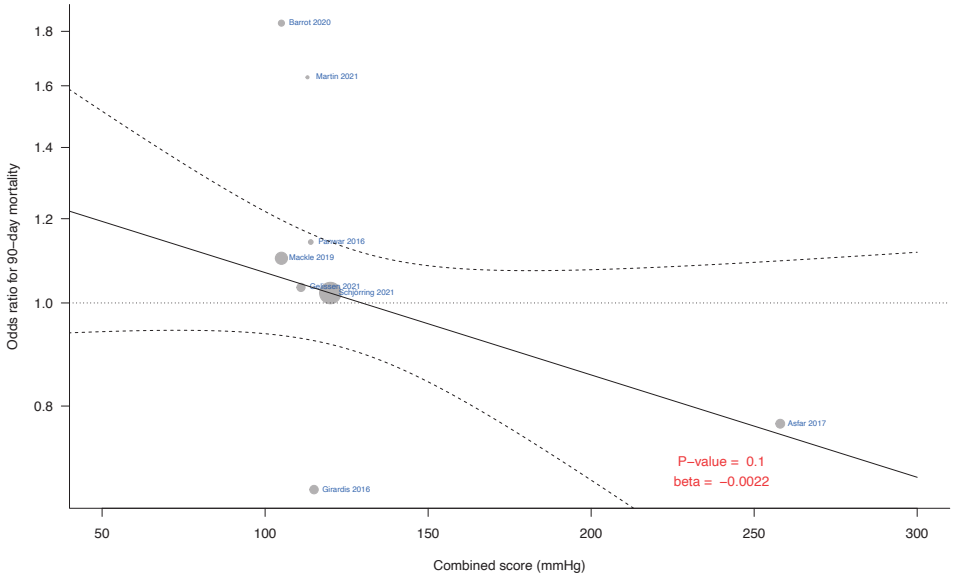

Figure 6. Meta regression analysis for the crude effects of lower oxygenation on 90-day mortality by combined score. Scatters indicate odds ratios for 90-day mortality for lower oxygenation on a logarithmic scale, according to the combined score in the indicated studies. The combined score is calculated as the difference between achieved oxygenation (PaO_2) of lower and higher group plus the achieved oxygenation (PaO_2) of the higher group. The point sizes are inversely proportional to the standard error of the mean of the individual studies (i.e., larger/more precise studies are shown as larger *circles*). The predicted effect sizes are modeled in a linear mixed-effects model with corresponding 95% CI boundaries and a β-coefficient with *p* value for the meta-regression line. An OR <1 is beneficial to the lower oxygenation group.

DISCUSSION

This systematic review and meta-analysis showed no difference in mortality at day 90 when aggregating data from RCTs comparing lower and higher oxygenation targets. For secondary outcomes, a significant effect favoring lower oxygenation targets was identified with regards to serious adverse events.

The following study strengths should be considered. First, this meta-analysis is the most recent update on RCT's, including the four most recently published high impact trials (13, 14, 19, 21), a unique novel meta-regression analysis and a meta-analysis on important secondary outcomes (e.g. serious adverse events), unlike other recently published data aggregations on this subject (9-12). Second, in order to ensure comprehensiveness of the data, corresponding authors were contacted for additional data. Also, established guidelines, such as the PRISMA and GRADE approach, were used to ensure the quality of our methodology and certainty of evidence, of which especially the GRADE approach is lacking in earlier published meta-analyses (10-12).

A key limitation is that all trials on oxygenation used varying thresholds for PaO_2 targets and study durations. For example, a patient randomised in the high oxygenation group can be assigned to a target of 90-105 mmHg for 7 days, whereas a patient included in the higher group of another trial may follow a target of 105-135 mmHg for 14 days (14, 21). Moreover, some trials used SpO_2 targets rather than PaO_2 targets and one study managed liberal oxygenation by applying an FiO_2 of 1.0 (irrespective of SpO_2) during the first 24 hours while not using different SpO_2 or PaO_2 targets afterwards. A PaO_2 of 90 mmHg can correspond with a SpO_2 of 100% but also 93%, partially depending on the underlying disease. Therefore, a higher PaO_2 cannot be consistently translated into a fixed SpO_2 (26). As thresholds differ, a patient could be categorized in the higher oxygenation group in one trial, whereas this could be the lower oxygenation group in the other trial. Moreover, in some studies chosen oxygenation targets can overlap (19, 22), suggesting there may not be a true comparison between a 'high' and a 'low' group. In order to address this issue of contrast but also of heterogeneity in targets we implemented a meta-regression framework for both the *achieved* high and low groups (supplemental figures 5&6) and for the combined score (figure 6), thereby providing a useful visual understanding of targets and its impact on the outcome effects. We also re-analyzed the data excluding the Hyper2S trial since the higher group (normobaric hyperoxia) was considered the intervention group in this study, whereas conservative oxygenation was the intervention group in the other studies (20). Also, the chosen targets differ from the other included trials. In this sensitivity analysis, the results were virtually unchanged (data not shown).

Another limitation is the heterogeneity of the ICU population in combination with the heterogenous treatment effect that can be expected from oxygen therapy in certain subgroups. For example, in vasodilatory septic shock, arterial hyperoxia may be beneficial due to antibacterial properties and the counteraction of vasodilation (27, 28), while in ischemia and reperfusion injuries, such as myocardial infarction, hyperoxia may have detrimental effects (29). Recent reviews explored the optimal oxygen targets per subgroup by underlying disease (30, 31) and no optimal oxygen target per subgroup

could be identified, though it seems justifiable to avoid both hypoxemia and excess hyperoxemia. Hence, the key question remains whether we should settle for a one-strategy-that-fits all (optimal) oxygen therapy approach, or whether optimal oxygen strategies can be applied per subgroup.

None of the included trials were blinded, which can be considered a limitation since the latest literature could have imposed bias towards the beneficial effect of lower oxygenation targets (32, 33). Therefore, clinicians may be more prone to adhere to the lower targets, making it more difficult to create contrast in oxygenation between two different groups. However, owing to the design of the trial, it was essentially unfeasible to blind clinicians for the assigned treatment group. Also, our main outcome mortality is not subjective and probably unlikely to be influenced by blinding. Though, the 95% CI's around the mortality treatment effect estimates remain wide, therefore we cannot exclude the possibility of important increases (or decreases) in mortality attributable to the oxygen regimens evaluated.

Our findings are in line with recent systematic reviews showing that different oxygenation strategies did not have a significant impact on mortality (9-12). However, the findings are in contrast to previously published reviews (5, 34, 35), that support a conservative oxygen strategy. A simple explanation for these contradictions might be that patients either simply do not benefit from a lower oxygenation strategy or that the achieved lower and higher PaO_2 in both groups lack sufficient contrast to be able to detect a difference. In the included trials it has proven to be difficult to accomplish a clinical contrast between the intervention and the control group. The majority of the trials that reported on the achieved oxygenation show a difference of 10 to 20 mmHg (14, 19, 21-23). Our sensitivity analysis using a meta-regression framework (figure 6, supplemental figures 5, 6) shows that trials with a smaller achieved difference (10-20 mm Hg) (14, 19, 21-23) and studies with a larger achieved difference (25-70 mm Hg) (13, 20, 25) both show heterogenous results. It should be noted that achieved differences are in the same order of magnitude for most studies (10-30 mm Hg) despite one outlier (70 mm Hg). When a large difference is achieved there is a sign that patients may benefit from a lower oxygenation target. Though, due to lack of significant results, this may also be originated by chance. Furthermore, when specifically targeting a very high or low target a significant clinical difference may be achieved but neither the intervention nor the control group may then represent usual care. Accordingly, the present study may demonstrate that a broad range of less extreme achieved oxygenation falls within a fairly safe category.

The different results amongst included trials can also be explained by secondary factors such as early stopping bias, subgroup analysis and not choosing a truly hyperoxic

target. Taking all included trials that reported on achieved targets together, an average higher oxygenation around 110 mm Hg was achieved, with an individual maximum of 185 mm Hg (20). The hypothesis that 110 mm Hg is not a truly hyperoxic target is supported by earlier literature that showed a significant increase in mortality in the hyperoxic group, where hyperoxia was defined as PaO_2 > 300 mmHg (29). Our meta-regression analysis (figure 5) shows that when a hyperoxic target of 185 mm Hg is achieved (20), patients may have a lower risk of mortality in the lower oxygenation group. In line, these results are not significant and the more severe the higher target, the less it represents usual care and the higher the chances of mortality.

Three recent meta-analyses reported on serious adverse events (10-12). However, other study designs than RCTs were included (12), no forest plots or only a small selection of serious adverse events were included (10-12) or important high impact trials were missing (10-12). Our updated meta-analysis including only RCTs confirms that serious adverse events are more likely to occur in the higher oxygenation groups. As in previous studies, serious adverse events should be critically reviewed to evaluate whether the event is consistent with the natural history of the critical illness (36). If a large difference is observed, similar to the difference found in our meta-analysis, it might be attributable to the different interventions. As serious adverse events can highly impair patient health and quality of life, the potential negative impact of higher targets may also be a compelling argument to adhere to a lower oxygenation strategy. However, the results on adverse events are dominated by one study (22) and a low number of studies reported on the individual adverse events groups. To add, the evidence was graded low to very low. Even though this finding may be an important signal for clinical practice guidelines, more robust data is needed for a compelling conclusion.

CONCLUSION

In the present meta-analysis comparing higher and lower oxygenation targets we found no difference in 90-day mortality for the adult ICU population. Importantly, we did find a significant difference in serious adverse events favoring lower oxygenation targets. Differences in methodology, oxygenation targets and primary and secondary endpoints may hamper a comparison of studies. Robust future clinical trials remain of paramount importance, ideally adequately separating the intervention groups based on achieved oxygenation and focusing on the impact of important side effects.

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ICONIC study – conservative versus conventional oxygenation targets in intensive care patients:

study protocol for a randomized clinical trial

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ABSTRACT

Background

Oxygen therapy is a widely used intervention in acutely ill patients in the Intensive Care Unit (ICU). It is established that not only hypoxia, but also prolonged hyperoxia is associated with poor patient centered outcomes. Nevertheless, a fundamental knowledge gap remains regarding optimal oxygenation for critically ill patients. In this randomized clinical trial we aim to compare ventilation that uses conservative oxygenation targets with ventilation that uses conventional oxygen targets with respect to mortality in ICU patients.

Methods

The "Conservative versus CONventional oxygenation targets in Intensive Care patients" trial (ICONIC) is an investigator–initiated, international, multicenter, randomized clinical two–arm trial in ventilated adult ICU patients. The ICONIC trial will run in multiple ICUs in The Netherlands and Italy to enroll 1512 ventilated patients. ICU patients with an expected mechanical ventilation time of more than 24 hours are randomized to a ventilation strategy that uses conservative (PaO_2 55-80 mmHg (7.3-10.7 kPa)) or conventional (PaO_2 110-150 mmHg (14.7-20 kPa)) oxygenation targets. The primary endpoint is 28-day mortality. Secondary endpoints are ventilator free days at day 28, ICU mortality, in-hospital mortality, 90-day mortality, ICU- and hospital length of stay, ischemic events, quality of life and patient opinion of research and consent in the emergency setting.

Discussion

The ICONIC trial is expected to provide evidence on the effects of conservative versus conventional oxygenation targets in the ICU population. This study may guide targeted oxygen therapy in the future.

Trial registration

Trialregister.nl, under: NTR7376. Registered on 20th of July, 2018.

Introduction

INTRODUCTION

Background and rationale

Arterial oxygenation may be influenced by different factors, including lung function, lung mechanics, ventilator settings, hemodynamics and the amount of oxygen administered. The risks of hypoxia are well-established, prolonged exposure to severe hyperoxia has also been shown to induce lung injury (1-4). In two meta-analyses arterial hyperoxia and liberal use of oxygen therapy were associated with hospital mortality and poor functional outcome in various subsets of critically ill patients (5, 6). However, the retrospective nature of the meta-analyzed studies hamper general acceptance of lower target ranges and supraphysiological oxygenation is still frequently pursued in order to avoid hypoxemia. In a Dutch study the nadir for unadjusted mortality was retrospectively determined at oxygenation levels of 110-150 mmHg (7), but pilot data suggest that more conservative oxygenation targets may also be safe and even improve clinical outcomes (8). Accordingly, a fundamental knowledge gap regarding optimal oxygenation has been recognized in international literature (9-15).

In a randomized clinical trial on optimal oxygenation in ICU patients that was published in 2016, improved survival was demonstrated in patients who received oxygen according to the conservative strategy (PaO_2 targeting 70-100 mmHg or arterial oxyhemoglobin saturation (SpO_2) targeting 94-98%) in comparison to a conventional control group (PaO_2 up to 150 mmHg or SpO_2 targeting 97-100%) (16). This trial was the first randomized clinical study to demonstrate a potential harm of liberal oxygen administration, which earlier had been suggested by observational and preclinical studies (17-21). However, after this first RCT, three comparable trials have been completed that did not support the previous findings that favored lower oxygenation targets (22-24). Thus uncertainty still exists on optimal oxygenation targets in ICU patients.

Objectives

As a replication study, we have set up a multicenter trial comparing conservative and conventional oxygenation targets in ICU patients, to confirm findings from a previous study that showed improved survival in ICU patients treated with lower oxygenation targets (16). To that end we applied similar in- and exclusion criteria and similar oxygenation targets.

Trial design

The ICONIC study is an investigator–initiated, multicenter, international, open-label, parallel, 1:1 randomized clinical two–arm equivalence trial in mechanically ventilated ICU patients.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

Patients are recruited from ICUs` from participating hospitals, academic and non-academic, in Europe. The participating hospitals are as follows:

- Leiden University Medical Centre, Leiden, The Netherlands
- Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands
- Martini Hospital, Groningen, The Netherlands
- Amsterdam University Medical Centre, Amsterdam, The Netherlands
- Ikazia Hospital, Rotterdam, The Netherlands
- Reinier de Graaf Gasthuis, Delft, The Netherlands
- Medisch spectrum Twente, Enschede, The Netherlands
- Diakonessenhuis, Utrecht, The Netherlands
- San Martino Hospital, Genoa, Italy

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years
- Admission to an ICU participating in this study
- Need for intubation and mechanical ventilation
- Expected mechanical ventilation time of 24 hours or longer
- Inclusion within 2 hours after start of invasive ventilation in the ICU or if previously intubated and ventilated within 2 hours after admission to the ICU

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Readmission to the ICU within the same hospital admission
- Prior ICONIC study inclusion
- Invasive ventilation longer than 12 hours directly preceding admission
- Decision to withhold life sustaining treatment at the time of inclusion
- Acute respiratory distress syndrome (ARDS) with a PaO2/FiO2 ratio less than 150 mmHg
- Acute decompensation of chronic obstructive pulmonary disease (COPD) and chronic hypoxemia
- Use of home oxygen therapy
- Severe not rapidly reversible low cardiac output shock (for example: cardiac

index ≤2 L/min/m2)
- Documented severe pulmonary hypertension
- Veno-Arterial Extra Corporeal Membrane Oxygenation (VA-ECMO)
- Underlying disease indication for hyperoxygenation (for example: carbon monoxide intoxication, decompression sickness, gas embolism)
- Severe anemia (Hemoglobin< 4.0 mmol/l) that is not rapidly reversible (e.g. if blood transfusions are not possible or not allowed for religious reasons)
- Uncontrollable intracranial hypertension
- Participation in other interventional trials which could influence ICONIC study intervention and/or endpoints
- Suspected or confirmed pregnancy

Who will take informed consent?
Informed consent will be obtained according to local legal regulations. Informed consent will be obtained, if possible, prior to start of intervention. However, due to the emergency setting of this trial, this will occur in the minority of subjects. For the majority of subjects inclusion will take place in an emergency setting when the patient is incapacitated and deferred consent from a proxy will be obtained as soon as possible. Information about the trial will be given by the treating physician to the proxy. After deferred proxy consent is obtained decisional capacity of the participant will be assessed frequently and when regained during the ICU stay deferred subject consent must be obtained.

If the patient dies before informed consent or deferred (proxy or subject) consent is obtained the study data will be used. The Dutch central committee of research in humans (Centrale Commissie Mensgeboden Onderzoek (CCMO)) states that legal representation of a patient ends after death and that therefore the obligation to obtain signed consent no longer applies after death of the patient (26).

Additional consent provisions for collection and use of participant data and biological specimens
This trial does not involve collecting biological specimens for storage.

INTERVENTIONS

Explanation for the choice of comparators
The comparators were chosen based upon previously found oxygenation targets associated with greater survival in ICU patients (8, 27) and to have sufficient contrast in PaO_2 between the two randomization groups.

Intervention description

In patients randomized to the 'conservative-targets'–arm, oxygenation will be targeted at PaO_2 55-80 mmHg (7.3-10.7 kPa). Because PaO_2 is not continuously measured, oxygenation targets can be steered on SpO_2 in between PaO_2 measurements. Corresponding SpO_2 to conservative PaO_2 targets needs to be determined per individual patient (usually approximately 91-94%).

Patients randomized to the 'conventional-targets'–arm, oxygenation will be targeted at PaO_2 between 110-150 mmHg (14.7-20 kPa). Corresponding SpO_2 to conventional PaO_2 targets will also be determined per individual patient (usually approximately 96-100%).

Invasive ventilation

The allowed ventilation modes are volume-controlled ventilation, pressure controlled ventilation, pressure support ventilation, closed loop ventilation and combined modes. Furthermore, INTELLiVENT-ASV (Hamilton Medical AG, Bonaduz, Switzerland) is allowed with the automatic oxygenation (FiO_2 and PEEP) adjustment turned off.

The inspired oxygen fraction (FiO_2) and positive end-expiratory pressure (PEEP) values are determined and titrated by means of the pre-specified and randomly assigned oxygenation targets. The respiratory rate is adjusted to maintain a blood pH of 7.20 to 7.45. In case of metabolic acidosis or – alkalosis, a lower or higher than normal $PaCO_2$ can be accepted, left to the discretion of the attending physician. The lowest level of PEEP is 5 cmH_2O; recommended FiO_2–PEEP–combinations are provided in Table 1. Deviation from the table is allowed in individual patients when indicated and is left to the discretion of the attending physician. Recruitment maneuvers are allowed, when deemed necessary by the attending physician.

Table 1. Recommended combinations of FiO_2 and PEEP. Deviation from the table is allowed in individual patients when indicated and is left to the discretion of the attending physician.

FiO_2	PEEP (cm H_2O)
0.21	5
0.30	5
0.40	5
0.40	8
0.50	8
0.50	10
0.60	10
0.70	10
0.70	12
0.70	14
0.80	14
0.90	16

Table 1. Continued.

FiO_2	PEEP (cm H_2O)
0.90	18
1.00	18
1.00	20
1.00	22
1.00	24

In both arms, tidal volume is titrated per predicted bodyweight (PBW), which is calculated according to a previously used formula: 50 + 0.91 x (centimeters of height – 152.4) for males and 45.5 + 0.91 x (centimeters of height – 152.4) for females. Tidal volumes are targeted at 6-8 ml/kg PBW.

Weaning

Daily assessment of the ability to breathe with pressure support ventilation is required as soon as $FiO_2 \leq 0.4$ or when the PEEP level and FiO_2 level are lower than the day before.

In addition, the ventilator can be switched to pressure support ventilation at any moment if the attending nurse or physician consider the patient awake enough to breathe with pressure support ventilation. Assessment of the ability to breathe with pressure support is also required in case patient–ventilator asynchrony is noticed (ineffective breathing; double triggering, use of accessory respiratory muscles). A patient is assumed to be ready for extubation when the following criteria are met for at least 30 minutes, the final decision for extubation is made by the attending physician:

- Responsive and cooperative
- Adequate cough reflex
- PaO2/FiO_2 of > 200 mmHg with $FiO_2 \leq 40\%$
- Respiratory rate of 8 to 30 per minute
- No signs of respiratory distress (i.e., marked accessory muscle use, abdominal paradox, diaphoresis, marked dyspnoea)
- Pressure support level < 8 cm H_2O
- Hemodynamically stable (systolic blood pressure 80 to 160 mmHg and heart rate 40 to 130/min) and no uncontrolled arrhythmia
- Temperature > 36.0°C and < 38.5°C

If a patient is able to breathe without assistance but subsequently requires additional ventilation within 28 days after randomization, the same oxygenation targets protocol is resumed.

After invasive ventilation

When a patient is extubated the PaO_2 targets should still be pursued within the type of oxygen support for which the patient has a medical indication. High-flow nasal oxygen or non-invasive ventilation should not be started solely for the ICONIC study PaO_2 targets, because this could influence duration of ICU admission. If this means the PaO_2 targets are not achieved after extubation, this should be accepted. The following rules apply:

- For patients randomized to the conventional oxygenation target: always give a nasal cannula with 5L of oxygen, except if PaO2>150 mmHg (>20 kPa).
- For patients randomized to the conservative target: preferably no oxygen therapy, except if PaO_2<55 mmHg (<7.3 kPa).

Criteria for discontinuing or modifying allocated interventions

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. When deferred consent is not obtained after randomization and provisional inclusion of a patient or when a patient withdraws consent. The replacement of the randomization subject will be done in the automated randomization scheme.

To avoid prolonged exposure to very high inspiratory oxygen concentrations, the allocated intervention can temporarily be modified in the conventional PaO_2 target group when FiO_2 is above 80% for more than 2 hours and/or PEEP is above 15 cm H_2O for more than two hours. In order to provide guidance when clinicians are in a situation with high inspiratory oxygen concentrations, we created a flowchart (Figure 1).

Strategies to improve adherence to interventions

At least one blood gas analysis per shift (three per 24 hours) will be required whilst mechanically ventilated.

If a participating ICU has difficulty adhering to the oxygenation targets and there is risk of overlap between the groups, the "aiming point PaO_2" provides guidance to the bedside clinicians:

- Conservative arm aiming point PaO_2 60 mmHg (8 kPa)
- Conventional arm aiming point PaO_2 135 mmHg (18 kPa)

Relevant concomitant care permitted or prohibited during the trial -

Among other concomitant care; sedation, selective oropharyngeal- or digestive tract decontamination, thrombosis prophylaxis, fluid regimens and nutrition follow the local guidelines in each participating ICU and are permitted during the trial.

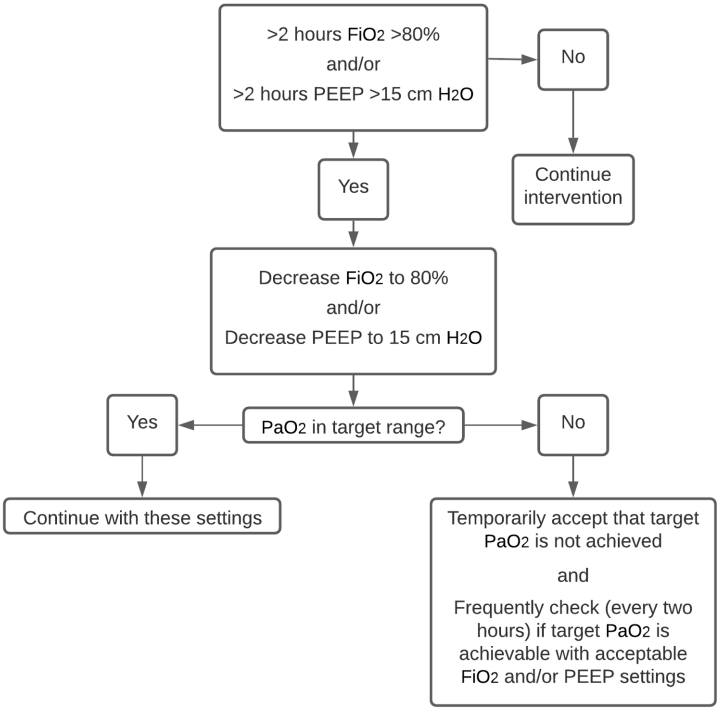

Figure 1. Flowchart high FiO_2 and/or high PEEP

Provisions for post-trial care

No provisions or restrictions are applicable for post-trial care. The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Outcomes

The primary endpoint is all-cause mortality at 28 days after randomization. The secondary study endpoints are as follows:

- The number of ventilator–free days and alive at day 28, defined as the number of calendar days from day 1 to day 28, the patient is alive and breathes without assistance of the mechanical ventilator. Ventilator-free days are according to the definitions by the Dutch National Intensive Care Evaluation (NICE) registry (28).
- ICU length of stay (LOS)
- Hospital LOS
- ICU mortality

- Hospital mortality
- 90–day mortality
- Ischemic events (cardiac, neurological and peripheral)

Follow up (in participating subjects from the Netherlands):

- Quality of life at 6 and 12 months
- Patient opinion of research and consent in the emergency setting at 6 months after randomization

PARTICIPANT TIMELINE

Sample size

Based on an expected mortality in the control group of 24% (source: Dutch NICE foundation; NICE online (28)) we will include 1,512 patients to detect an absolute difference in mortality of 6% (2-sided, alpha 0.05, power 80%, similar allocation of subjects to each group and corrected for 4% dropouts). The choice of 6% was motivated by the difference of 8% found in a previous trial (16) comparing conventional to conservative oxygenation targets and what could be considered clinically acceptable.

Recruitment

All patients admitted to participating ICUs or intubated on participating ICUs will be screened for eligibility.

	Study period								
	Screening	Randomization	Post-randomization			Follow-up			
TIMEPOINT	*Start of ventilation or ICU admission*	*<2 hours after start of ventilation or ICU admission -24:00*	*Day 0*	*Daily: Day 1-28*	*Discharge*	*Day 28*	*Day 90*	*6 Months*	*12 Months*
ENROLLMENT									
Eligibility screen	X								
Deferred consent		X*							
Allocation		X							
INTERVENTIONS									
Conservative oxygenation		←	—	→					
Conventional oxygenation		←	—	→					
ASSESSMENTS									
Baseline: demographic data, date, location and reason for intubation, medical history, APACHE score, SOFA parameters			X						
Arterial- and venous blood gas data			X	X					
Ventilation data			X	X					
SOFA parameters			X	X					
Delirium			X	X					
Type of endpoint: death, discharge from ICU, transferal non ICONIC, day 28					X				
Infection: surgical site, bloodstream, respiratory tract					X				
Ischemic events					X				
Transfusion					X				
Live status: dead or alive						X	X		
Experience of consent procedure								X	X
Quality of life								X	X

Figure 2. Schedule of enrollment, intervention and assessments.

**Deferred consent, obtained as soon as possible after randomization.
Abbreviations: acute physiology and chronic health evaluation (APACHE), sepsis related organ failure assessment score (SOFA).

ASSIGNMENT OF INTERVENTIONS: ALLOCATION

Sequence generation
Randomization sequence is generated by a dedicated computer randomization software program (Castor EDC, Amsterdam, The Netherlands) using variable block sizes and is stratified per participating center. Details of blocking are provided in a separate document that is unavailable to those who enroll participants or assign interventions.

Concealment mechanism
Randomization will be performed using a dedicated, password protected, SSL–encrypted website (Castor EDC, Amsterdam, The Netherlands).

Implementation
The allocation sequence is generated by a dedicated computer randomization software program (Castor EDC, Amsterdam, The Netherlands). Patients will be enrolled by local investigators and/or treating physicians in participating ICUs and the intervention will be randomly assigned by the computer randomization software.

ASSIGNMENT OF INTERVENTIONS: BLINDING

Who will be blinded
Due to the nature of the intervention, the clinicians and the outcome assessors are not blinded.

Procedure for unblinding if needed
Not applicable, there is no blinding of care providers.

DATA COLLECTION AND MANAGEMENT

Plans for assessment and collection of outcomes
Only data needed to assess primary- and secondary objectives will be collected in electronic case report forms and extraction from the patient registry systems. Data will be regularly checked on quality, errors, outliers and corrected if possible.
Two questionnaires are used for the follow-up of subjects from the Netherlands:

- EQ-5D (29, 30)
- A self-developed questionnaire assessing patient opinion and experience of the consent procedure of research in the emergency setting, which is a

modified and translated version of the questionnaire used in a previous trial (31).

Subjects will receive these questionnaires per mail or e-mail.

Plans to promote participant retention and complete follow-up

No or minimal losses to follow-up for the primary outcome is anticipated. Complete-case analysis will be carried out for all the outcomes. However, if more than 5% of missing data is found for the primary outcome, a sensitivity analysis using multiple imputations will be carried out.

Data management

All patients will be allocated with a random patient identification code. Patient identifying data will be omitted. The codebook will be stored digitally and in paper and will be safeguarded by the site investigator. The paper version will be stored behind a lock and the digital form will be encrypted. Source data will be stored at the specific study site where it originated and will be safeguarded by the site investigator. Data sent to the project leader or principal investigator will only contain this code and will not contain patient identifying information.

Confidentiality

A codebook of enrolled participants will be collected and stored digitally or in paper, encrypted or behind a lock. The personal information in these files will not be shared with other investigators.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable, no biological specimens are collected.

STATISTICAL METHODS

Statistical methods for primary and secondary outcomes

Primary outcome

The primary endpoint, all-cause mortality at day 28, is analyzed using Kaplan Meier. The statistical analysis will be based on the intention-to-treat principle, with patients analyzed according to their assigned treatment arms, except for cases withdrawn or without informed consent. The primary outcome will be assessed using a two sided superiority hypothesis test, with a significance level of 0.05 and presented with two-sided 95% confidence intervals. In addition, we will perform a per-protocol analysis

to check for robustness of results. The per-protocol group analysis only considers patients of the conservative group if 50% or more of the PaO_2s in the blood gas analysis is equal to or above 10.7 kPa (80 mm Hg), and patients of the conventional group if 50% or more of the PaO_2 in the blood gas analysis is equal to or above 14.7 kPa (110 mm Hg).

Secondary outcome

Secondary endpoints that fall under the category of continuous normally distributed variables will be expressed as frequencies and percentages. Differences between groups in continuous normally distributed variables will be expressed by their means and standard deviations or when not normally distributed, as medians and their interquartile ranges. Secondary endpoints that fall under the category of categorical variables will be expressed as frequencies and percentages. Differences between groups in continuous variables will be analyzed with Student's *t* test or, if continuous data is not normally distributed, the Mann-Whitney *U* test will be used. Categorical variables will be compared with the chi-squared test or Fisher's exact test, as appropriate. Statistical significance is considered to be at a p-value <0.05 with a two-sided test. When appropriate, statistical uncertainty will be expressed by 95% confidence levels. In addition to the unadjusted p-values for secondary outcomes, a procedure will be applied to control for multiple testing.

All statistical analyses will be performed with the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Interim analyses

No planned interim analysis will be performed. The data safety monitoring board (DSMB) will analyze a proxy endpoint, in-hospital mortality, for subject safety.

The stopping guidelines are defined as follows: The primary endpoint will be analyzed for safety reasons if a difference in in-hospital mortality of >6% is found with a p-value <0.005 (Chi square test). The study will only be stopped early for safety reasons if a difference in primary endpoint (28-day mortality) is found of >6% with a p-value of <0.001.

Methods for additional analyses (e.g. subgroup analyses)

Subgroup-analyses are planned to investigate the effects of oxygenation targets on the primary endpoint in the following subgroups: ARDS at ICU admission, patients with sepsis as reason for admission, patients with stroke, patients with myocardial infarction and patients with elevated plasma lactate (> 2 mmol/l).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Analysis will primarily be performed following the intention to treat principle. To handle protocol non-adherence a secondary per protocol analysis will be performed.

No or minimal losses to follow-up for the primary outcome is anticipated. Complete-case analysis will be carried out for all the outcomes. However, if more than 5% of missing data is found for the primary outcome, a sensitivity analysis using multiple imputations will be carried out.

Plans to give access to the full protocol, participant level-data and statistical code

The full protocol will be publicly accessible. Upon reasonable request the dataset and statistical code will be made available.

OVERSIGHT AND MONITORING

Composition of the coordinating center and trial steering committee

The coordinating center and steering committee will provide trial oversight and is composed of the principal investigator, leading investigators and experts of ventilation who contributed to the design and revision of the study protocol. The leading investigators are responsible for the daily management of the trial and provide assistance to participating ICUs in training in study related procedures for the local staff, trial management, data management and monitoring. Local investigators in each site will screen the patients who require mechanical ventilation and check if they are eligible for participation, perform randomization, supervise data collection and ensure adherence to the ICH-GCP guidelines during the trial.

Composition of the data monitoring committee, its role and reporting structure

An independent Data Safety and Monitoring Board (DSMB) watches over the ethics of conducting the study in accordance with the Declaration of Helsinki, monitors safety parameters and the overall conduct of the study. The DSMB is composed of three independent individuals. The DSMB will meet at least yearly. No competing interests were reported by the DSMB.

Adverse event reporting and harms

Adverse events (AE) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure and intervention strategies. Since this is a low-risk study in critically ill patients, comparing two currently used PaO_2 targets, additional undesirable events related to the study

protocol are not anticipated. Therefore, we will only register serious adverse events (SAEs) and will not record AEs.

Because this is a study in critically ill patients, SAEs are expected to occur frequently. Therefore, the following SAEs are not considered untoward in this population and will not be treated as SAE:

- Death not related to the study intervention
- Infections
- Bleeding
- Organ Failure

The following events occurring during ICU admission will be treated and registered as SAE:

- $PaO_2 \leq 5$ kPa (37.5 mmHg)
- Ischemic events (limbs, cerebral, myocardial, intestinal)
- In hospital cardiac arrest (IHCA)
- SpO_2 <80% for longer than 10 minutes (not explained by technical failure)
- Death possibly related to the study intervention

The site investigator will report all SAEs to the leading investigator without undue delay after obtaining knowledge of the events.

The sponsor or lead investigator will report the SAEs through the web portal to the accredited ethical reviewing board that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Frequency and plans for auditing trial conduct

On-site monitoring will comprise controlling presence and completeness of the research files and the informed consent forms, source data checks will be performed as described in the monitoring plan. Every participating center will be visited at least once every year.

Monitoring in the Leiden University Medical Center, the coordinating site, will be executed by internal monitors of the LUMC according to the monitor plan. Independent monitoring of participating sites will be arranged by the coordinating investigator and principal investigator.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

A substantial amendment is defined as an amendment to the terms of the ethical reviewing board application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the ethical reviewing board and to the competent authority.

Dissemination plans

The study protocol and analysis plan will be published before start of the study on trialregister.nl (trial number: 7376). The results of the study will be presented to (inter–) national scientific journals, professional societies and guideline committees. We will submit analyses to scientific journals in the field of Intensive Care medicine as well as anesthesiology, since both ICU physicians and anesthesiologists apply ventilation in the ICU setting. The results of this study will be disclosed unreservedly according to the Central Committee on Research Involving Human Subjects (CCMO) statement on publication policy (http://www.ccmo.nl/attachments/files/ccmo-statement-publicatiebeleid-3-02-en.pdf). Material for public dissemination will be submitted to the sponsor for review prior to submission for publication. Each study site will provide one co-author, when at least ten subjects have been included. If more than one hundred subjects have been included or reasonable efforts have been made to reach this number the study site will provide two co-authors. The co-authors will be determined in accordance with general accepted academic standards for authorship. Prior to submission co-authors will look through the manuscript. No parties involved have veto right.

DISCUSSION

The ICONIC study is a randomized clinical trial that is sufficiently powered to investigate whether a difference in outcome exists between mechanically ventilated ICU patients targeted at conservative or conventional oxygenation. Our aim is to replicate the study that was conducted by Girardis et al, in order to see if we would come to equivocal conclusions. After starting the ICONIC trial the evidence of the previously mentioned Italian trial (16) and beforementioned studies resulted in clinical practice guidelines

that emphasized a more conservative approach of oxygen therapy (6, 22-24, 27). This encouraged the start of several other randomized trials, including the ICU-ROX, $LOCO_2$, the HOT-ICU and the present trial.

The ICU-ROX investigators compared conservative oxygen therapy (targeting SpO_2 of 90-96%) to usual care (SpO_2 > 90%) in 1000 adults undergoing mechanical ventilation in Australia and New Zealand. Conservative oxygen therapy did not improve ventilator free days or survival in mechanically ventilated adults. However, the interventions compared were conservative oxygen therapy and usual care targeting SpO_2, and the actual difference in achieved SpO2 values between the two groups was minimal. Possibly the chosen target ranges were too close and did not allow sufficient discrimination, reducing the chance to detect any difference in endpoint.

The $LOCO_2$ trial planned to randomize 850 French ARDS patients to conservative (target PaO_2 55-70 mmHg; target SpO_2 88-92%) or liberal oxygen therapy (target PaO_2 90-105 mmHg; target SpO_2 ≥96%). However, the trial was stopped prematurely after enrolling 205 patients because of safety concerns due to ischemic events occurring in the conservative group.

Lastly, the most recent published trial from the HOT-ICU group randomized 2928 mechanically ventilated ICU patients to a PaO_2 of either 60 mmHg or a PaO_2 of 90 mmHg. No difference in death within 90 days was found. A limitation of this study was that possibly two 'normoxia' targets were compared and that there was limited contrast in the applied intervention.

The most recent trials do not support the previously found benefits of conservative oxygen use (16). Potential explanation for the negative findings in later trials is the lack of contrast between the oxygenation targets (intervention) in both study groups. To add, no truly hyperoxic targets were included in the negative trials. In the literature hyperoxia or higher targets are either defined as an PaO_2 of >100 mm Hg, an PaO_2 >150 mm Hg or even an PaO_2 of > 300 mm Hg (32-36). In the study by Girardis, that did show benefit in the lower oxygenation group, the PaO_2 target in the control group was up to 150 mmHg, thus more hyperoxic than the oxygenation targets in the negative RCTs.

In order to build on previously published results we hope to answer questions that remained unanswered in existing literature. Therefore, one of the strengths of the ICONIC is that we chose targets that are further apart, namely 55-80 mm Hg vs 110-150 mm Hg. To add, to maximize generalizability, we plan to not only focus on ARDS but include patients with a variety of conditions. Due to evidence of ischemia in the

conservative group in the LOCO$_2$ trial we will monitor occurrence of ischemic events (cardiac, intestinal, cerebral and peripheral) closely.

A limitation of this study can be the difficulty for patients to reach their target range. The ability to reach a higher target range highly depends on the lung function and underlying disease. Therefore, it might be possible that a patient is randomized to the higher group but due to underlying condition or clinical deterioration is not able to reach the higher target. We attempted to minimize this risk by excluding patients with ARDS and a P/F ratio <20, but we can unfortunately not anticipate on the risk of future clinical deterioration. Also patients with healthy lungs that are randomized in the lower oxygenation group might easily reach an SpO_2 of above 80 mm Hg with the slightest additional oxygen. For this reason, patients with an expected duration of ventilation of less than 24 hours are also excluded. Another limitation of this study could be that we focus on the whole ICU population instead of subgroups. Suggestions in literature have been made that some subgroups might benefit from a higher or lower oxygenation strategy, but a recent mini-review by Demiselle et al shows that when pooling the data from different subgroups that still no "optimal" oxygenation target for subgroups can be chosen (37). Also groups in which a specific oxygen target is proven to be beneficial, for example in COPD patients, were excluded from the study.

In conclusion, the ICONIC study is an investigator initiated international randomized clinical trial aiming to answer the question how to target oxygen therapy by investigating whether a difference in outcome exists between mechanically ventilated ICU patients targeted at conservative or conventional oxygenation.

Trial status

Protocol version number: Version 11, 13 February 2020
Date recruitment began: 19 November 2018
Approximate date when recruitment will be completed: 1 January 2022

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4

Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients:

a randomized clinical trial

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ABSTRACT

Rationale
Supplemental oxygen is widely administered to intensive care unit (ICU) patients, but appropriate oxygenation targets remain unclear.

Objective
This study aims to determine whether a low-oxygenation strategy would lower 28-day mortality compared to a high-oxygenation strategy.

Methods
This randomized multicentre trial included mechanically ventilated ICU patients with an expected ventilation duration of at least 24 hours. Patients were randomized 1:1 to a low-oxygenation (PaO_2 55-80 mmHg or SpO_2 91-94%) or high-oxygenation (PaO_2 110-150 mmHg or SpO_2 96-100%) target until ICU discharge or 28 days after randomization, whichever came first. The primary outcome was 28-day mortality. The study was stopped prematurely due to the COVID-19 pandemic when 664 of the planned 1512 patients were included.

Measurements and main results
Between November 2018 and November 2021, a total of 664 patients were included in the trial: 335 in the low-oxygenation group and 329 in the high-oxygenation group. The median achieved PaO_2 was 75 mmHg (IQR, 70-84) and 115 mmHg (IQR 100-129), in the low- and high-oxygenation groups, respectively. At day 28, 129 (38.5%) and 114 (34.7%) patients had died in the low- and high-oxygenation group, respectively (Risk Ratio 1.11, 95% Confidence Interval 0.9-1.4, P=0.30). At least one Serious Adverse Event was reported in 12 (3.6%) and 17 (5.2%) patients in the low- and high-oxygenation group, respectively.

Conclusion
Among mechanically ventilated ICU patients with an expected mechanical ventilation duration of at least 24 hours, using a low-oxygenation strategy did not result in a reduction of 28-day mortality compared to a high-oxygenation strategy.

Trial registration
This trial was registered in the National Trial Register (NTR) and the International Clinical Trials Registry Platform (ICTPR) under number NTR7376.

INTRODUCTION

Arterial oxygen levels are fundamental in maintaining a physiological balance and ensuring proper function of various organ systems. Hypoxic patients are at risk for cell injury, tissue damage, and organ failure. In this context, oxygen therapy is a lifesaving intervention and is therefore widely and liberally applied to acutely ill patients. The administration of high oxygen concentration has also been associated with beneficial effects due to antibacterial properties and counteraction of vasodilation (1,2). However, several studies have shown that liberal oxygen therapy with supranormal arterial oxygen levels is not without risks (3,4). Excessive oxygen administration may cause atelectasis, vasoconstriction, inflammation, and toxicity due to an imbalance in reactive oxygen species (ROS) (5,6).

Several randomized clinical trials (RCTs) have been conducted to identify the optimal oxygenation targets in mechanically ventilated intensive care unit (ICU) patients (7-13). One trial showed a lower mortality rate with lower oxygenation targets (9), while six other trials reported no difference in mortality between the higher and lower targets (7, 8, 10-13). Results from individual or aggregated data analyses have been inconclusive so far, which may be influenced by differences in the study population (subgroups), different targets (either SpO_2 or PaO_2), lack of power, or insufficient contrast between groups (14, 15). Goals for arterial oxygenation are increasingly implemented but clinical practice guidelines and clinician behaviour do not consistently rely on directive data from robust interventional studies (16).

Our aim was to provide additional data regarding the general adult ICU population using PaO_2 targets that are widely used in clinical practice. Accordingly, we conducted a multicentre, binational trial to test whether the use of conservative oxygen therapy results in reduced 28-day mortality compared to liberal oxygen therapy in mechanically ventilated ICU patients. Some of the results of this study have been previously reported in the form of an abstract (17,18).

METHODS

Study design

This investigator-initiated parallel group RCT was conducted in eight ICUs in the Netherlands and one in Italy. Ethical approval was granted for all centres by the Medical Ethical Committee of Leiden, The Hague and Delft (P18.109). The protocol was prospectively registered in the National Trial Register (NTR) and the International Clinical Trials Registry Platform (ICTPR) under number NTR7376 and published (19).

The study was funded by the Dutch Research Council (NWO) (Project number 401.16.009). An independent Data and Safety Monitoring (DSMB) committee periodically reviewed blinded efficacy and safety data, with the option to request unblinded data if required.

Participants

All patients aged 18 or older with an expected mechanical ventilation time of 24 hours or longer were screened for eligibility. The main exclusion criteria included a decision to withhold life-sustaining treatment, acute respiratory distress syndrome (ARDS) with a PaO_2/FiO_2 ratio of less than 150 mmHg, acute decompensation of chronic obstructive pulmonary disease (COPD), severe not rapidly reversible low cardiac output shock (cardiac index $\leq$ 2L/min/m^2), veno-arterial extracorporeal membrane oxygenation (VA-ECMO), underlying diseases with an indication for hyperoxygenation, severe anaemia (haemoglobin < 4.0 mmol/l) that is not rapidly reversible and uncontrollable intracranial hypertension (19). Patients with ARDS who had a PaO_2/FiO_2 ratio less than 150 mmHg were excluded from the study because they were likely to require very high FiO_2 for prolonged periods if assigned to the high PaO_2 target group. Patients with COPD were excluded from the study because they commonly have chronically low PaO_2 values. The full list of in- and exclusion criteria can be found in the online data supplements 1 and 2.

Randomization and blinding

Patients were assessed for eligibility by clinicians and, when appropriate, randomized within 2 hours after intubation to either the low- (conservative) or the high- (liberal) oxygenation group with secure web-based randomization software developed by Castor EDC/CDMS (20) using computer-generated variable block randomization with a 1:1 ratio and stratification based on study site. Clinicians and outcome assessors were not blinded for the intervention, while data analysts remained blinded. Informed consent was obtained according to national regulations and if possible, prior to randomization. Given the emergency setting of this trial, deferred consent from a proxy was permitted. If a patient died before delayed informed consent could be obtained, their data was still included in the analysis. Patients were excluded from the study if informed consent was not obtained within 5 days after randomization.

Trial procedures

Oxygenation was targeted at maintaining a PaO_2 level between 55-80 mmHg for patients in the low-oxygenation group and between 110-150 mmHg for patients in the high-oxygenation group. In addition to blood gas measurements, oxygen could also be adjusted based on peripheral saturation (SpO_2). The target SpO_2 range was 91-94% for the low-oxygenation group and 96-100% for the high-oxygenation group.

Oxygenation targets were pursued until ICU discharge or 28 days after randomization, whichever came first. At least one arterial blood sample per shift was collected while patients were mechanically ventilated (three per 24 hours). If PaO_2 values fell outside the specified ranges, the FiO_2 or positive end-expiratory pressure (PEEP) could be adjusted accordingly at the discretion of the treating physician. To guide this process, the protocol specified a recommended PEEP and FiO_2 table (Table E1 in the online data supplements). To prevent prolonged exposure to high inspiratory oxygen concentrations used solely to achieve the high oxygenation target, the protocol allowed clinicians to temporarily decrease FiO_2 to 0.8 and limit the PEEP to a maximum of 15 cm H_2O, if the FiO_2 was higher than 0.8 or the PEEP was higher than 14 cm H_2O for more than 2 hours. In those cases, the achievability of the PaO_2 targets was reassessed every two hours. When the patient was extubated, oxygenation targets were still pursued. For patients randomized to the low-oxygenation group, supplemental oxygen was generally avoided, unless PaO_2 fell below 55 mmHg. Patients in the high-oxygenation group received a nasal cannula of 5L oxygen, unless the PaO_2 exceeded 150 mmHg.

Rescue therapy, e.g. prone position, recruitment manoeuvres or Extracorporeal Membrane Oxygenation (ECMO) were only applied on clinical indications and not solely to achieve the study PaO_2 targets. The use of a high FiO_2 during planned interventions involving upper airways (e.g. bronchoscopy) was permitted but restricted to the shortest possible duration. Further details of the study protocol have been previously published (19).

Data collection

Data from the patient data management system and from the Dutch National Intensive Care Evaluation (NICE) registry database were collected and recorded in an electronic case report form (eCRF) designed with Castor EDC (20,21). The APACHE IV score (22) was used to assess disease severity upon admission, while Sequential Organ Failure Assessment (SOFA) scores (23)nwere used to evaluate daily disease severity. Acute and chronic diagnosis were registered based on the data definitions provided by the NICE registry (21). Further details regarding the data collected in the eCRF can be found in the published study protocol (19).

Outcomes

Primary outcome measure was all-cause mortality at day 28 after randomization. Secondary outcomes included the number of ventilator-free days and alive at day 28 (VFDs), ICU and hospital length of stay (LOS), ICU, hospital and 90-day mortality, and ischemic events. Ventilator free days were defined as the number of days that a patient was alive and free from invasive ventilation, calculated from the time of randomization, provided that the period of unassisted breathing lasted at least 24 consecutive hours

(24). Serious adverse events (SAE) were categorised as follows: PaO_2 of < 37.5 mm Hg, SpO_2 <80% for longer than ten minutes, cardiac arrest, or intestinal, cerebral, cardiac, or peripheral limb ischemia.

Statistical analysis

Based on an expected mortality of 24% in the control group (25), the original sample size was determined to be 1512 patients in order to detect an absolute difference of 6% between the two study groups, with a two-sided α of 0.05 and a power of 80%.

After careful consideration and in concordance with the DSMB we decided to stop the study prematurely after inclusion of 664 patients. The main reason for the early termination of the study was the corona pandemic, which significantly increased the workload for all participating ICUs and resulted in a substantial decrease in patient enrolment. An estimation was made that continuing at the current pace of enrolment would require an additional 5 years to reach the intended inclusion range. As a result, recruitment was stopped on November 21, 2021.

For the primary endpoint of 28-day mortality, rates were calculated according to a modified intention-to-treat principle, including all patients, except those who did not provide signed informed consent or were excluded after randomization on the basis of exclusion criteria. Differences were assessed using a chi-squared test. A two-sided hypothesis test was performed with a significance level of 0.05, and presented as relative risk with two-sided 95% confidence intervals. In addition, a per-protocol analysis was performed that only considered patients in the low-oxygenation group if 50% or more of the PaO_2 values in the arterial blood gas (ABG) analysis were equal to or below 80 mmHg, and patients in the high-oxygenation group if 50% or more of the PaO_2 values in the ABG analysis were equal to or above 110 mmHg.

For the secondary endpoints, continuous variables with a normal distribution were presented as means and standard deviations (SDs), while variables with a non-normal distribution were presented as medians and interquartile ranges (IQRs). Differences between groups were assessed using a Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, and a chi-squared test was used to analyse differences. Survival curves were calculated using the Kaplan Meier methods and compared using the log-rank test. Statistical significance was defined as a P-value of <0.05 in a two-sided test. When appropriate, 95% confidence intervals were used to express statistical uncertainty. In addition, an exploratory post-hoc subgroup analysis was conducted to assess the heterogeneity of treatment effects. Patients were divided into subgroups based on the diagnosis criteria of the NICE APACHE IV admission diagnosis model (21). Solely the largest subgroups were included in the analysis,

including patients with sepsis, pneumonia, cardiac arrest, abdominal causes and stroke. Additionally, predefined subgroups defined as patients with ARDS (PaO_2/FiO_2 < 200 mmHg) or elevated lactate level (>2mmol/l) at ICU admission, were included in the analysis. Statistics for both primary and secondary endpoints were calculated as described above.

As randomization was stratified by site, we conducted an additional analysis that involved including the study site in the analysis of both primary and secondary endpoints. For binary endpoints, we performed a logistic regression analysis while for continuous endpoints, we conducted a linear regression analysis. In both cases, we included the randomization group and study site as categorical variables.

Interim analyses were not planned beforehand, but after the study started, the DSMB deemed it necessary to conduct interim analyses of mortality. These analyses were planned after the inclusion of 500, 750, and 1000 patients to ensure the safety of both treatment targets. As per request of the DSMB, an interim analysis was performed after 500 patients. The interim analysis indicated no significant difference in in-hospital mortality between the two groups. Stopping rules were defined beforehand and can be found in the protocol (19).

All statistical analyses were performed using the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3).

RESULTS

From 19th of November 2018 until 21st of November 2021, 972 patients were screened for eligibility. In total, 882 patients met the inclusion criteria and were randomized to either the low or the high-oxygenation group. Deferred written informed consent was available for 664 patients (Figure 1). Baseline characteristics were comparable between the groups (Table 1). No patients were lost to follow up, and end-point data was available for all patients.

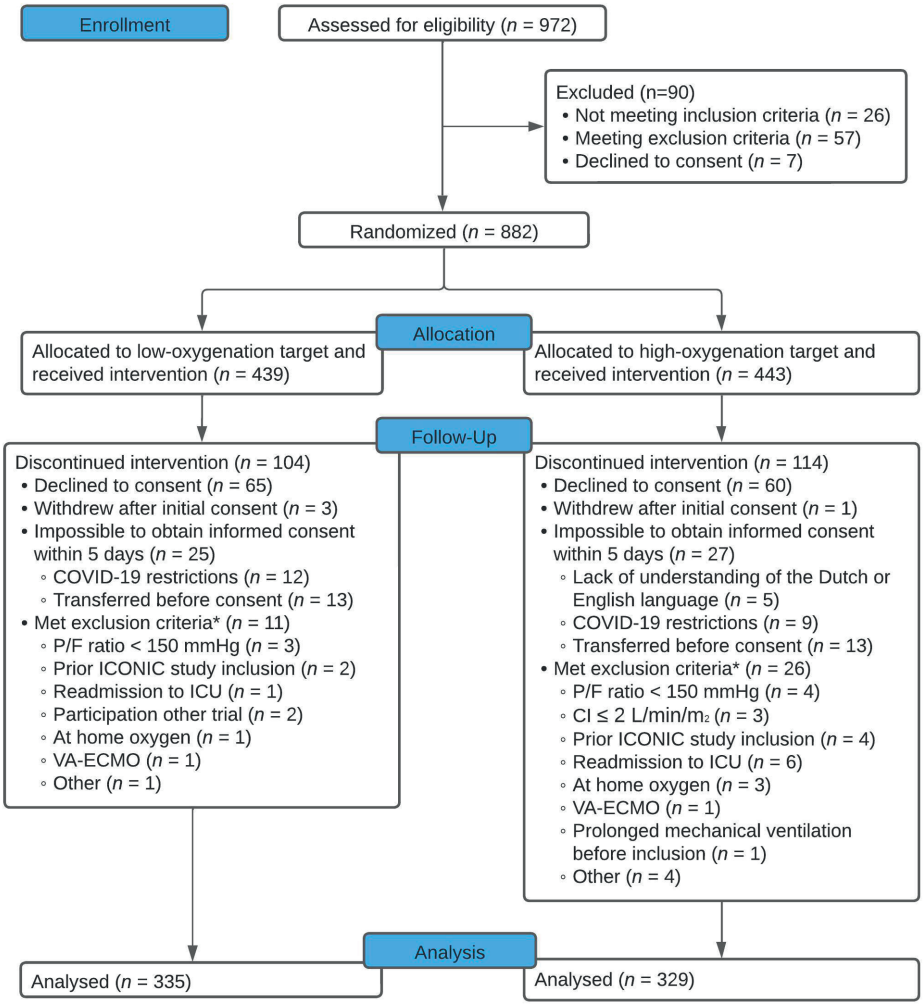


Figure 1. Consort flow diagram. The full list of in- and exclusion criteria can be found in Appendix 1-2 in the online data supplement. Data was available on primary and secondary outcomes for all patients. *Patients were only withdrawn from the study if exclusion criteria were present at the time of inclusion. This was checked within 24 hours after randomization. CI=cardiac index; P/F=Pa_{O2}/FI_{O2} ratio; VA-ECMO=venoarterial extracorporeal membrane oxygenation

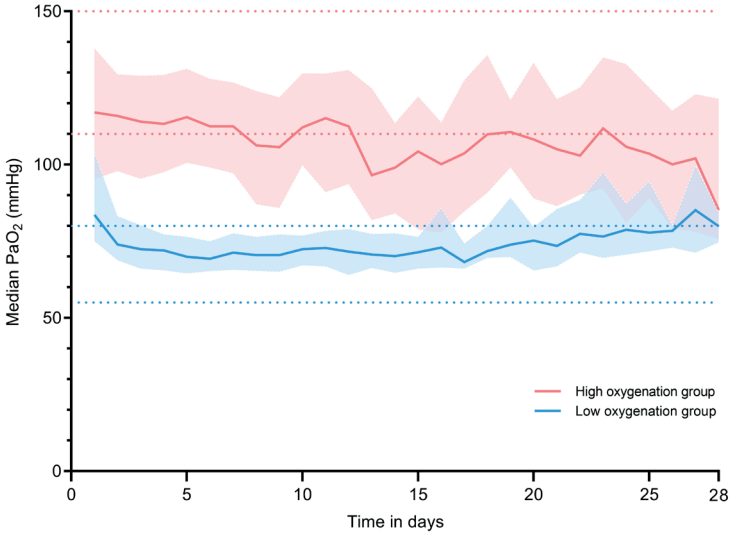
Table 1. Baseline characteristics of included patients.

	Low- oxygenation targets (55-80 mmHg) (N=335)	High-oxygenation target (110-150 mmHg) (N=329)
Sex = female, No. (%)	111 (33.1)	118 (35.9)
Age (median (IQR))	67 (59, 74)	67 (56, 73)
SOFA admission score (median (IQR))	9 (7, 11)	9 (7, 11)
Apache IV score on admission (median (IQR))	87 (66, 107)	86 (65, 113)
Mechanical ventilation in the first 24h of admission, No. (%) *	289 (87.3)	296 (92.2)
Duration mechanical ventilation prior to enrolment (minutes) (median (IQR))	0 (0, 58)	2 (0, 61)
Type of admission, No. (%) †		
Medical	258 (77.2)	251 (76.3)
Emergency surgery	61 (18.3)	56 (17)
Elective surgery	15 (4.5)	22 (6.7)
Acute diagnosis, No. (%) ‡		
Sepsis	53 (15.8)	42 (12.8)
Pneumonia **	54 (16.1)	43 (13.1)
Cardiac arrest	89 (26.6)	96 (29.2)
Abdominal	29 (8.7)	37 (11.2)
Neurologic	32 (9.6)	32 (9.7)
Trauma	12 (3.6)	12 (3.6)
Other	66 (19.7)	67 (20.4)
Chronic diagnosis on admission, No. (%) §		
Chronic kidney failure	20 (6)	22 (6.7)
Chronic dialysis	6 (1.8)	3 (0.9)
COPD (drug dependent)	39 (11.6)	37 (11.2)
Chronic respiratory insufficiency	6 (1.8)	1 (0.3)
Cardiovascular insufficiency (NYHA IV)	2 (0.6)	9 (2.7)
Liver cirrhosis	14 (4.2)	14 (4.3)
Diabetes	52 (15.5)	52 (15.8)
Metastasized neoplasm	8 (2.4)	5 (1.5)
Haematological malignancy	14 (4.2)	19 (5.8)
Immunological insufficiency	33 (9.9)	43 (13.1)

Abbreviations: SOFA, sequential organ failure assessment; RRT, renal replacement therapy; COPD, chronic obstructive pulmonary disease, NYHA,, New York Heart Association.
* Information on mechanical ventilation in the first 24 hours of admission was missing for four patients in the low-oxygenation group and eight patients in the high-oxygenation group.
† Information on type of admission is missing for one patient in the low-oxygenation group
‡ Acute diagnosis is classified according to the APACHE IV model
** In the low and high oxygenation groups, 11 and 8 patients admitted with pneumonia had COVID-19 disease. Information on whether patients were admitted with a COVID-19 infection was only available for patients included in the Netherlands.
§ More than one chronic diagnosis can be present in the same patient

Oxygenation

The first PaO2 measured after inclusion in the study was 92.3 mmHg (IQR, 76.5, 123.2) and 106.5 mmHg (IQR, 83.3, 147) in the low- and high-oxygenation group, respectively. More information about the first blood gas analysis can be found in Table E2 in the online data supplement. During the whole period of mechanical ventilation, the median PaO_2 was 75 mmHg (IQR, 69.8-83.5) in the low-oxygenation group and 115 mmHg (IQR, 100.3 - 129.0) in the high-oxygenation group (P<0.001) (Table 2, Figure 2). Corresponding median SpO_2 values were 95% (IQR, 94-97) and 99% (IQR, 98-100), respectively (P<0.001) (Table 2, Figure E1 in online data supplement). While spontaneously breathing without mechanical ventilation, the median PaO_2 was 75 mmHg (IQR, 68.3-82.9) in the low-oxygenation group and 85.5 (IQR, 73.8-102.8) in the high-oxygenation group. The corresponding median SpO_2 values were 95 (IQR, 94-97) and 99 (IQR, 98-100), respectively (P<0.001) (Table 2, Figure E2 and E3 in the online data supplements). Additional data on ventilation is displayed in Table E2 and Figure E4 in the online data supplement.



No. of patients

High oxygenation group	328	186	80	40	28	20	12
Low oxygenation group	328	192	82	46	24	19	10

Median no. of arterial blood gasses per day

High oxygenation group	4	4	4	4	4	3	4
Low oxygenation group	4	4	4	4	4	4	3

Figure 2. Median PaO_2 per day during mechanical ventilation. The PaO_2 values were calculated based on the median PaO_2 values per day by study group, where median values were taken per patient per day before aggregating the data. Lines represent the achieved median PaO_2 per oxygenation group. Faded areas around the lines represent the interquartile ranges. The dotted horizontal lines represent the boundaries of the higher and lower target. Blood gas data was not available for seven patients in the low-oxygenation group and one patient in the high-oxygenation group.

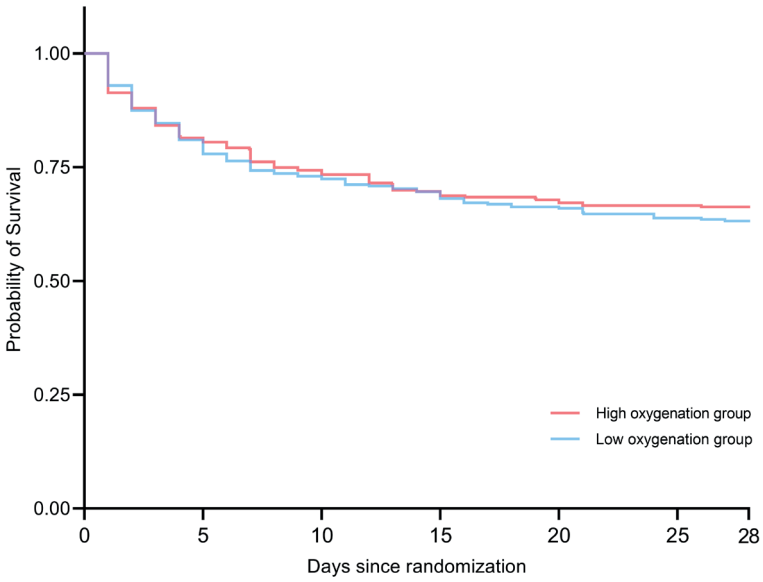
Table 2. Ventilation data and outcomes

	Low-oxygenation target (55-80 mmHg) (N=335)	High-oxygenation target (110-150 mmHg) (N=329)	P-value
Ventilation data			
No. of arterial blood gasses (mean (SD)) *	30.8 (30.8)	33.1 (37.6)	0.38
Duration mechanical ventilation - days (median (IQR))	3 (1.4, 6.5)	2.8 (1.4, 6.1)	0.6
Mechanical ventilation			
PaO_2 (mmHg) (median (IQR))	75 (69.8, 83.5)	115 (100.3, 129)	<0.001
SpO_2 (%) (median (IQR))	95 (94, 97)	99 (98, 100)	<0.001
$PaCO_2$ (mmHg) (median (IQR))	39.8 (36, 44.3)	41.3 (36.8, 45)	0.054
Off mechanical ventilation			
PaO_2 (mmHg) (median (IQR))	75 (68.3, 82.9)	85.5 (73.8, 102.8)	<0.001
SpO_2 (%) (median (IQR))	95 (94, 97)	99 (98, 100)	<0.001
$PaCO_2$ (mmHg) (median (IQR))	37.2 (34.5, 40.6)	39.8 (36, 43.5)	0.001
Primary endpoint			
28 day mortality, No. (%)	129 (38.5)	114 (34.7)	0.34
Secondary endpoints			
ICU mortality, No. (%)	109 (32.5)	94 (28.6)	0.29
Hospital mortality, No. (%)	127 (37.9)	111 (33.7)	0.3
90 day mortality, No. (%)	144 (43)	133 (40.4)	0.56
ICU length of stay - days (median (IQR))	4.9 (2.3, 10.8)	4.7 (2.5, 9.9)	0.89
Hospital length of stay - days (median (IQR))	14 (5, 26)	12 (5, 23)	0.65
Ventilator free days at day 28 - days (median (IQR))	18.3 (0, 25.4)	20.2 (0, 25.7)	0.36
Serious adverse events, No. (%) †			
Serious adverse events	13	22	
Patients with at least one SAE	12 (3.6)	17 (5.2)	
Patients with more than one SAE	1 (0.3)	3 (0.9)	
PaO_2 <37.5 mm Hg	0 (0)	0 (0)	
Ischemia	10 (3)	15 (4.6)	
Cerebral	4 (1.2)	4 (1.2)	
Cardiac	0 (0)	3 (0.9)	
Intestinal	4 (1.2)	7 (2.1)	
Extremities	2 (0.6)	1 (0.3)	
SpO_2 < 80% longer than 10 minutes	1 (0.3)	2 (0.6)	
Cardiac arrest	2 (0.6)	4 (1.2)	
Other	0 (0)	1 § (0.3)	

Abbreviations: ICU, intensive care unit; SAE, serious adverse event.
* During the whole study period
† As reported in the case report form in Castor
§ Severe refractory hypotension most likely due to tamponade

Outcomes

The modified intention-to-treat analysis showed no significant difference in the primary outcome between the two oxygenation groups (P=0.34). In total, mortality at day 28 occurred in 129 (38.5%) patients in the low-oxygenation group and 114 (34.7%) patients in the high-oxygenation group (Risk Ratio 1.11, 95% Confidence Interval 0.9-1.4, P=0.30). The Kaplan Meier survival curve (Figure 3) showed no difference in the probability of survival between the two groups (log rank test P=0.4). Similar results on 28-day mortality were observed when applying a per protocol analysis, namely, 82/229 (35.8%) patients died in the low-oxygenation versus 67/171 (39.2%) patients in the high-oxygenation group (Table E3 in the online data supplement).



No. at risk

High oxygenation group	329	263	240	225	219	215	215
Low oxygenation group	335	264	238	227	216	208	206

Figure 3. Kaplan Meier survival curve of survival until day 28. On day 28 129 (38.5%) patients had died within the low-oxygenation group and 114 (34.7%) in the high-oxygenation group. Statistical analysis of the Kaplan Meier curve showed no significant difference (P=0.4, P-value adjusted for study site P=0.4).

No significant differences were observed between the two groups with respect to ICU, hospital, and 90-day mortality (Table 2, Figure E5 in the online data supplement). In addition, the analyses of ICU LOS, hospital LOS and number of VFDs at day 28 yielded no significant differences (Table 2). The median LOS in the ICU was 4.9 (IQR,

2.3-10.8) days in the low-oxygenation group versus 4.7 (IQR, 2.5-9.9) days in the high-oxygenation group. Adjusted analysis for study site for both primary and secondary endpoints can be found in Table E4 in the online data supplement.

A total number of 13 versus 22 SAEs occurred in the low- and high-oxygenation group, respectively (Table 2). Ischemic events were the most frequently reported SAE, 10 (3.0%) and 15 (4.6%) occurred in the low- and high-oxygenation group, respectively. Most common ischemic events were cerebral and intestinal (Table 2).

During the ICU admission, maximal and daily SOFA scores were comparable in both groups (Figure E6 in the online data supplement). No differences were found for predefined primary and secondary endpoints within the subgroups. Details of this analysis can be found in Table E5 of the online data supplement.

DISCUSSION

In this multicentre randomized trial, which included mechanically ventilated adult ICU patients, no significant difference was found in 28-day mortality between patients treated with a low- or a high-oxygenation strategy. Additionally, we did not find evidence of a between group difference in ICU-, in-hospital or 90-day mortality, ventilator-free days, length of stay, or ischemic events.

Our findings are in line with recent studies showing similar outcomes of ICU patients irrespective of oxygenation targets (8, 10-12) but are in contrast with earlier studies suggesting better survival with less oxygen (9) or a benefit for high-oxygenation targets regarding serious adverse events (7). The first publication reporting higher mortality after adjustment for severity of illness in ICU patients with high PaO_2 values, originated from an ICU registry in the Netherlands in 2008 (6). Since then, many observational studies were performed in various subsets of ICU patients. A meta-analysis of these studies showed that hyperoxia was associated with higher mortality, but the heterogeneity of studied populations and the observational nature of studies warranted cautious interpretation of these findings (4). Results from the first RCT on oxygenation in ICU patients were published in 2016 and demonstrated that a conservative protocol for oxygen therapy versus conventional therapy resulted in lower ICU mortality (9) (9). This RCT appeared to confirm the results from earlier observational studies. However, since then four additional RCTs have been published all showing no differences in mortality between patients treated with conservative versus liberal oxygen targets (7, 8, 10, 11). In addition, the very recent cluster-randomized PILOT-trial, which compared three SpO_2 targets (90%, 94% and 98%), also showed no differences in outcome (12). It should

be noted that in every previous trial other definitions of low- and high-oxygenation targets were used.

The fact that several large RCTs performed in different countries do not show an effect of oxygen targets on outcomes of ICU patients can be considered as evidence that different oxygenation strategies don't have an impact on mortality. However, it can't be ruled out that the absence of an effect from these strategies may be caused by a lack of contrast between the studied targets**.** In previous studies contrast between study groups were at times small, from as low as a difference of 7.5 mmHg to 15 mmHg (7-10) or 22 mmHg in arterial oxygen levels (11). Such differences may be to be too small to demonstrate effects of a certain oxygenation target. The findings of our study add important contributions to the existing literature, as the tested intervention resulted in more contrast between achieved oxygen levels, as high as 40 mmHg. However, we still did not observe an effect on mortality. Thus, we don't consider a lack of contrast to be the main explanation for the absence of a benefit. It is worth nothing that a larger contrast in oxygenation between intervention groups doesn't necessarily mean that a PaO_2 related mortality difference can be detected. It is also possible that the lowest mortality risk falls in between the studied targets. However, considering that previous RCTs (7, 8, 10, 11) examining slightly different target ranges also showed no difference in outcomes, it is less likely that in all of these studies the optimal PaO_2 target would have fallen between the studied targets.

One would expect that adhering to higher PaO_2 targets would result in increased reliance on invasive mechanical ventilation and a higher need for sedative drugs, potentially leading to a prolonged mechanical ventilation time. However, our results demonstrated that mechanical ventilation time was similar for both groups. This finding is consistent with the ICU-ROX and the PILOT-trial, which also reporting similar numbers of ventilator free days (10, 12). When considering length of stay, ICU-, hospital- and 90-day mortality, ischemic events, and other SAEs, no differences were found between the groups. These findings are in line with earlier studies (8, 10-12). Notably, in one of the previous RCTs a trend towards a higher incidence of intestinal ischemic events in the low-oxygenation group was reported (7). However, in our trial, we did not find any difference in intestinal or other ischemic events for the two study groups.

The latest literature indicates that the general ICU population does not derive benefits from a low- or a high-oxygenation strategy. Yet, there are thoughts that specific subgroups of ICU patients, such as those following cardiac arrest, could benefit from specific targets. The ICU-ROX investigators reported improved outcomes in patients with hypoxic-ischemic encephalopathy when treated with a conservative oxygen strategy (10). Similarly, Kilgannon and colleagues found a higher mortality when

cardiac arrest patients were treated with high levels of oxygen (26). However, it should be noted that high oxygenation in the latter study was defined as a PaO_2 > 300 mmHg, which is twice as high as the upper limit of our high target. This disparity may explain why our results did not show a difference in outcome for cardiac arrest patients. In addition, two recent RCTs comparing oxygenation strategies (SpO_2 of 90%-94% and 98%-100% or PaO_2 68-75 mmHg or 98-105 mmHg) in cardiac arrest patients also found no difference in outcomes (27, 28).

The absence of a difference in mortality related to lower or higher oxygenation targets could also be caused by a lack statistical of power. Interestingly, both the present study and previous RCTs have shown non-significant trends towards lower mortality in patients treated with higher oxygenation targets (8, 10, 11). The absolute differences in 90-day mortality ranged from 0.5 to 1.2 % in the previously published trials and 2.6% in the present study. However, none of these RCTs did have the power to rule out small mortality effects. Interestingly, two very large trials are ongoing at the moment (UK-ROX and MEGA-ROX) including 16.500 and 40.000 patients, respectively (29). The results of these trials will provide important insights in the possible smaller effects on survival, potentially in favour of higher oxygenation targets.

Some relevant limitations of this study must be considered. First, due to early termination, we were only able to include 664 of the planned 1512 patients which resulted in lack of statistical power to detect clinically important differences. However, with 664 patients the ICONIC trial remains one of the larger RCTs in this field. Second, because inclusion in the study was allowed before consent was obtained (deferred consent), a substantial number of patients were withdrawn from the study after initial inclusion and randomization if written informed consent could not be obtained. Excluding patients after inclusion raises concerns about potential selection bias. According to Dutch legislation, we are not allowed to provide data about this population and we therefore can't compare characteristics of excluded patients with patients that were included in our study. To minimize the risk of selection bias, the protocol had strict criteria for patient withdrawal, which was only permitted if patients declined consent or if consent was not given within 5 days after inclusion. In addition, patients could be withdrawn within 24 hours after inclusion if exclusion criteria became apparent at the time of inclusion. Patients who died within 5 days before consent could be obtained remained in the study. Third, some patients randomized to the high PaO_2 group were unable to reach this target. If, for example, a patient needed 100% oxygen to reach the high-oxygenation goal for prolonged periods, the protocol allowed lowering the FiO_2 to 0.8 to decrease the risk of pulmonary toxicity. This may have diminished the contrast in oxygenation between groups. Nevertheless, the difference between median PaO_2 values was still 40 mmHg. Furthermore, this is representative for real life

treatment in the ICU: high-oxygenation targets are not feasible in patients with very severe pulmonary dysfunction. Fourth, due to the nature of the intervention it was not possible to blind clinicians to the study intervention. However, the chosen endpoints such as 28-days mortality and ventilator-free days are objective and are less likely to be influenced by bias. Moreover, data analysts of this study were blinded for the study intervention. Finally, the findings of our study cannot be generalized to patients with severe ARDS or COPD, as these patients were excluded from participation in this study. Both the present study and previous RCTs showed no differences between the intervention groups. This is in contrast with popular believes and common practices, as over the last years there appeared to be a strong opinion among health care professionals that low-oxygen targets are better than high-oxygen targets (30, 31). While it is still possible that marked hyperoxia with PaO_2 much higher than studied in the RCTs may increase mortality, it is unlikely that new RCTs comparing conservative oxygenation with marked hyperoxia will ever be conducted in ICU patients.

In conclusion, among adult mechanically ventilated ICU patients with an expected mechanical ventilation duration of at least 24 hours, using a low-oxygenation strategy did not result in a reduction in 28-day mortality when comparing to a high-oxygenation strategy. It is noteworthy that the trend towards lower mortality in patients treated with higher oxygen targets, as also found in previous studies, precludes definite conclusions regarding what the best oxygen targets are and urges for additional studies.

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Perspectives of ICU Patients on Deferred Consent in the Context of Post-ICU Quality of Life - a substudy of a randomized clinical trial

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ABSTRACT

Objectives

Deferred consent enables research to be conducted in the intensive care unit (ICU) when patients are unable to provide consent themselves, and there is insufficient time to obtain consent from surrogates before commencing (trial) treatment. The aim of this study was to evaluate how former ICU patients reflect on their participation in a study with deferred consent and examine whether their opinions are influenced by the quality of life (QoL) following hospital discharge.

Design

Survey study by questionnaire

Setting

Eight ICUs in the Netherlands

Patients

Former ICU patients that participated in the ICONIC trial, a multicenter randomized clinical trial that evaluated oxygenation targets in mechanically ventilated ICU patients.

Interventions

Participants enrolled in the ICONIC trial in one of the eight participating centers in the Netherlands received a questionnaire six months after randomization. The questionnaire included 12 close-ended questions on their opinion about the deferred consent procedure. QoL was measured using the EQ-5D-5L questionnaire. By calculating the EQ-5Dindex, patients were divided in 4 QoL quartiles, where Q1 reflects the lowest and Q4 the highest.

Measurements and main results

Of 362 participants who were contacted, 197 responded (54%). More than half of the respondents (59%) were unaware of their they participation in the ICONIC study. In total 61% was content with the deferred consent procedure, 1% not content, 25% neutral, 9% did not know and 9% answered "other". Those with a higher QoL were more likely to be content (P=0.02). In all QoL groups the legal representative was the most often preferred individual to provide consent.

Conclusion

Former ICU patients who participated in the ICONIC study often did not remember their participation but were predominantly positive regarding the use of deferred consent. Those with a higher QoL were most likely to be content.

INTRODUCTION

Informed consent is an ethical cornerstone of medical research (2). In the Intensive Care Unit (ICU), however, patients are often unable to provide informed consent due to their critical condition (3). An alternative would be to ask a proxy or other legal representative for consent, although clinical practice often shows that a representative is either not available or overwhelmed by the situation and therefore not able to make a well-considered decision in the narrow time window of inclusion (3, 4). For such cases, deferred consent procedures have been developed in which patients can participate in medical research before obtaining informed consent under the condition that consent is sought from the subject or their legal representative as soon as circumstances allow it (5). Ethical concerns, however, have been raised due to the fact that patients cannot express their preferences in real-time, possibly impacting their autonomy.

In recent years, the use of deferred consent procedures in clinical studies has increased considerably. Some studies have demonstrated the feasibility and acceptability of deferred consent in the ICU setting (6). In a small study from Finland, 9 of 11 patients who had survived after participating in a study on therapeutic hypothermia after cardiac arrest agreed to research in emergency settings without consent of the patient or proxy (7). Nearly all ICU patients that participated in the NICE-Sugar study would have consented to study participation if asked for consent before enrollment (8).

An important factor that may influence patients' opinion on deferred consent procedures is their overall quality of life (QoL). While QoL can be seriously impaired after ICU stay (9), the influence of QoL on patients' opinion of deferred consent has not been evaluated. A prior study evaluating patients perspectives on Exception from Informed Consent (EFIC) in the "Progesterone for the treatment of Traumatic Brain Injury" (ProTECT III) trial found that the acceptance of the use of EFIC was generally high, however, patients with unfavorable outcomes were less accepting of their EFIC inclusion compared to those with favorable outcomes (10, 11). The ICONIC study (1, 12), a multicenter randomized controlled trial in ICU patients, comparing two oxygenation targets, allowed inclusion without prior consent and provided a population to evaluate this question. The aim of this substudy was to evaluate patients' perspectives on deferred consent and explore the influence of QoL. We hypothesized that patients with an impaired QoL after ICU are less likely to accept participating in studies without prior consent.

MATERIALS AND METHODS

Participants and setting

This is a substudy of the ICONIC trial (12), an international, multicenter, randomized, parallel-group trial, in which 664 patients were enrolled between November 2018 and November 2021. In addition, 125 patients were initially enrolled with deferred consent but subsequently excluded because consent was declined by the patient or his/her representative (appendix 1). The original trial was conducted in 8 ICUs in the Netherlands and 1 ICU in Italy. Ethical approval was granted on October 25 2018 for all centres by the Medical Ethical Committee of Leiden, The Hague and Delft (approval number: NL65236.058.18, study title: "ICONIC: Arterial oxygenation targets in mechanically ventilated patients in the intensive care unit, a randomized controlled trial"). A detailed description of the ICONIC study regulations can be found in the published protocol (1). In short, adult patients with an expected mechanical ventilation time of 24 hours or more were screened and randomized within two hours after intubation to either the low-oxygenation group (PaO2 55-80 mmHg or SpO2 91-94%) or the high-oxygenation group (PaO2 110-150 mmHg or SpO2 96-100%). Due to the emergency setting of this trial, the majority of the patients were included by deferred consent. The aim was to obtain delayed informed consent as soon as possible from either the patient or the representative. If this had not been achieved within 5 days after the study's commencement, patients were excluded from the study. In this trial no differences in mortality or other relevant clinical endpoints were observed between both groups.

For this substudy, participants were eligible if they were proficient in Dutch and if they were enrolled in the ICONIC study in one of the Dutch ICUs by deferred consent. Patients were excluded if informed consent was obtained before randomisation. The Medical Ethical Committee of Leiden The Hague and Delft reviewed and approved the study. Written informed consent was obtained from all patients or from their legal representatives. Patients were contacted for this study between May 2019 and November 2022. This study was conducted in accordance with the Declaration of Helsinki.

Questionnaire

To assess patient perspectives and experiences on the deferred consent procedure, a questionnaire used in a previous trial was modified and translated (appendix 2) (8). The questionnaire included 12 closed-end questions, and three options to provide a textual response to the choice "other". Participants were asked whether they were aware of their participation, if they provided consent themselves or if consent was provided by their legal representative, and if they would have participated if we could have asked them before the start of the study. Responses were "Yes", "No" or "I don't know". For questions regarding the most suitable substitute decision maker, if they

were content with the decision made on their behalf, whether this was similar to the decision they would have made, and whether participating in the study would help future intensive care patients, a 5-point Likert scale ranging from "Strongly agree" to "Strongly disagree" was used. Participants were given eight response options to indicate their preferred decision-maker. Additionally, in order to evaluate Quality of Life the EQ-5D-5L questionnaire was used (13) (appendix 3).

Procedures

At six months after enrollment in the ICONIC study, a research nurse checked in the electronic patient record if the patient was still alive and reviewed whether the patient consented to participate in the current study. Upon confirmation, patients received a questionnaire on deferred consent and the EQ-5D-5L (after 6 months) either digitally or by post, based on their preference. Reminder telephone calls were made to patients who did not respond within two weeks, and the questionnaire was resent if necessary. If patients still did not respond, a final reminder was sent out, either by e-mail or telephone, 3 weeks after the initial reminder. Patients who failed to respond within nine months of enrollment were excluded from the study. The same procedure was followed after twelve months to collect the second EQ-5D-5L questionnaire. All responses were automatically or manually registered in an electronic case report form (eCRF designed with Castor EDC) (14).

Statistical analysis

Data were extracted from Castor EDC (14) and analysed using R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3). We conducted a comparative analysis of the responses obtained through the questionnaires, and aimed to evaluate acceptance of the deferred consent procedure by patients, whether patients could remember who gave consent and the process involving the substitute decision maker. Responses were presented for the different quality of life groups. Our primary focus was to evaluate whether respondents found deferred consent acceptable and whether this was influenced by quality of life. Continuous variables were presented as means and standard deviations (SDs), or as medians and interquartile ranges (IQRs) depending on the data distribution. Differences between groups were assessed using a Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, and differences were evaluated using a chi-squared test or Fisher's exact test. Statistical significance was considered to be at a P-value of <0.05. The free text comments in the option "Other" were categorized by one investigator, and checked by a co-author. Differences were resolved by consensus.

In order to summarise the different health states of the EQ-5D-5L questionnaire the EQ-5D index value was calculated, including the five dimensions of health included in

the EQ-5D-5L questionnaire: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (15). Each individual dimension can be scored from 1 (no problems) to 5 (extreme problems). In order to calculate the EQ-5D index predefined weights are assigned to each answer of the individual EQ-5D dimensions. The EQ-5D index value ranges from 0 (worst health) to 1 (full health). To categorize QoL, patients were divided in QoL quartiles based on the calculated EQ-5Dindex, where Q1 reflects the lowest and Q4 the highest. The EQ-5D-5L questionnaire also includes the EQ-VAS score which is a visual analogue scale allowing patients to provide a global assessment of their health status, ranging from 0 (worst imaginable health) to 100 (best imaginable health). To examine the responses to the deferred consent questionnaire in relation to QoL, we performed an ordinal or regular logistic regression, considering EQ5D-index, age, and sex as the independent factors. In order to create an ordinal scale, the answer options "I don't know", "other" and "not applicable", were omitted from the analysis. For one question in which the different answers could not be represented as ordinal items, a chi square test was performed.

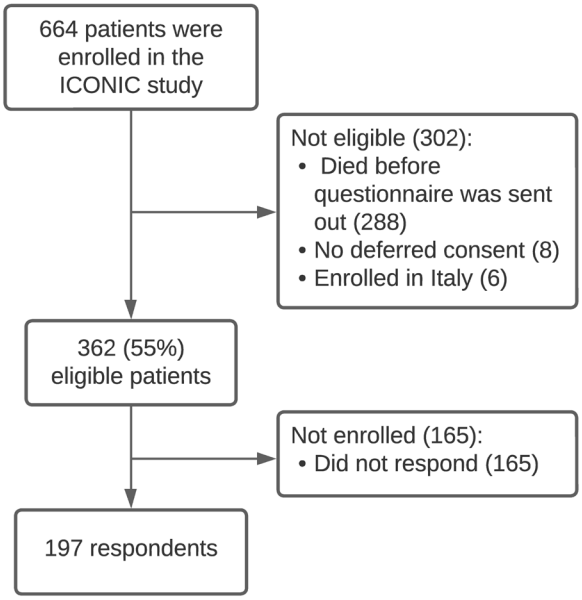

Figure 1. The screening and enrollment process for patients who were enrolled in the ICONIC study.

RESULTS

Participants and Quality of Life

Between November 19, 2018 and November 21, 2021, a total of 664 patients were enrolled in the ICONIC study, of which 362 (55%) were eligible to participate in this substudy because deferred consent was obtained. Questionnaires were completed by 197 respondents, resulting in a response rate of approximately 54% (Figure 1). The median time from enrollment until completion of the questionnaire was 29 weeks (IQR, 26-33). The median EQVAS score on subjective health status of all respondents was 80 (IQR, 60-90). The median EQ-5D index score of all respondents was 0.85 (IQR, 0.70-1.00). Baseline characteristics of respondents, non-responders and the total ICONIC population are presented in appendix 4. Table 1 presents the baseline characteristics of respondents categorized by QoL group. Patients who reported a lower QoL had a longer hospital stay (P=0.04). The remaining baseline characteristics were similar between groups.

Deferred consent procedure

Details of the answers to the questions in the four QOL groups are listed in Table E2 in appendix 5. Most patients were either content (61%) or neutral (25%), when asked how they felt about the ICONIC study starting without having been able to give consent (Figure 2). Patients with a higher EQ-5D index were more likely to be content (P=0.02). Only one person (in the highest QoL group) reported not to be content. In addition to the multiple choice answers, two respondents stated they felt forced to consent because the study had already started (appendix 6). When respondents were asked if they knew they had participated in the ICONIC study, the majority of the respondents answered "No" (59%), regardless of their QoL. If consent could have been asked before start of the study, the majority of the respondents would have given consent to participate (89%). These results were similar across QoL groups. Almost all respondents either agreed (55%) or strongly agreed (35%) with the statement "Participation in the ICONIC study will help intensive care patients in the future". These results were independent of QoL.

Table 1. Characteristics of respondents per Quality of life group. To assess QoL life patients were divided in 4 QoL quartiles (Q1, Q2, Q3, Q4) based on the calculated EQ-5Dindex. Q1 reflects the lowest QoL, Q4 the highest. Differences between QoL quartiles were not significant with the exception of hospital length of stay (p=0.04).

Variable	Q1 (N=49)	Q2 (N=49)	Q3 (N=49)	Q4 (N=49)
Age (median (IQR))	63 (50, 68)	62 (53, 73)	63 (51, 72)	67 (56, 72)
Sex = female (%)	19 (39)	14 (29)	15 (31)	16 (33)
Time from randomization to informed consent (days) (median (IQR))	3 (1, 5)	2 (1, 4)	2 (1.75, 5.25)	1 (1, 4)
Apache IV score on admission (median (IQR))	75 (57, 92)	77 (56, 94)	73 (59, 89)	77 (61, 91)
SOFA admission score (median (IQR))	8 (6, 10)	8 (6, 10)	9 (7, 11)	8 (7, 9)
Type of admission (%)				
Medical	34 (70)	39 (80)	36 (74)	34 (69)
Emergency surgery	10 (20)	8 (16)	10 (20)	11 (22)
Elective surgery	5 (10)	2 (4)	3 (6)	4 (8)
Admission diagnosis (%)				
Sepsis	6 (12)	9 (18)	7 (14)	2 (4)
Pneumonia	9 (18)	7 (14)	9 (18)	5 (10)
Cardiac arrest	8 (16)	16 (33)	15 (31)	25 (51)
Abdominal	8 (16)	1 (2)	3 (6)	2 (4)
Neurologic	6 (12)	4 (8)	3 (6)	1 (2)
Trauma	3 (6)	3 (6)	2 (4)	1 (2)
Other	9 (18)	9 (18)	10 (20)	13 (27)
ICU length of stay (days) (median (IQR))	6.6 (4, 16)	5.2 (3, 12)	4.6 (3, 0)	4.5 (3, 8)
Hospital length of stay (days) (median (IQR))	22 (12, 45)	17 (8, 29)	16 (10, 23)	15 (8, 21)
Randomization group = High oxygenation target (110-150 mmHg) (%)	20 (41)	27 (55)	25 (51)	25 (51)
Highest level of education completed (%)				
None	1 (2)	0 (0)	0 (0)	1 (2)
Primary school	4 (8)	5 (10)	3 (6)	4 (8)
Pre-vocational secondary education	13 (27)	12 (25)	9 (18)	9 (18)
Secondary vocational education	17 (35)	17 (35)	22 (45)	18 (37)
Senior general secondary education/ pre-university education	4 (8)	5 (10)	4 (8)	4 (8)
Higher professional education	5 (10)	8 (16)	5 (10)	11 (22)
University	5 (10.2)	2 (4.1)	6 (12)	2 (4)
EQ-5D-index at 6 months (median (IQR))	0.47 (0.29, 0.56)	0.79 (0.74, 0.81)	0.88 (0.85, 0.89)	1 (1, 1)

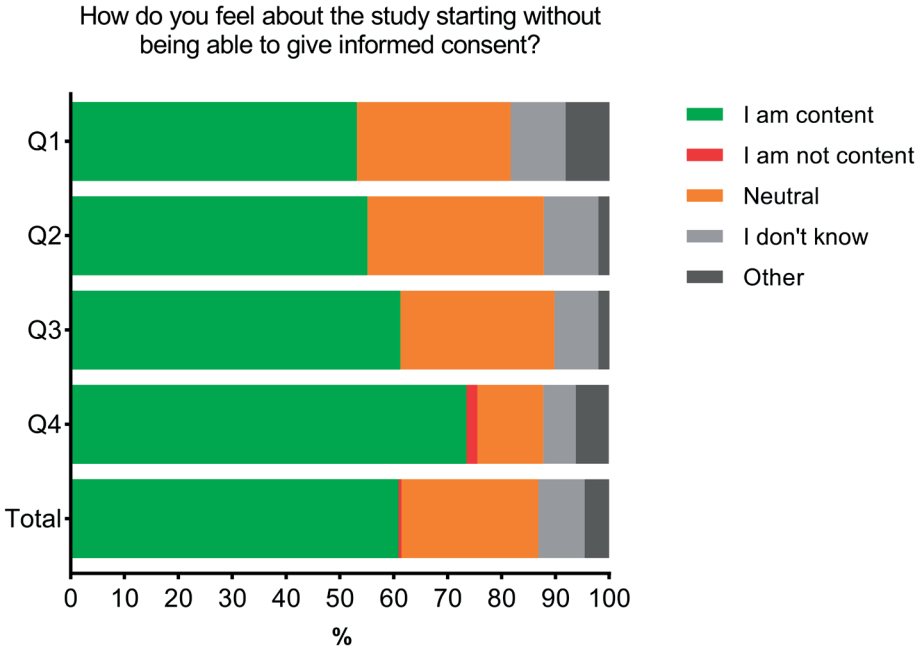

Figure 2. Results of the level of satisfaction regarding the deferred consent procedure. In the figure, the responses to the question: "How do you feel about the study starting without being able to give consent" are presented an stratified by Quality of Life (QoL) quartiles. Q1 reflects the lowest QoL, Q4 the highest.

Recollection of consent

For 197 respondents, consent was given by a representative only in 136 cases (69%), by the patient only in 55 cases (28%) and by both a representative and the patient in 6 cases (3%). More information on recollection of consent is shown in figure 3. In total, 61 patients had provided written consent themselves. However, when these respondents were asked if they provided consent themselves, 21 (34%) answered "Yes", 21 (34%) answered "No", and 19 (31%) answered "I don't know". The 136 respondents who did not provide their own consent, 9 (7%) erroneously believed they did, while 97 (71%) remembered correctly, and 30 (22%) could not remember. For 142 patients, consent was provided by a legal representative. Among those 142, 104 (73%) could remember correctly (Figure 3). In the 55 cases where a representative did not provide consent, 27 patients (48%) believed they did, 18 (32%) could not remember and 11 (20%) remembered correctly.

Substitute decision maker

Details of responses to questions about substitute decision makers are listed in

Table E2 in appendix 5. In response to the question who participants would prefer to make a decision on their behalf, the majority of respondents preferred the same legal representative who received information about their medical situation during the ICU admission (84%), irrespective of QoL. Most respondents strongly agreed (49%) or agreed (39%) that the doctors asked the right person to provide consent. Patients with a higher QoL were more likely to agree (p=0.005). When asked whether the person who provided consent on their behalf made the same decision as they would have made, most respondents strongly agreed (41%) or agreed (47%). A higher QoL was associated with being more likely to agree (p=0.005). The majority of the patients either strongly agreed (33%) or agreed (55%) with the decision made on their behalf, and patients with a higher QoL were more likely to agree (p<0.001). Only one respondent (in QoL group Q2) disagreed.

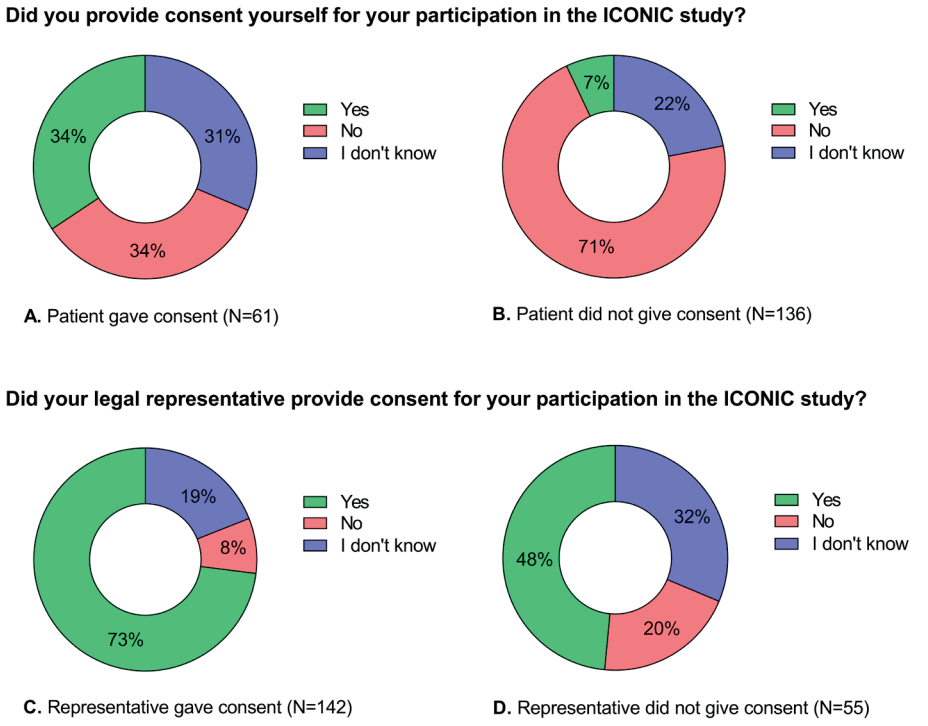

Figure 3. Patients' memory of who gave consent. In the upper panel 61 patients who had given consent (A) and 136 patients who had not given consent (B) answered the question if they had provided consent themselves to participate in the ICONIC study. The lower panel shows answers to the question if a representative had provided consent for them for 142 patients for whom a representative had given consent (C) and for 55 patients for whom no consent was provided by a representative (D).

DISCUSSION

This study assessed the perspectives of ICU patients on the deferred consent procedure as used in the ICONIC study, and the influence of QoL on these perspectives. Despite many patients being unaware of their participation in the ICONIC study, even though deferred consent had been obtained in the process, most patients were positive regarding the use of deferred consent. Patients with a higher QoL were most likely to be content. In all QoL groups legal representatives were the most preferred individuals to provide consent, and overall, our findings suggest general acceptance of the deferred consent procedure among ICU patients, with a trend of higher acceptance in patients with a higher QoL.

Over the years, literature has shown high levels of patient acceptance of the deferred consent procedure, with acceptance rates ranging from 82-95.6% (7, 8, 16-18). The level of acceptance can be influenced by several factors (6). In the ESCAPE trial, a trial investigating endovascular thrombectomy for acute stroke patients, 78% of the patients disagreed with the use of deferred consent likely due to the high risk nature of the intervention (19). In the ProTECT trial, a trial in which EFIC was used, patients and surrogates of patients with unfavorable clinical outcomes were less accepting compared to patients with favorable outcomes (10, 11). Factors that increased the level of acceptance regarding the use of deferred consent were: perceived benefit of the research, the time-critical nature of the event, and the impact of the condition and emergency situation on the ability to provide consent (6). Other factors that were presumed to affect the level of acceptability of deferred consent were age, ethnicity, previous ICU or research experience, and gender (6). This is the first study to show that QoL affects the level of acceptability.

We hypothesized that patients with an impaired QoL after ICU were less likely to accept having participated in a study without their explicit consent. This was confirmed by the results of our study showing that patient with a higher QoL were more likely to be content with the deferred consent procedure compared to patients with a lower QoL. However, we found that it is difficult to evaluate the effect of QoL on patients' attitudes regarding the use of deferred consent when the vast majority of the patients were content with the procedure. Furthermore, in our study the median EQ-value and median EQ-VAS score were higher after 6 months compared to previous studies evaluating functional status and QoL after ICU stay (20, 21). Therefore, we cannot rule out that results will differ in patients with a severely impaired QoL. To add, some responses, such as 'I don't know', 'Not applicable', and 'other', were excluded from the analysis in order to create an ordinal scale. While a multinomial regression including these answers showed similar results (data not shown), it is something that needs to

be considered in the interpretation of our findings.

Despite patients being mostly positive regarding the use of the deferred consent procedure, our study showed that patients were generally poor at remembering their participation, which is in line with the results of a study evaluating the deferred consent procedure in obstetric emergency research (22). It is important to note that if patients do not recall giving consent, interpreting their attitudes towards enrollment, as assessed through questionnaire responses, becomes challenging. One could argue that it is not surprising that patients do not remember participating in the study because the majority of the patients did not give consent themselves. However, also in patients who did provide consent themselves, only a third of them could remember correctly. Even more remarkable, participants were given a detailed description of the ICONIC study as part of the introduction of the questionnaire, and still they struggled to recall their participation. These findings highlight the importance of effective post-study communication methods to improve patients' awareness of study participation. Consent is not a one-off event, but needs to be a continuous process. Therefore, in the future, we need to focus on strategies for communicating with participants after enrollment to ensure they understand what they have been part of.

Our study found that a small percentage (4.1%) of patients post hoc disagreed with study participation. These results are consistent with earlier studies indicating similar low numbers (4, 8). Even though this proportion is very low, it is important to consider when performing studies with deferred consent. In line with another study (23) a few but considerable number of respondents reported feeling pressured when asked to provide consent because the study had already started. Careful and open communication about the procedure and about the research components they can still decide about is important when they are able to give consent themselves.

The following study strengths and limitations should be considered. First, this trial is the first to integrate a QoL assessment into the evaluation of patients' opinion of deferred consent procedures. Second, our trial had a relatively high inclusion rate compared to previous studies in this area. Additionally, earlier studies with larger sample sizes were mainly based on hypothetical scenarios with deferred consent, and did not include patients who had actual experience with the procedure. Therefore, a strength of our study is that we included critically ill patients with real-life experience with the deferred consent procedure in the ICONIC trial.

The response rate of 54% may limit the generalizability of our findings to all eligible patients who survived after participating in the ICONIC trial. Although respondents and non-responders were comparable in most baseline characteristics, it is possible

that non-responders may hold different opinions on the deferred consent procedure. Additionally, the opinions of patients who died within 6 months after inclusion or those who declined to consent were not obtained, therefore a group of patients that might have objections to deferred consent could not be included in the analysis. Also, the time from enrollment until responding to the questionnaire for the present study was 6 months and may be considered relatively long. Opinions on having participated in a study with deferred consent may change over time. We choose for studying opinions at 6 months because we anticipated that administering the QoL questionnaire immediately upon or shortly after hospital discharge might result in a less accurate reflection of the actual QoL. Finally, it is important to emphasize that this analysis only included patients from the Netherlands, and it should be noted that the ICONIC trial is classified as a low risk study. Therefore, the results from this trial may be confined to this specific cultural population and the context of a low risk study.

CONCLUSIONS

The present study provides more insight on perspectives of Dutch ICU survivors on their participation in research with deferred consent. It appears that the majority of ICU patients who took part in the ICONIC trial were positive regarding the use of the deferred consent procedure, with patients with a higher QoL status 6 months post-ICU discharge being most likely to be content with the deferred consent procedure. These findings confirm that deferred consent is a suitable option for obtaining consent from ICU patients.

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Volume of oxygen administered during mechanical ventilation predicts mortality in ICU patients

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The appropriate administration of oxygen to mechanically ventilated patients in the ICU remains a challenge. While clinical guidelines advocate for conservative oxygenation targets, recent trials have produced conflicting results (1, 2). The use of different surrogates to assess oxygen exposure and oxygenation, along with confounding by indication, may explain the heterogeneity in findings. We aim to explore a novel parameter of cumulative oxygen exposure, the volume of oxygen administered during mechanical ventilation (MV). We hypothesize that this parameter is a more precise and direct measure of oxygen exposure than previously used surrogates and therefore may be more reliably linked to outcome. We performed a cohort study using patient data from a tertiary ICU in the Netherlands and included hourly MV settings, arterial blood gas analyses, outcome and demographic data for all patients admitted to the ICU from July 2011 to September 2015.

The volume of oxygen administered to each patient during MV was calculated by estimating the area under the curve of the product of FiO_2 and ventilatory minute volume as a function of MV time in minutes (FiO_2 * ventilatory minute volume (L/min) * MV time (minutes)). The result was a metric of total oxygen volume in liters administered to the patient during invasive MV (cumulative oxygen volume). Because this metric was strongly confounded by the duration of ventilation (high level of collinearity, Pearson's r = 0.93), we calculated a time weighted metric by dividing cumulative oxygen volume by duration of MV (oxygen volume per minute). Patients were categorized into three MV time categories: patients ventilated for less than 24 hours, 24-96 hours, and for 96 hours or longer. The primary outcome of interest was hospital mortality and a logistic regression model was used to analyze the association, adjusted for age, sex, APACHE III score and ventilator time categories. To account for a possible difference of effect size of oxygen volume per minute across MV time categories, we included an interaction term in the adjusted model (ventilatory time categories*oxygen volume per minute). The validity of the prediction model was evaluated by comparing it with logistic regression models of SpO_2, PaO_2 and PaO_2 /FiO_2 ratio for hospital mortality and a Nagelkerke R^2 was determined.

5,017 eligible patients were included. Compared to non-surviving patients, surviving patients were younger, had lower APACHE III scores, higher SpO_2, higher PaO_2, higher PaO_2/FiO_2 ratio, lower oxygen volume, shorter MV time and shorter ICU length of stay. Oxygen volume per minute was significantly associated with hospital mortality after adjustment for APACHE III score and MV time (OR 2.2 (95%C.I.: 1.9-2.4) (Table. 1). The interaction term of ventilatory time categories and oxygen volume per minute was not significantly associated with hospital mortality (OR 1.00 (95%C.I.: 0.75-1.34), and OR 1.01 (95%C.I.: 0.76-1.34), for MV time 24 hours compared to ventilation 24-96 hours and >96 hours, respectively). Both SpO_2 and PaO_2/FiO_2 ratio models were associated with

hospital mortality. Nagelkerke R^2 for the PaO_2/FiO_2 ratio with hospital mortality model was 0.53, for the SpO_2 model 0.53 as well, and for the oxygen volume model 0.58. A detailed description of the methods and results are provided as additional material.

This cohort study analyzed patient data from one ICU in the Netherlands to investigate the association between oxygen exposure during mechanical ventilation (MV) and hospital mortality. Oxygen volume per minute administered during MV was independently associated with hospital mortality, with a change of 1L per minute in oxygen volume per minute increasing the OR for hospital mortality by a factor of 3.26. The effect of oxygen volume per minute of oxygen on in-hospital mortality was not different across ventilator time categories, proposing an effect of oxygen exposure independent of ventilation time on mortality. If our findings are the result of a causal relationship between oxygen volume and mortality, it suggests direct toxic effects of oxygen and its supplemental use. The volume of administered oxygen was a stronger predictor of hospital mortality compared to existing parameters of oxygen exposure.
The study has several strengths, including the development of a novel and more accurate measure of oxygen exposure, a comprehensive dataset consisting of complete hourly data of the mechanically ventilated period per individual patient admitted to the ICU over a four-year period, and the automatic extraction of data from the patient data management system. However, the study also has limitations, including its observational nature, residual confounding, the single-center dataset, and the lack of control for specific diagnosis.

Table 1. Logistic regression model of hospital mortality and oxygen volume per minute

	OR (95% C.I.)	P-value
Crude model		
Oxygen volume per minute	3.26 (2.96-3.60)	<0.001
Adjusted model		
Oxygen volume per minute	3.62 (3.27-4.03)	<0.001
Fully adjusted model		
Oxygen volume per minute	2.15 (1.91-2.43)	<0.001
Fully adjusted model with interactions terms		
Oxygen volume per minute	2.15 (1.83-2.54)	<0.001
Ventilatory time 24-96 hours	2.21 (1.07-4.48)	0.03
Ventilatory time >96 hours	2.82 (1.32-5.91)	0.007
Oxygen volume per minute * Ventilatory time 24-96 hours	1.00 (0.75-1.34)	0.98
Oxygen volume per minute * Ventilatory time >96 hours	1.0 (0.8-1.3)	0.97

SE: standard error. OR: odds ratio. C.I.: confidence interval. Oxygen volume per minute was calculated by dividing cumulative oxygen volume by MV time. Adjusted model: adjusted for age and sex. Fully adjusted model: adjusted for age, sex, ventilatory time categories and APACHE III score. Fully adjusted model with interaction terms: adjusted for age, sex, ventilator time categories, APACHE III score and included interaction term (ventilatory time categories* oxygen volume per minute). APACHE: Acute Physiology and Chronic Health Evaluation.

In conclusion, oxygen volume per minute is a stronger predictor of mortality than established oxygen metrics. Therefore, oxygen volume per minute administered during MV seems to be a reliable parameter of oxygen exposure. Previously used oxygenation parameters may not completely capture the direct effect on outcome of exposure to oxygen as a vital but potentially toxic agent. Future studies should evaluate the replicability of the results of our study.

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PART II

ANTI-COAGULANT TREATMENT

Early effects of unfractionated heparin on clinical and radiological signs and D-dimer levels in patients with COVID-19 associated pulmonary embolism:

an observational cohort study

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ABSTRACT

Introduction

Pulmonary embolism (PE) is a frequent complication in Coronavirus disease 2019 (COVID-19) patients. The pathogenesis of COVID-associated activation of coagulation is not fully understood, which makes it uncertain whether unfractionated heparin (UFH), or anticoagulation in general, is effective. The aim of this study is to determine the effects of intravenous UFH on clinical, radiological and laboratory parameters in patients with COVID-19 and PE.

Materials and Methods

We conducted an observational cohort study in 19 Intensive Care Unit (ICU) patients with COVID-19 and computed tomography (CT) scanning proven PE. According to the local protocol, repeated CT-scanning was indicated if no pulmonary improvement was present after 7 days following start of anticoagulant treatment. We defined three endpoints: laboratory markers (d-dimer at day 0 vs day 2), clinical success (resolution of PE at follow-up CT-scan or discharged alive from ICU) and radiological response (Qanadli index at follow-up CT-scan vs CT scan at diagnosis PE). Statistical tests used were a T-test and Wilcoxon Signed Rank test.

Results

UFH resulted in clinical success in 14 out of 19 patients. Pulmonary emboli were completely resolved on the follow-up CT-scans in 5 out of 6 patients and partly resolved in the 6th patient. D-dimer levels decreased on average from 7074 ng/mL to 4347 ng/mL (p=0.001) within 48 hours after start of UFH.

Conclusion

In this observational study, we showed a rapid clinical, laboratory and radiological improvement in patients with COVID-19 and proven PE. Standard anticoagulant treatment was effective in this setting, supporting current guideline recommendations.

BACKGROUND

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a firm grip on public health globally since December 2019. To this date, over 35 million people have been infected worldwide with more than 1 million deaths (1). Patients with progressive disease almost invariably show profound pulmonary inflammation and may require mechanical ventilation and prolonged Intensive Care Unit (ICU) admission. Mortality rates in ICU patients can reach up to 50% (2). Despite adequate thromboprophylaxis the majority of patients are in a prothrombotic state which results in thrombotic complications, mainly pulmonary embolism, in up to 31% of the cases (3-6).

The pathogenesis of Corona Virus Disease 2019 (COVID-19)-associated activation of coagulation is currently not fully understood. It differs from disseminated intravascular coagulation (DIC) as seen in patients with sepsis. In DIC coagulopathy is initiated by tissue factor leading to consumption of platelets and coagulation factors with thrombocytopenia and prolonged PT and APTT (7). In contrast, in patients with COVID-19, d-dimer levels are high (up to 20.000 ng/mL or higher), but platelets and coagulation tests are normal in most patients suggesting a different mechanism of activation of coagulation and a high rate of fibrin degradation (8). Differences between COVID-19 pulmonary embolism (PE) and non – COVID-19 PE have been also been observed in Computed Tomography (CT) findings, suggesting that COVID-19 associated PE has a different phenotype than 'conventional' PE. In COVID-19 patients PE is frequently located in peripheral lung segments and less extensive compared to PE in patients without COVID-19. It has been hypothesized that the coagulopathy in COVID-19 patients may be driven by a local process associated with severe pulmonary inflammation and in situ thrombosis (9).

Established PE is treated with anticoagulants, which often is unfractionated heparin (UFH) in patients in cardiocirculatory shock or respiratory distress (10). As the pathophysiology of coagulation in COVID-patients is unknown, it is uncertain whether UFH -or anticoagulation in general- is effective in the attenuation of the procoagulant state. Since insufficient treatment of PE can be fatal, this observational study aims to study the effect of UFH on clinical, radiological and laboratory signs of PE in patient with COVID-19.

MATERIAL AND METHODS

Patient selection

This observational cohort study was conducted in the ICU of the Leiden University Medical Center (LUMC) in the Netherlands. This study was approved by the Institutional

Review Board of the LUMC for COVID-19 studies. The need for consent was waived by the Institutional Review Board of the LUMC for COVID-19 studies. Inclusion criteria were age >18 years, proven COVID-19 disease by PCR sampling of nasal/oral airway swab, mechanical ventilation, proven PE documented by CT scanning and treatment with unfractionated heparin. Exclusion criteria were: therapeutic doses of UFH within 48 hours prior to the diagnosis of PE, treatment with reperfusion techniques including fibrinolytic drugs or no data on d-dimer levels prior to the start of UFH therapy. Standard treatment included prophylactic low molecular weight heparin (LMWH) with nadroparin 2850 IU/day subcutaneously or 5700 IE/day if bodyweight >90 kg. Double prophylactic LMWH was defined as nadroparin 5700 IE/day. According to the local protocol, repeated CT-scanning was indicated if no pulmonary improvement was present after a minimum of 7 days following start of anticoagulant treatment.

Clinical and biological data

Data was collected for a maximum of 21 days or until ICU discharge. The following clinical and laboratory data were extracted from medical records: age, sex, year of birth, body mass index (BMI), date of ICU admission, date of ICU discharge, reason for discharge, condition 28 days after admission, starting time of UFH therapy and available D-dimer levels which were measured as a part of routine care every day. D-dimer has been measured in citrated plasma on a STA-R MAX analyzer with latex-based immunoturbidimetric reagents from STAGO BNL, Leiden, the Netherlands. Successful treatment was defined as either no PE on follow-up CT or survival at ICU discharge.

CT data acquisition and analysis

A CT-scan was performed in case of suspected PE. Standard contrast-enhanced CT pulmonary angiography (CTPA) was performed using a 320-MDCT scanner (AquilionONE, Canon) with collimation of 80 x 0.5 mm section thickness. Rotation time was 0.275 second, with a helical pitch of 65. Tube current was with automated exposure control and tube voltage was 100 kVp. The amount of iodinated contrast (Xenetix 350) was 50-80 mL with a flow of 4.5-6.0 mL/s followed by a saline flush of 45-50 mL. Images were reconstructed with 1 and 3 mm thickness using AIDR 3D enhanced technique. All scans were evaluated on a dedicated PACS workstation by a radiologist with >20 years of experience in chest CT. The diagnosis of PE was established on CTPA based on filling defect in a pulmonary artery. The thrombus load within the pulmonary arteries was determined by using the Qanadli obstruction index and calculated as percentage vascular obstruction (11). Parenchymal lung tissue involvement regarding pathology due to COVID-19 infection and pre-existing pathology, comprising a composition of ground-glass- or alveolar consolidation, atelectasis, emphysema, and fibrosis, was visually assessed by evaluation of axial, coronal, and sagittal reconstructions and expressed as percentage.

Outcomes

We defined three endpoints: Laboratory markers (d-dimer at day 0 vs day 2), clinical success (resolution of PE at follow up CT scan or discharged alive from ICU) and radiological response (Qanadli index at follow up CT scan vs CT scan at diagnosis PE). Severe bleeding was defined according to the definition of the International Society on Thrombosis and Haemostasis (ISTH) of 'major bleeding in non-surgical patients' (12).

Statistical analysis

Statistical analysis was performed by using IBM SPSS statistics version 25. Normality of the data was tested using the Shapiro-Wilk-test. Normally distributed data are presented as means with standard deviation (SD); data outside normal distribution are presented as medians with interquartile range (IQR). Categorical variables are presented as numbers and percentages. To calculate a significant difference between the two groups, a T-test and Wilcoxon Signed Rank test was used. A two-sided $p<0.05$ was considered statistically significant. The graphs are created using GraphPad Prism version 8.

RESULTS

In total, between March 15 and May 1st 2020, 90 patients were admitted to the ICU with confirmed COVID-19. Nineteen patients fulfilled the in- and exclusion criteria (Figure 1).

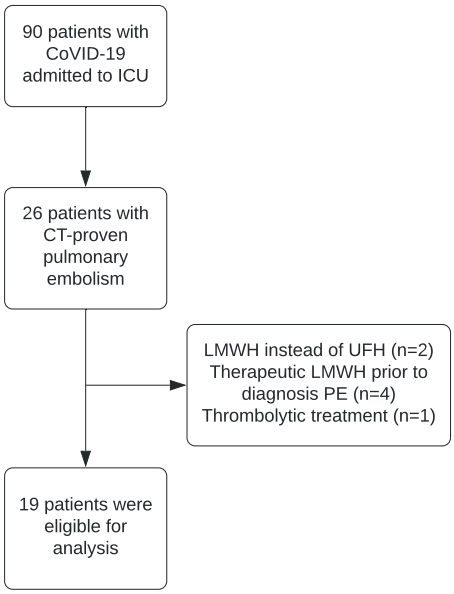

Figure 1. Flow chart of patient selection

All patients were mechanically ventilated and had PE proven by CT-scanning. Baseline, radiological and laboratory characteristics are shown in Table 1 and 2. All patients received either prophylactic, or double prophylactic doses of thromboprophylaxis with nadroparin (low molecular weight heparin (LMWH)) which was switched to therapeutic unfractionated heparin when the diagnosis of PE was confirmed.

Table 1. Baseline characteristics

Patient characteristics	
Mean Age, year (SD)	63 (6.6)
Male, n(%)	16 (84)
Mean body mass index, kg/m^2 (SD)	27.5 (2.8)
Thrombosis prophylaxis when admitted at ICU	
- Prophylactic, n (%)	16 (84.2)
- Double prophylactic, n (%)	2 (10.5)
- Therapeutic, n (%)	0 (0)
- Unknown, n (%)	1 (5.3)
Status at 28 days after admission	
- ICU, n (%)	9 (47.4)
- Hospital, n (%)	5 (26.3)
- Death, n (%)	2 (10.5)
- Rehabilitation, n (%)	1 (5.3)
- Home, n (%)	1 (5.3)
- Other, n (%)	1 (5.3)

Table 2. Radiological and laboratory characteristics

Radiological presentation	
Qanadli index first CT, mean (%) ±SD	17.5 (±10.8)
Location pulmonary embolism on first index CT	
- Subsegmental, n(%)	2 (10.5)
- Segmental, n(%)	16 (84.2)
- Main/lobar, n(%)	1 (5.3)
Patients with follow-up CT	6
Qanadli index first follow-up CT	
- 0% (n)	5
- 5% (n)	1
D-dimers	
D-dimers day -2 Median + IQR	5379 ng/mL (2460-10604)
D-dimers day -1 Median + IQR	5555 ng/mL (4317-9769)
D-dimers day 0 Median + IQR	6197 ng/mL (4682-9360)
D-Dimers day 1 Median + IQR	4766 ng/mL (3047-7773)
D-dimers day 2 Median + IQR	3665 ng/mL (2470-5437)

Radiological outcome

The mean Qanadli index of the CT-scans before start of heparin was 17.5% (SD 10.8%), with the segmental artery being the most frequent location of the thrombi. Follow-up CT-scans were performed in 6 patients with an average follow-up of 18 days. The Qanadli index decreased significantly from baseline to follow-up (p=0.03 for difference with baseline CT-scan). A Qanadli index decrease to 0% was observed in 5 patients and a decrease to 5% was seen in the remaining patient. Two patients had a third follow-up CT-scan. In one patient there was already no remainder of PE on the first follow-up CT-scan and in the other patient the CT-scan remained stable with a Qanadli index of 5% at 25 days. Both were still receiving heparin at the time of the second follow-up CT-scan.

Clinical outcome

In at least 14 (74%) patients, UFH treatment was successful: in 6 patients (32%) PE was found to be completely resolved on follow-up CT, whereas 8 patients (42%) were discharged from the ICU following clinical improvement. One patient died in the ICU without follow-up CT-scan to evaluate treatment. From the remaining 4 (21%) patients it is unknown whether treatment was successful, because they were transferred to another ICU.

At 28 days after admission 9 (47,4%) patients were still in the ICU (including 3 of the 4 patients that were eventually transferred to another ICU), 7 (36.8%) patients were discharged from the ICU to either the nursing ward (n=5, 26.3%), a rehabilitation center (n=1, 5.3%) or home (n=1, 5.3%). In total, 2 (10.5%) patients died (of which 1 had clinical improvement on the follow-up CT) in the ICU and 1 (5.3%) was transferred to another ICU.

In our cohort, 6 patients (32%) suffered from bleeding complications, of which 2 patients (10.5%) were classified as severe bleeding. These severe bleedings were located in the lung (n=1) and the lower gastrointestinal tract (n=1). None of these bleedings resulted in death.

Laboratory outcome

D-dimer levels from all patients from approximately 2 days before the start of heparin until 21 days after start heparin or until ICU-discharge are shown in Figure 2. The percentage change of D-dimer levels in relation to start of heparin per 24-hours period from two days before UFH to 2 days after start of UFH are shown in Figure 3. All blood samples used to determine D-dimer levels were taken at 6 AM. Therefore T=0 in this graph represents the D-dimer taken at 6 AM at the day UFH was started. The actual start of UFH varied for every patient. Mean start of heparin was 9 hours (SD 4.9) after blood sampling. From the first time point, from day -2 to day -1, the D-dimer dropped

on average 6.7% (SD 26.9) after which, from day -1 to day 0, it increased 5.6% (SD 25.6). The first day after start of UFH, a mean drop of 17.9% (SD 19.4) and the second day a drop of 14.6% (SD 15.9) was seen. The average D-dimer at day 0 was 7074ng/mL compared to 4347ng/mL at day 2 (p=0.001). The mean difference from day 0 to day 2 was -2810ng/mL (95%CI -721 ng/mL to -4347 ng/mL).

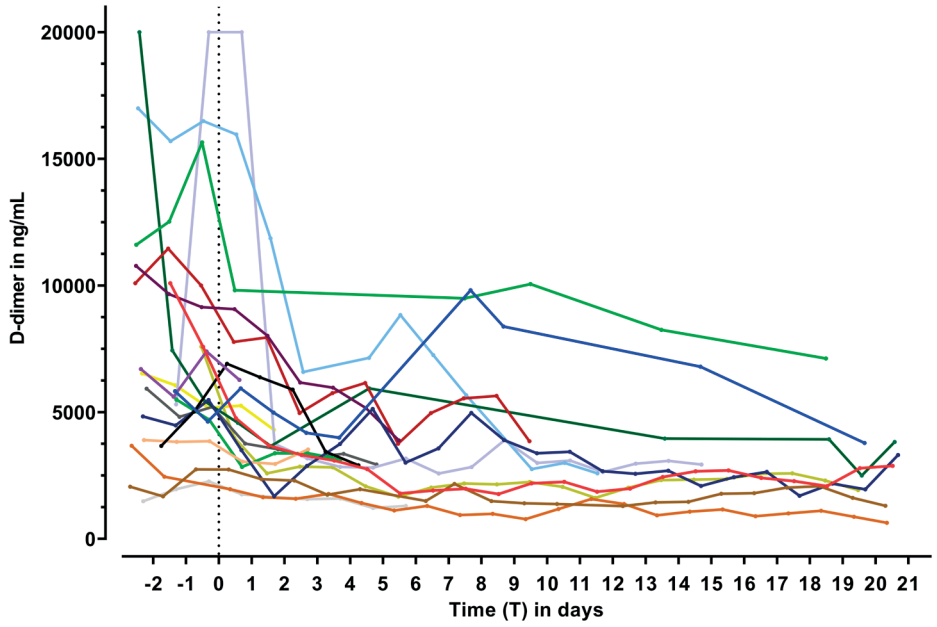

Figure 2. Course of D-dimers before and after start of heparin. D-dimer levels from 2 days before the start of UFH until 21 days after start of UFH or until ICU discharge are shown. T=0 represents the start of heparin for each individual patient, which is marked by the dotted line.

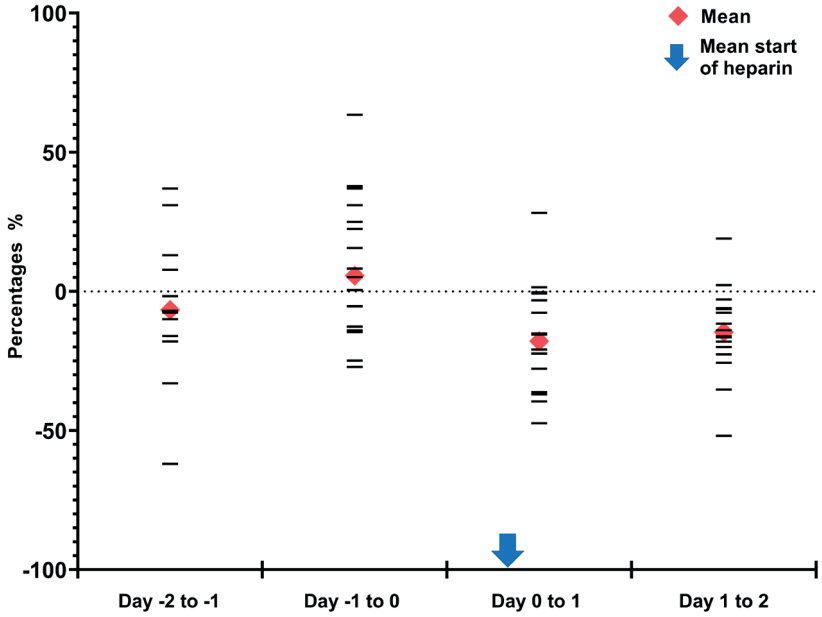

Figure 3. Percentage change of D-dimer levels for different time frames before and after start of heparin. All samples were taken at 6:00 A.M. For every patient T=0 represents the time of blood sampling at 6:00 AM of the day that heparin was started. The horizontal lines represent the percentage change in that time frame for each individual patient. The arrow represents the mean actual time of start of heparin.

DISCUSSION

In this study we show that clinical and radiological signs of PE and plasma D-dimer levels decreased after administration of UFH in patients with COVID-19 and PE. This is the first study on the effect of heparin (either UFH or LMWH) on thrombosis in COVID-19 patients. Earlier, Tang and others (13) studied the effect of LMWH in 449 COVID-19 patients. They found an association between increasing D-dimer and higher mortality in non-LMWH treated patients. Also, a reduced mortality was seen in patients with coagulopathy who were treated with LMWH compared with patients with coagulopathy who were not treated with LMWH (40% vs 64.2%, p=0.029). However, the effect of UFH on D-dimer levels or PE resolution was not reported.

Despite the fact that our results suggest that therapeutic UFH is an effective treatment of COVID-19 associated PE, thrombo-embolic complications are common despite prophylactic LMWH (3, 14). An explanation for this might be the route of administration or the dose. Giving subcutaneous LMWH prophylaxis in the ICU might lead to lower

anti-Xa activity by the concurrent use of vasoconstrictors such as norepinephrine (15). Norepinephrine was also administered in most COVID-19 patients in the ICU (data not shown). Furthermore, prophylactic doses of LMWH are lower than therapeutic doses and result in lower anti-Xa activity. Consequently, anticoagulant effects will be lower and may be insufficient to prevent PE. It is currently unknown if increasing the doses of LMWH would be beneficial in preventing thrombotic complications in COVID-19 patients. Some authors suggest to treat severe COVID-19 pneumonia, even without serious obstructive signs of pulmonary embolism, with thrombolysis in order to improve oxygenation (16). However, our results show that those measures are not necessary: regular treatment is effective and can resolve PE on short notice. Therefore we support current guideline recommendations to reserve thrombolysis to patients with high-risk PE and apply standard dose thromboprophylaxis.

There have been concerns about a high incidence of Chronic Thrombotic Pulmonary Hypertension (CTEPH) after COVID-19 associated PE, in particular because inflammatory states have been associated with poor thrombus resolution.(17, 18). Although our sample size is small, the rapid clot resolution observed in our study suggests that the incidence of CTEPH in COVID-19 associated PE survivors may not be notably increased. Even so, physicians should remain vigilant on the presence of CTEPH in patients treated for COVID-19 associated PE who have not been recovered after a 3-month follow-up period.

In our study population with UFH, 6 out of 19 patients experienced bleeding complications with 2 severe bleeding episodes. To properly outweigh the risk of bleeding and the risk of thrombosis, properly designed randomized controlled trials (RCTs) are needed to establish the optimal dose and route of administration for COVID-19 patients. Currently, several RCTs are underway (19).

Our study had several limitations. The change in D-dimer levels may have been influenced by other factors than administration of UFH. A fall in D-dimer may for instance also reflect an improvement of the inflammatory state. In this uncontrolled observational study we cannot exclude confounding by factors modifying the severity of illness. Therefore, the decline in D-dimers that we found in the two days after start of heparin could also be caused by clinical improvement in general. Another limitation is the limited sample size of 19 patients with only 6 patients having had a follow-up CT scan. Strongpoints of the study include the strict protocol in our ICU dictating repeated CT-scanning if no improvement of pulmonary status was present after one week of treatment of UFH, and the meticulous comparison of index and follow-up CTPA scan images.

CONCLUSION

In conclusion, we show a considerable clinical and radiological improvement in patients with COVID-19 and proven PE after starting UFH therapy. Standard anticoagulant treatment therefore seems to be effective in this setting, supporting current guideline recommendations.

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Elevated Unfractionated Heparin Requirement in COVID-19 patients:

exploring influencing factors

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Submitted

Supplemental digital content of this article is available upon request

ABSTRACT

Objectives

It has been reported that in patients with COVID-19 associated pulmonary embolism high doses of unfractionated heparin (UFH) are required to achieve activated partial thromboplastin time (APTT) levels within the therapeutic range. The aim of this study was to compare the UFH dose in ICU patients with COVID-19 and control ICU patients and to explore possible explanatory factors.

Design

Retrospective cohort study

Setting

ICU in Leiden University Medical Center in the Netherlands

Patients

COVID-19 patients admitted to the ICU between March 15 2020 and January 1st 2022, and control patients admitted to the ICU between January 1st 2014 and January 1st 2020

Intervention

All patients had an indication for therapeutic UFH. Primary endpoint was the UFH dose given. A mixed linear model was used to assess the relationship between APTT and UFH dose, antithrombin (AT), CRP and BMI.

Measurements and main results

COVID-19 patients received a median UFH dose of 383 (IQR, 303-461) international units (IU) per kilogram per day (IU/kg/day) compared to 308 IU/kg/day (IQR, 253-387 in controls ($p<0.001$). Median APTT was 63 sec (IQR, 53-68) for COVID-19 patients and 66 sec (IQR, 60-70) for controls ($p<0.001$). Overall, median CRP was lower (67 mg/l, IQR 18-145 vs 103 mg/l, IQR 56-180) and median AT values were higher (92%, IQR 78-104 vs 71% IQR, 62-84) in COVID-19 patients. In the mixed linear model, only UFH dose showed a significant relationship with APTT ($p=0.0316$).

Conclusion

COVID-19 patients were administered higher UFH doses but had lower APTT values compared to controls. Lower APTT values could not be explained by either BMI, CRP, or AT levels. Other patient-related factors may account for the difference in heparin administration.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has seriously impacted global public health, leading to more than 750 million infections and almost 7 million deaths (1). Severe cases often involve pulmonary inflammation, necessitating mechanical ventilation and extended intensive care unit (ICU) stay. Patients with COVID-19 may exhibit a prothrombotic state, with venous and arterial thrombotic complications despite receiving adequate thromboprophylaxis (2, 3).

The coagulation activation in COVID-19 differs from the disseminated intravascular coagulation (DIC) seen in sepsis. COVID-19 patient generally have high D-dimer levels but, contrary to patients with DIC, normal platelet and coagulation tests, with CT scans showing pulmonary embolism (PE) mainly in peripheral lung segments, indicating a unique coagulation mechanism (3, 4). Critically ill patients with COVID-related PE are often treated with unfractionated heparin (5). It has been reported that high doses of unfractionated heparin (UFH), often higher than 35000 IU per day, are required to achieve activated partial thromboplastin time (APTT) levels within the therapeutic range (6).

It has been shown that APTT can be impacted by a wide range of preanalytic, analytic or biological factors (7). For instance, during UFH administration elevated levels of FVIII and fibrinogen, along with decreased antithrombin (AT) can shorten APTT levels, while increased CRP, lupus anticoagulants or decreased levels of clotting factors secondary to liver disease can all prolong APTT (7-11). Anti-Xa activity is less affected by the previous mentioned factors, but high antiphospholipid antibody titers can increase measured anti-Xa activity (8). High FVIII, fibrinogen, CRP, and antiphospholipid antibodies as well as low AT hallmarks of COVID-19 coagulopathy, potentially influence UFH dosing (12-14).

The aim of our study was to compare the administered doses of UFH in patients with COVID-19 related PE with a historical cohort of ICU patients treated with UFH for venous thromboembolic disease not related to COVID-19. Furthermore, factors that could explain these differences were explored.

MATERIAL AND METHODS

This retrospective observational cohort study was conducted at ICU of the Leiden University Medical Center (LUMC) in the Netherlands and included two cohorts of patients. The first cohort consisted of all consecutive patients who were admitted to the ICU between March 15, 2020 and January 1st, 2022 for COVID-19 respiratory

failure and treated with UFH for pulmonary embolism. The second cohort included patients admitted to the same ICU between January 1st 2014 and January 1st 2020 who were treated with UFH for venous thromboembolic disease not related to COVID-19. This study was approved by the Institutional Review Board of the LUMC for COVID-19 studies on March 24th 2022, and was registered on clinicaltrials.gov under number NCT05509647. The requirement for informed consent was waived by the medical ethics committee (reference number: CoCo 2022-020, approval date: 24-09-2022) and the study was conducted in accordance with the Declaration of Helsinki.

Patients

Inclusion criteria for the COVID-19 group were as follows: a confirmed COVID-19 diagnosis proven by PCR of nose- or airway sample, admitted to the ICU between March 15, 2020, and January 1st, 2022, aged 18 years or older, and receiving UFH treatment targeting an APTT range of 60-80 seconds and anti-Xa level of 0.3-0.5 IU/ml. For the control group, inclusion criteria were: admitted to the ICU between January 1st 2014 and January 1st 2020, aged 18 years or older, and receiving UFH treatment for any indication targeting an APTT range of 60-80 seconds. Patients who were treated with anticoagulants other than UFH or fibrinolytic agents were excluded from both groups.

Measurements

Data was collected for the entire period patients received UFH therapy. General information on ICU length of stay, hospital length of stay, ICU mortality, hospital mortality, admission type, acute diagnosis, chronic diagnosis, and the use of vasoactive drugs were extracted from the Dutch National Intensive Care Evaluation (NICE) registry database (15). Data on sex, age, BMI, ICU admission and discharge date, anti-Xa (when available), and APTT every 8 hours with corresponding UFH dose were extracted from the electronical medical patient record. Additionally, both CRP and AT levels were measured routinely in COVID-19 patients, but only measured if indicated in control patients. The APTT assays were performed using STA Cephascreen reagent on the STA-R (Evolution) analyser from 2014 to 2017, and the STA-R Max analyser from 2017 to present (STA series: Diagnostica Stago, Asnières-sur-Seine, France). The anti-Xa assays were performed using Chromogenix anti-Xa reagent (Werfen, Barcelona, Spain) on the the STA-R (Evolution) analyser from 2014 to 2017, and from 2017 to 2022 using STA Liquid anti-Xa reagent on the STA-R Max analyser (STA series: Diagnostica Stago, Asnières-sur-Seine, France). Antithrombin activity was analyzed using Chromogenix Coamatic Antithrombin reagent (Werfen, Barcelona, Spain) on the STA-R Evolution analyser from 2014 to 2017, and from 2017 to 2022 using STAChrom AT III reagent on the STA-R Max analyser (STA series: Diagnostica Stago, Asnières-sur-Seine, France). CRP was analyzed using Tinaquant C-Reactive Protein reagent on a Roche Modular

from 2014 to 2017 and from 2017 onwards on a Roche Cobas 8000 analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

Treatment procedures

Patients with confirmed thrombosis or embolism were all treated with intravenous UFH during the complete study period. The detailed UFH dosing protocol can be found in appendix 1. Patients received a loading dose of 70 IU/Kg (max 5000 IU) and a starting dose of 300 IU/kg/24 hours (max 30.000 IU/24 hours). The target APTT was established at 60-80 seconds and APTT was checked every 8 hours. When APTT measurements fell outside the target range, doses were adjusted based on the provided dosing schedule and pump setting adjustments that can be found in appendix 1. Because of apparent difficulties in reaching the target APTT range in COVID-19 patients additional monitoring of anti-Xa levels in addition to APTT, was standard procedure in the cohort of COVID-19 patients, but not in controls. Details on the influence of anti-Xa values on dosing of UFH in COVID-19 patients can be found in appendix 2.

Statistical analysis

All statistical analysis were performed using R language and environment (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3). Descriptive statistics were used to summarize patient demographics, with comparisons made using unpaired t-tests or Mann-Whitney U tests for continuous variables and Chi-square test for categorical variables.

Our primary endpoint, median UFH dose, was presented as median with interquartile range (IQR). For secondary endpoints, continuous variables were reported as median with IQR. Differences between groups were assessed using a Mann-Whitney U test. The concordance between APTT and anti-Xa was presented using a cross-tabulation with absolute numbers and percentages. Given that APTT values outside the range of 60-80 seconds may reflect the initial titration phase of treatment, we also performed a subgroup analysis focused on cases with APTT levels within the 60-80 range. The lme4 package (Bates, Maechler and Bolker, 2012) in R studio was used to perform a linear mixed effects analysis of the relationship between APTT and various clinical factors. As fixed effects we entered UFH dose, CRP, BMI and AT and as random effects we added intercepts for individual subjects in order to adjust for inter-patient correlation due to repeated measurements. The Restricted Maximum Likelihood (REML) method was employed for model fitting, and the distribution of scaled residuals was examined to validate model assumptions. R2 was calculated to evaluate the predictive value of the model using the performance package (Lüdecke, Ben-Shachar, Patil, Waggoner and Makowski, 2021) in R studio. The linear mixed model was based solely on APTT values ranging from 60 to 80, as values outside this range were considered less

reliable because extreme APTT values, either low or high, are frequently encountered during the adjustment phase of treatment and including these values could potentially compromise the reliability of the model.

Table 1. Patient characteristics. Abbreviations: UFH, Unfractionated Heparin; SAPS, Simplified Acute Physiology Score; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

Variables	COVID-19 patients (N=162)	Control patients (N=1006)	P-value
Age (mean (SD))	64 (10)	62 (14)	0.022
BMI (mean (SD))	29 (4)	27 (6)	<0.001
Sex = Female (%)	33 (20)	342 (34)	0.001
ICU length of stay (days) (median (IQR))	15 (10, 29)	8 (3, 19)	<0.001
Hospital length of stay (days) (median (IQR))*	21 (13, 34)	23 (10, 44)	0.619
Duration of UFH therapy (days) (median (IQR))	9 (5, 18)	5 (2, 11)	<0.001
ICU mortality (%)*	58 (36)	254 (25)	0.011
Hospital mortality (%)*	62 (38)	320 (32)	0.183
SAPS II score (median (IQR))*	45 (35, 59)	43 (33, 55)	0.049
Type of admission*, No. (%)			<0.001
Medical	160 (99)	559 (57)	
Emergency surgery	1 (1)	141 (14)	
Elective surgery	1 (1)	282 (29)	
Acute diagnosis*‡, No. (%)			<0.001
Cardiac (including cardiac surgery)	3 (2)	496 (51)	
Sepsis	0 (0)	53 (5)	
Gastrointestinal	0 (0)	94 (10)	
Pneumonia	157 (97)	77 (8)	
Respiratory (other)	2 (2)	124 (12)	
Neurologic	0 (0)	24 (2)	
Trauma	0 (0)	10 (1)	
Transplant	0 (0)	52 (5)	
Other	0 (0)	52 (5)	
Chronic diagnosis*§, No. (%)			
Chronic kidney failure	7 (4)	138 (14)	0.001
Chronic dialysis	0 (0)	32 (3)	0.038
Metastasized neoplasm	2 (1)	25 (3)	0.460
COPD (drug dependent)	8 (5)	68 (7)	0.441
Chronic respiratory insufficiency	6 (4)	27 (3)	0.675
Cardiovascular insufficiency (NYHA IV)	2 (1)	79 (8)	0.003
Liver cirrhosis	1 (1)	43 (4)	0.037
Diabetes	32 (20)	210 (21)	0.713
Haematological malignancy	0 (0)	24 (2)	0.086
Immunological insufficiency	1 (1)	52 (5)	0.015
Vasoactive drugs at ICU admission	128 (79)	779 (79)	1

*Data was missing for 24 patients in the Control group.
‡ Acute diagnosis is classified according to the APACHE IV model
§ More than one chronic diagnosis can be present in the same patient

RESULTS

All 162 consecutive COVID-19 patients and 1006 control patients were included in this study. Patient characteristics are shown in Table 1. Hospital length of stay and hospital mortality were comparable between groups, yet COVID-19 patients were older with a higher BMI and Simplified Acute Physiology Score (SAPS), were more often male, had longer ICU stays, and higher ICU mortality. Furthermore, COVID-19 patients were administered UFH for a median of 9 days (IQR, 5-18), while control patients received UFH for a median duration of 5 days (IQR, 2-11) (p<0.001).

Measurements

The analysis included 7372 APTT measurements in 162 COVID-19 patients and 30946 measurements in 1006 control patients. Median APTT values were 63 sec (IQR, 53-68) for COVID-19 patients and 66 sec (IQR, 60-70) for controls (p<0.001). Median anti-Xa for COVID-19 patients was 0.5 U/ml (IQR 0.4-0.6) (not available in controls). Median UFH dose was 383 (IQR, 303-461) international units (IU) per kilogram per day (IU/kg/day)) in the COVID-19 group and 308 IU/kg/day (IQR, 253-387) in controls (p<0.001). Median CRP was 67 mg/l (IQR, 18-145) for COVID-19 and 103 mg/l (56-180) for controls (p<0.001), and median AT levels were 92% (78-104) for COVID-19 (N=118) and 71% (62-84) for controls (N=18) (p<0.001).

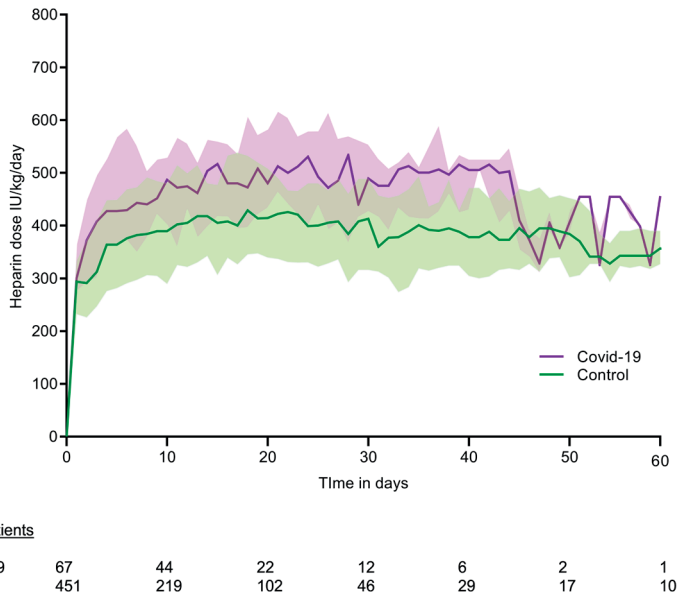

Figure 1. Heparin administration over time. Values represent the median of median values per day per patient. Heparin dosages were only included when APTT was within therapeutic range (60-80 sec).

Measurements within therapeutic range of APTT 60-80

A subgroup analysis only including episodes with APTT 60-80 sec included 3154 measurements in 151 COVID-19 patients and 18450 measurements in 868 control patients. Median APTT values were 68 sec (IQR, 66 – 70) in both the COVID-19 and control group (p=0.5), with a median anti-Xa of 0.6 U/ml (IQR, 0.4-0.9) in the COVID-19 group (not available in controls). The corresponding median UFH dose was 399 IU/kg/day (IQR 330-490) and 330 IU/kg/day (IQR, 267-419) in COVID-19 and control patients (p<0.001, fig 1). Median CRP was lower in COVID-19 patients at 82 mg/l (IQR, 29-150), compared to 103 mg/l (IQR 60-180) in controls (p<0.001). Median AT values were 89% (IQR, 18-145) for COVID-19 (N=97) and 67% (IQR, 56-180) for controls (N=12) (p<0.001).

APTT vs anti-Xa

The distribution of APTT and anti-Xa levels in COVID-19 patients is shown in Figure 2. In table 2, the concordance of APTT and anti-Xa is shown. Concordant APTT and anti-Xa values were observed in 31% of the cases, namely when both APTT and anti-Xa were low (556/4167), both in target (525/4167) or both high (190/4167). In 1471 episodes, APTT was within the therapeutic target-range. In 190 of these cases (13%), anti-Xa was less than 0.3 U/ml, fulfilling the criteria of the local protocol to increase the dose of UFH, and in 756 (51%) anti-Xa was above 0.5 IU/ml, fulfilling the criteria to decrease the dose.

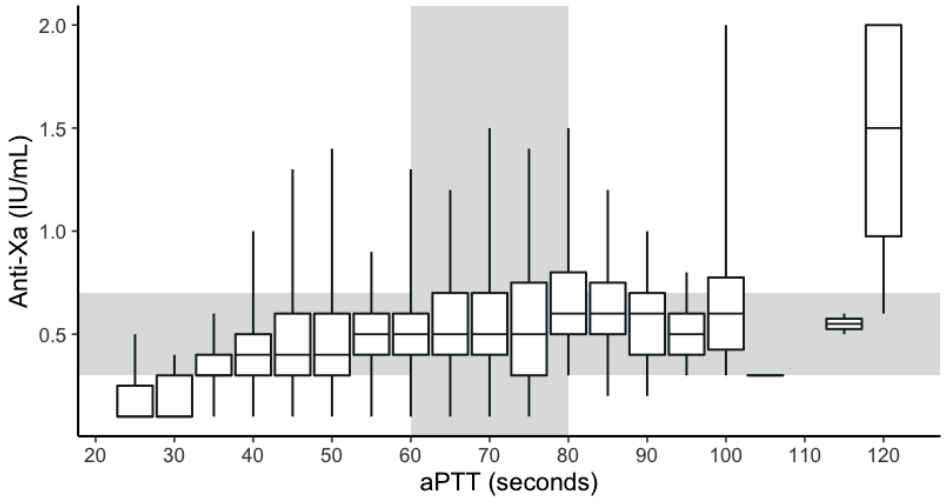

Figure 2. Distribution of APTT and anti-Xa levels in patients with COVID-19. The faded areas represent the ranges for APTT and anti-Xa that were considered 'therapeutic anticoagulation' at the study site (60-80 seconds for APTT, and 0.3-0.5 IU/mL for anti-Xa).

Table 2. Relationship between anti-Xa and APTT values in COVID-19 patients. The gray field indicates that both APTT and anti-Xa measurements were concordant, either falling below, within or above the respective target values.

Categories	Total	anti-Xa <0.3 IU/mL	anti-Xa 0.3-0.5 IU/mL	anti-Xa > 0.5 IU/mL
APTT <60	2392 (100%)	556 (23%)	1066 (45%)	770 (32%)
APTT 60-80	1471 (100%)	190 (13%)	525 (36%)	756 (51%)
APTT >80	304 (100%)	23 (8%)	91 (30%)	190 (63%)
Total	4167	769	2785	613

Association APTT and various clinical factors

A linear mixed model was applied to describe the association between APTT and UFH, CRP, BMI and AT, adjusting for individual differences (cluster effect). The full output of the model can be found in appendix 3. UFH demonstrated an association with APTT (p=0.02). Other potential predictors, including CRP (p=0.1), BMI (p=0.9), and antithrombin (p=0.3) were not associated with APTT. Individual differences, that could not be explained by CRP, AT, BMI, accounted for a substantial proportion of the variability in the model (Variance = 2.429, SD = 1.559). Conditional R2 (0.111) and Marginal R2 (0.030) were both low, indicating that a relevant proportion of the variability in APTT is not explained by the model. The differences between the observed APTT and the predicted APTT for COVID-19 patients can be observed in figure 3.

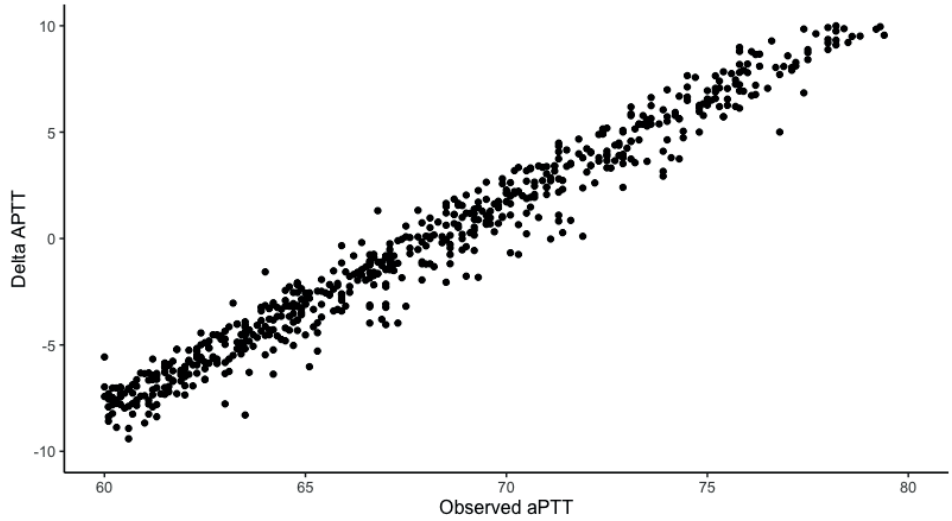

Figure 3. Observed APTT versus the delta APTT in a selection of measurements with APTT between 60 and 80 sec. Delta APTT was calculated as the observed APTT minus the predicted APTT. The mean delta APTT was -0.7 sec with a standard deviation (SD) of 5.4 sec. The model to predict APTT was developed in patients/measurements with APTT between 60 and 80 sec.

DISCUSSION

In this retrospective observational study we show that substantially higher UFH doses were administered to ICU patients with COVID-19 associated pulmonary embolism compared to ICU patients treated with heparin for other indications. This is in accordance with earlier studies reporting that COVID-19 patients may require heparin doses above the conventional therapeutic amounts, often fulfilling the criteria for heparin resistance, in these studies defined as an UFH dose exceeding 35.000 IU/24 hours while APTT is in the therapeutic range (6, 14, 16).

There are several potential explanations for the higher heparin requirements in patients with COVID-19. First, it could be that physicians target at a higher level of anticoagulation in COVID-19 patients. In our cohort, this appears an unlikely explanation. Both COVID-19 and control patients were treated using the same protocolized target range for APTT. In fact, APTT levels were slightly lower in COVID-19 patients compared to non-COVID ICU patients. Furthermore, when selecting only patients within the therapeutic APTT range, the difference in dosing of UFH between COVID and non-COVID patients was even more marked. Another potential explanation is the difference in protocol for dosing of heparin in COVID-19 patients. In contrast to the control population, not only APTT but also anti-Xa levels were measured. Thus, not only low APTT levels, but also low anti-Xa levels could have led to higher heparin doses. However, it is unlikely that additional monitoring of anti-Xa has led to higher heparin doses in our patients. In patients within the therapeutic APTT range, it was much more common that anti-Xa was higher than that it was lower than the target range of 0.3-0.5 IU/ml. Third, higher doses of heparin could also be explained if body mass was higher in patients with COVID-19. Indeed, body mass index was higher in patients with COVID-19, but the difference was limited. Also, in our mixed linear model on factors associated with APTT, BMI was not a relevant predictor. Thus, we conclude that it is highly unlikely that differences in body weight explain our findings.

From the literature, it is well known that higher plasma levels of CRP (6, 14, 16) prolong APTT depending on the type of reagent used. In addition, low AT levels may give rise to heparin resistance and consequently shorter APTT during heparin therapy. Thus, if CRP and /or AT plasma levels were lower in COVID-19 patients, that could be an explanation for relatively short APTT values and consequently lead to higher administered doses of heparin. In our patients with COVID-19 CRP was indeed lower, but AT levels were higher than in control patients. In our mixed linear model, neither CRP nor AT predicted APTT. Thus, there are several reasons why AT and CRP should not be considered as important factors influencing heparin dosing in COVID-19 patients.
As indicated by the low R2 our mixed linear model to describe the association between

APTT and heparin, CRP, AT, and BMI could only explain a small part of the variability of APTT values. Clearly, some other factors must have important influence. We can only speculate what these factors could be. It is known that COVID-19 patients may have a markedly hypercoagulable state, possibly explained by the acute phase response with high factor VIII and fibrinogen levels (9, 11, 17). Indeed, from the literature, we know that factor VIII may be very high in COVID-19 patients (18-20). Unfortunately, in our cohorts, factor VIII and fibrinogen levels were not measured.

In this study, heparin therapy in ICU patients was monitored primarily based on APTT values. In COVID-19 patients, anti-Xa may be more reliable than APTT to monitor UFH therapy (21). In our cohort, when APTT was in the therapeutic range, anti-Xa was higher than 0.5 IU/ml in 51% of measurements. Thus, it appears that monitoring based on APTT may lead to higher doses of UFH than dosing based on anti-Xa. It is possible that higher doses of heparin may lead to an increased risk of bleeding complications (22). A randomized controlled study comparing monitoring UFH with APTT versus anti-Xa in patients with venous thrombosis showed that monitoring based on anti-Xa led to lower doses of administered UFH but without a difference in efficacy or in bleeding complications (23). Unfortunately, in our study data on bleeding complications are not available.

Some limitations of this study should be discussed. Firstly, there were some baseline differences between the two groups. We did not have information on the specific indications for UFH use in individual patients. Whereas pulmonary embolism was the indication for UFH in all COVID-19 patients, in control patients different indications may have been present. Due to the retrospective design, some data, such as information on factor VIII and fibrinogen were not available. Also, different analyzers and methods were used to perform APTT, anti-Xa and antithrombin assays before and after 2017 which may have influenced those measurements in the non-COVID-patients. Since the same APTT reagents were used in both periods, the effect of a different analyzer on the APTT measurement is likely to be minimal. In our data, the median APTT values and UFH dose before and after 2017 were the same. Lastly, not all our findings may be generalizable for other ICUs due to specific local treatment protocols. It is unknown if differences in dosing between COVID-19 and non-COVID patients would still exist if only anti-Xa was used for monitoring of heparin effects. Also, our findings apply for patients treated with UFH, not with LMWH, and AT levels were not available in the majority of the patients.

In conclusion, our data shows a higher UFH dose in COVID-19 patients compared to a historical cohort of ICU patients. Despite a higher UFH dose, APTT values were lower in COVID-19 patients. The lower APTT values could not be explained by either CRP,

BMI, AT, or the additional use of anti-Xa in addition to APTT monitoring. Likely, some other factors may account for this difference in heparin administration. Based on the literature, we hypothesize that higher factor VIII or fibrinogen levels in COVID-19 patients may play a role but this should be investigated in future research.

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PART III

PAIN MANAGEMENT

Intraoperative use of the machine learning-derived nociception level monitor results in less pain in the first 90 min after surgery

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ABSTRACT

Severe postoperative pain remains a significant problem and associates with several adverse outcomes. Here, we determined whether the application of a monitor that detects intraoperative nociceptive events, based on machine learning technology, and treatment of such events reduces pain scores in the post-anesthesia care unit (PACU). To that end, we performed a pooled analysis of two trials in adult patients, undergoing elective major abdominal surgery, on the effect of intraoperative nociception level monitor (NOL)-guided fentanyl dosing on PACU pain was performed. Patients received NOL-guided fentanyl dosing or standard care (fentanyl dosing based on hemodynamic parameters). Goal of the intervention was to keep NOL at values that indicated absence of nociception. The primary endpoint of the study was the median pain score obtained in the first 90-min in the PACU. Pain scores were collected at 15-min intervals on an 11-point Likert scale. Data from 125 patients (55 men, 70 women, age range 21-86 years) were analyzed. Sixty-one patients received NOL-guided fentanyl dosing and 64 standard care. Median PACU pain score was 1.5 points (0.8-2.2) lower in the NOL group compared to the standard care; the proportion of patients with severe pain was 70% lower in the NOL group ($p = 0.045$). The only significant factor associated with increased odds for severe pain was the standard of care compared to NOL treatment (OR 6.0, 95% CI 1.4 -25.9, $p = 0.017$). The use of a machine learning-based technology to guide opioid dosing during major abdominal surgery resulted in reduced PACU pain scores with less patients in severe pain.

INTRODUCTION

Improvement of postoperative pain remains a challenging task for all involved in surgical patient care. A large number of patients still experiences moderate to severe postoperative pain despite the use of several analgesic techniques including multimodal pharmacological protocols, neuraxis and nerve blocks and various nonpharmacological interventions (e.g. music therapy, cold packs, distraction) (1-3). In addition to causing patient distress and anxiety, postoperative pain is associated with delayed discharge, increased morbidity, persistent pain and prolonged consumption of opioids (4-7). One approach to improve postoperative pain scores may be to modify anesthetic practice, i.e. to dose analgesic medication based on the nociceptive state of the patient rather than by using a fixed protocol based on hemodynamic measurements. In other words, we postulate that personalized management of nociceptive events during surgery may associate with improved postoperative pain scores, particularly in the post-anesthesia care unit (PACU). To this end, a novel monitor, the Nociception level (NOL), was developed with machine learning technology, that reliably tracks the patient nociceptive state and prompts analgesic dosing when the objective measure of nociception is high (9-13). We define nociception during surgery as "the central modulation of stimuli from surgical tissue damage into behavioral, autonomic and hormonal responses" (10). Note that the behavioral component of nociception (e.g. movement or a withdrawal response) is not detected during general anesthesia, particularly not when muscle relaxants are administered. Hormonal responses (see for example Fig. 4 in Ref. 13) may be measured in blood but are often only available at later times. Hence, the autonomic response us used to detect heightened nociception during clinical practice, however its sensitivity and specificity is often not optimal (10,11).

The NOL is a nonlinear multiparameter that measures nociception from the following parameters: heart rate, heart rate variability amplitude of the finger photoplethysmogram, skin conductance level and their time derivatives, with greater sensitivity and specificity than either parameter alone (9-11). Random forest analysis was used to create the NOL index. This machine learning technique uses the combination of multiple variables of different origin to discover their intricate nonlinear linkages without the need for a description of a stochastic data model. The NOL scale has a range from 0 to 100, i.e. from no nociception to extreme nociception. Validation studies showed with confidence that a NOL value of 25 distinguishes between non-nociceptive (NOL < 25) and nociceptive events (NOL > 25) (10-12). Therefore, the observation of NOL values that are greater than 25 (for at least 1-min) requires treatment with an analgesic drug such as an opioid, while values that are below 25 necessitate either no action or the reduction of analgesic medication that is administered continuously. Treatment is then independent of measured blood pressure and heart rate.

To strengthen our knowledge on the relationship between NOL-guided analgesic dosing during surgery and postoperative pain scores, we conducted a pooled analysis of two independent, randomized, controlled trials that compared the influence of intraoperative NOL-guided fentanyl to standard of care (SOC) on postoperative pain (13,14). The two studies were equivalent with respect to study protocol and had common efficacy measures (Supplemental Digital Table 1). The results of both studies were that NOL-guided fentanyl dosing during surgery reduces pain scores in the post-anesthesia care unit (PACU) by 1.4-1.5 pints on an 11-point pain scale (from 0 = no pain to 10 = most severe pain imaginable). While the two studies had an identical design they evaluated 50 patients with predominantly surgical patients in the first study (SOLAR), 13 and 75 patient with an almost equal distribution among three surgery types (surgical 33%, urology 30% and gynecology 37%) in the second one (AbdomiNol) (14). The pooling enables to evaluate the effect based on larger sample size with better representation of surgery type, enables us generalizing results to a wider context especially identifying the specific patient populations that benefit from NOL-guided analgesia and leading to improved power to detect whether postoperatively there is less pain following NOL-guided fentanyl dosing. Moreover, the enlarged sample size enables a multivariable model to identify the effect of NOL on severe pain adjusted for confounders (15), such as age, gender, BMI, Surgery type, ASA and Site and revealing the only factor significantly related is the NOL. Finally, the pooling of data allowed us to analyze the three pain cohorts: intense, moderate and sever pain. We contend that our strategy will eventually lead to an improvement of pain in the PACU and all of its sequelae.

METHODS

This is pooled analysis of two earlier conducted and published trials with a similar protocol, the SOLAR trial and the Abdomi-Nol trial (13,14). Both studies were prospective, double-blind (the patients and nurses who scored and treated the pain were unaware of the intraoperative treatment), parallel, randomized controlled trials on intraoperative nociception monitoring-guided opioid administration with primary endpoint median pain score in the first 90 min in the PACU and were conducted independently. The Abdomi-Nol study was designed to be confirmatory to the SOLAR trial. The SOLAR trial was conducted at two sites, a tertiary university center and a secondary referral center, both in the Netherlands (13). The Abdomi-Nol study was performed in a tertiary center in Israel (14).

Both studies utilized the PMD-200 nociception monitor, manufactured by Medasense Biometrics Ltd. (Ramat Gan, Israel). The device integrates several physiological variables that are known indicators of sympathetic activity to provide a single index of

nociception, the NOL index. The PMD-200 sensing unit consists of a finger probe with four distinct sensors: photoplethysmogram, galvanic skin response, accelerometer, and a thermistor. The information from the accelerometer and the thermistor are used as a guardrail to ensure the algorithm performance but is not directly incorporated into the NOL calculation. Thousands of samples of these physiological variables (including heart rate, heart rate variability, vaso-constriction, and sweating) and their derivatives were recorded during major surgery of adult anesthetized patients and were annotated by expert clinicians for stimuli intensity and level of analgesia. These data were then used to train a random forest machine learning model, which is at the heart of the NOL algorithm. Although the model is locked, the algorithm 'personalizes' its nociception index to the individual patient by implementing an adaptive weighting mechanism between the static model and the patient's unique physiologic responses during the surgical procedure. As the case progresses, the weighting of the patient's unique physiological response increases and the NOL output is adjusted accordingly. Separate datasets were used by the manufacturer to train, test and validate the NOL index (12).

In both studies, the NOL monitor finger clip was connected to the patient on the left or right middle finger before induction. In case of NOL-guided fentanyl dosing, the monitor screen was visible to the anesthesia providers. In case of SOC, the screen of the monitor was concealed. Pain scores in the PACU were obtained at 15 min intervals and intravenous doses of opioids were given according to local protocol until pain scores were considered acceptable (pain scores measured on a numerical rating scale, NRS, ranging from 0, no pain to 10, most imaginable pain), i.e. NRS < 4. In both studies SOC was identical and was performed according to widespread clinical practice. In brief, but see for details below, fentanyl was given preemptively, prior to induction, followed by dosing based on the patient's condition and course of surgery, preferably in such a way that hypertension and tachycardia were prevented. Still, in case of such hemodynamic instabilities further fentanyl was administered.

Study design

SOLAR study (13)

After approval of the study by the local medical ethics committee the study was conducted at Leiden University Medical Center and Alrijne Hospital, Leiderdorp, both in the Netherlands. All protocol specifics, including inclusion and exclusion criteria can be found in the original paper and in Supplemental Digital Table 1 (13). The study is registered at https://trialsearch.who.int, under identifier NL7845. All patients gave written informed consent prior to enrolment. The study was conducted by anesthesiologists and residents that were trained in the use of the NOL monitor. Adult patients with ASA class 1-III scheduled to undergo elective laparoscopic or robot-assisted abdominal surgery without epidural anesthesia, local blocks or infiltration,

were recruited. The patient, surgical team and PACU nurses were not informed on the patient allocation.

As stated above, in both groups preemptive fentanyl was given prior to intubation followed by dosing to preemptively prevent hemodynamic instabilities. The only difference between the NOL-guided and SOC groups was the trigger to administer additional fentanyl. In the test group, fentanyl dosing was dependent on the NOL-index, but blood pressure and heart rate were considered as well. In case the NOL index >25 for at least 60 s, 50-100 µg fentanyl was administered in a patient >70 kg, and 25-50 µg in a patient of 70 kg or less. Higher or lower fentanyl doses could be given or opioids could be given below the NOL threshold if felt needed by the attending anesthesiologist or resident. In case the index decreased below 25, no fentanyl was further administered. In the SOC group, fentanyl dosing was dependent on the course of surgery and on blood pressure and heart rate (NOL-index values were not available). This was left to the discretion of anesthesia care giver and based on local protocol.

Abdomi-Nol study (14)

This study was performed at the Shaare Zedek Medical Center, Jerusalem, Israel, after approval was obtained from the local medical ethics committee. Protocol details can be found elsewhere and Supplemental Digital Table 1 (14). The study was registered at www.clinicaltrials.gov under identifier NCT03970291. All patients gave written informed consent prior to enrolment. The study was conducted by anesthesiologists trained in the use of the NOL monitor. Adult ASA I-III patients scheduled to undergo elective laparoscopic abdominal, urologic or gynecologic procedures under general anesthesia without a planned epidural or local block were eligible for inclusion.

In the NOL-guided fentanyl dosing group, 0.5 µg/kg intravenous fentanyl was administered when NOL values were above 25 for at least 60s. Higher or lower fentanyl doses could be given or opioids if felt needed by the anesthesiologist. In the SOC group, fentanyl dosing was at the discretion of the anesthesiologist and based on hemodynamic variables and course of surgery (see also above).

Primary endpoint

The primary endpoint of both studies was the NRS for pain obtained by the PACU nursing staff in the first 90 min in the PACU. NRS < 4 was considered mild and acceptable, NRS from 4 to < 7 moderate pain and 7 or higher severe pain. Pain scores of 4 or greater were treated in the PACU using a multimodal approach consisting of acetaminophen and/or an opioid. In the analyses, we highlight severe pain and maximal pain scores, as we consider these most agonizing and harmful to the patient.

Statistical analyses

Prior to data pooling a comparison of general patient's characteristics between the two studies was conducted and there were no significant differences between the studies, except for surgery type distribution (Supplemental Table 2). Additionally, a comparison of NRS levels during PACU between two study arms demonstrated that groups were comparable with no significant differences between studies at all time points (NRS comparison between sites by Mann-Whitney U tests: $p > 0.05$ at all times points). The distribution of continuous variables was assessed using Shapiro & Wilk test. Continuous variables with non-normal distributions were expressed as median and interquartile range. Categorical variables were expressed as number and percentage. Comparisons of continuous variables between groups were performed with the Mann-Whitney U test for nonparametric variables, and the Fisher's exact-test or x^2-test for categorical variables. A logistic regression model was used to identify factors related to severe pain. Generalized linear models with the cluster bootstrap were applied to evaluate the difference in NRS accounting for the repeated measurement for each subject during the 90 minutes in PACU. This model was also used to evaluate the differences in specific subgroups. Pearson correlation coefficient were calculated for opioid dose during surgery versus NRS in the PACU. P-values < 0.05 were considered significant. Data were analyzed in R-4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), SPSS Statistics (v-28.0, IBM, Armonk, NY, USA, or GraphPad Prism v-9.4.1 for macOS (GarphPad Software, San Diego, CA, USA). The raw data included in the study are available from the authors after agreement on purpose and protocol.

RESULTS

The study protocols (Supplemental Table 1), enrolled patient characteristics (Supplemental Digital Table 2) and pain scores in the PACU (Supplemental Digital Fig. 1) from the two independent studies were sufficiently similar to allow a pooled analysis of the effect of the intervention (NOL-guided fentanyl dosing versus SOC) on pain scores in the PACU. Hundred-twenty-five patients of either sex were enrolled in the studies (Table 1), with age range 21-86 years. The majority of patients were ASA class 2 (64%), with equal number of patients in ASA class 1 or 3 (18%). The types of surgeries were divided among three specialties: surgery (all abdominal cases) 47%, gynecology 33% and urology 20%. The two intervention arms were well balanced with respect to demographics, ASA classification and distribution of surgical procedures (Table 1).

Table 1. Patient characteristics of the subjects enrolled in the NOL-guided and the SOC groups.

	NOL-guided fentanyl dosing group (*n* = 61)	Standard of Care group (*n* = 64)	Total (n = 125)	p-value
Sex				
Male, No. (%)	22 (36)	33 (52)	55 (44)	0.081
Female, No. (%)	39 (54)	31 (48)	70 (56)	
Age				
Median (IQR), year	61 (49-67)	60 (43-70)	60 (45-69)	0.778
Range, year	(21-84)	(21-86)	(21-86)	
BMI				
Median (IQR), kg/m^2	26 (22-30)	25 (24-29)	26 (23-29)	0.880
Range, kg/m^2	(18-48)	(20-41)	(18-48)	
Type of surgery				
Urology, No. (%)	9 (15)	16 (25)	25 (20)	0.356
Gynecology, No. (%)	21 (34)	20 (31)	41 (33)	
Surgery, No. (%)	31 (51)	28 (44)	59 (47)	
ASA				
1, No. (%)	10 (17)	13 (20)	23 (18)	0.662
2, No. (%)	38 (62)	41 (64)	79 (64)	
3, No. (%)	13 (21)	10 (16)	23 (18)	

Abbreviations: IQR, interquartile range; BMI body mass index; ASA American Society of Anesthesiologists.

The primary endpoint, postoperative pain during the first 90 min in the PACU, is presented in Figure 1. The figure demonstrates lower median NRS values at each time point in the NOL-guided group compared to SOC. With adjustments for time, sex, age and study site (Israel or the Netherlands), the two treatment groups differed significantly with median lower pain scores in the NOL-guided group compared to standard of care by 1.4 NRS points (95% CI 0.6-2.2), an effect that increased to 1.5 (0.8-2.2) NRS points after further adjustment for surgery type. The number of patients requiring no pain treatment increased from 10% (standard care) to 33% (NOL treatment; p = 0.002).

To identify specific patient populations that benefit from NOL-guided analgesia, generalized linear models with the cluster bootstrap were applied for each subgroup. Subgroups with the lower limit of the 95% confidence interval > 0 were: females (actual difference 1.9, 95% CI 1.0-3.0), patients ≤ 65 years (actual difference 1.8, 0.9- 2.9), ASA 1 patients (actual difference 2.0, 0.4-3.5), patients with a body mass index < 25 kg/m2 (actual difference 1.8, 0.6-3.0) or body mass index > 30 kg/m^2 (actual difference 2.1, 0.5-3.7), patients undergoing urological surgery (actual difference 2.5, 1.2-3.7) and patients undergoing abdominal surgery (actual difference 1.4, 0.5-2.4).

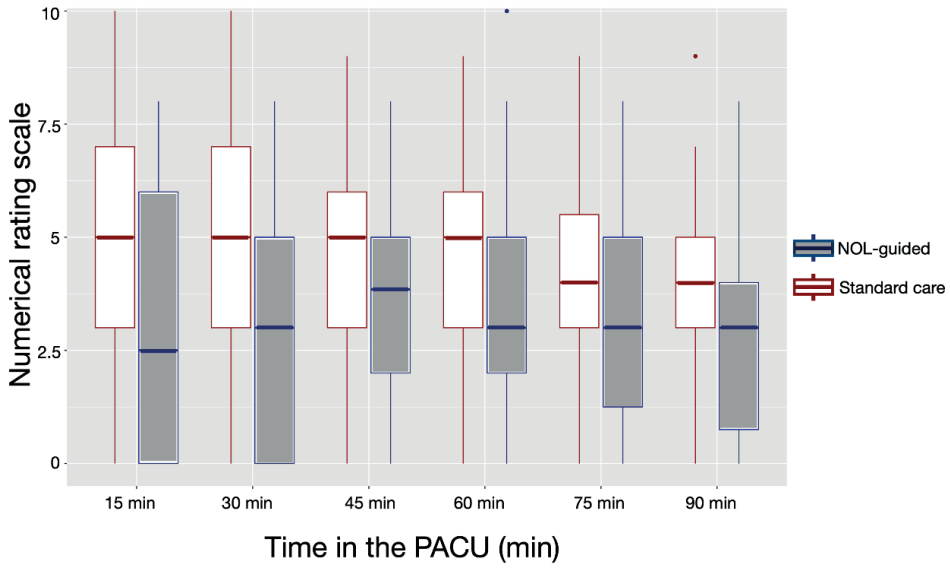

Figure 1. Boxplots of the effect of intraoperative Nociception level (NOL)-guided fentanyl dosing and standard care (SOC) on postoperative pain scores.

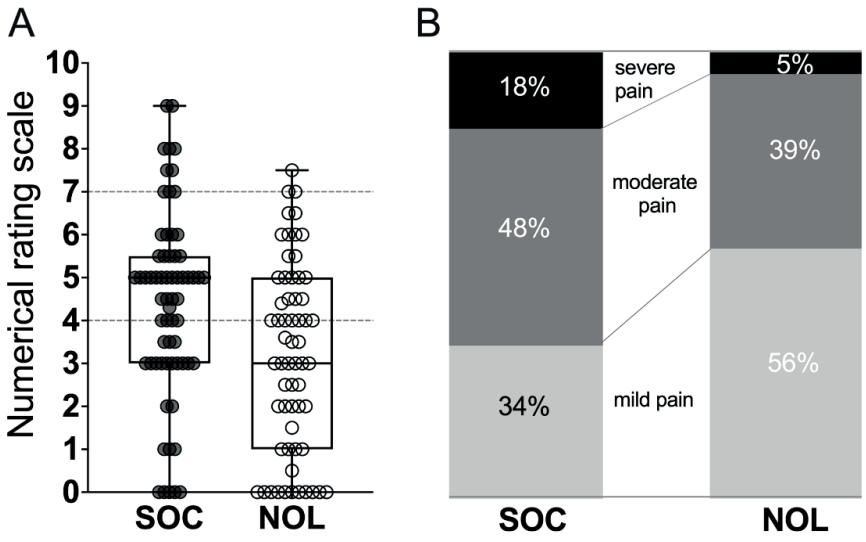

Figure 2. A. Boxplot of the individual median pain scores observed during the patients' stay in the PACU. **B.** Percentage of patients with mild pain (NRS < 4), moderate pain (NRS > 4 and < 7) and severe pain (NRS 7 or greater). SOC standard care, NOL Nociception Level-guided fentanyl dosing.

The highest pain scores observed at any time throughout the 90-min stay in the PACU were 4.6 (NOL-guided group) and 6.2 (SOC; mean values with actual difference 1.7, p = 0.001) with 66% of patients in the NOL-guided group that had pains scores < 4 throughout their stay in the PACU versus 10% in the SOC group. The number of patients with severe pain (NRS ≥ 7) was 11 in the SOC group and 3 in the NOL-guided group, p = 0.045 (Fig. 2). Logistic regression identified the factors that were related to severe pain. The only significant factor associated with increased odds for severe pain of all factors considered (Fig. 3) was the standard of care approach for intraoperative fentanyl dosing compared to NOL-guided dosing (OR 6.0 with 95% CI 1.4 to 25.9, p = 0.017). None of the other factors reached the level of significance.

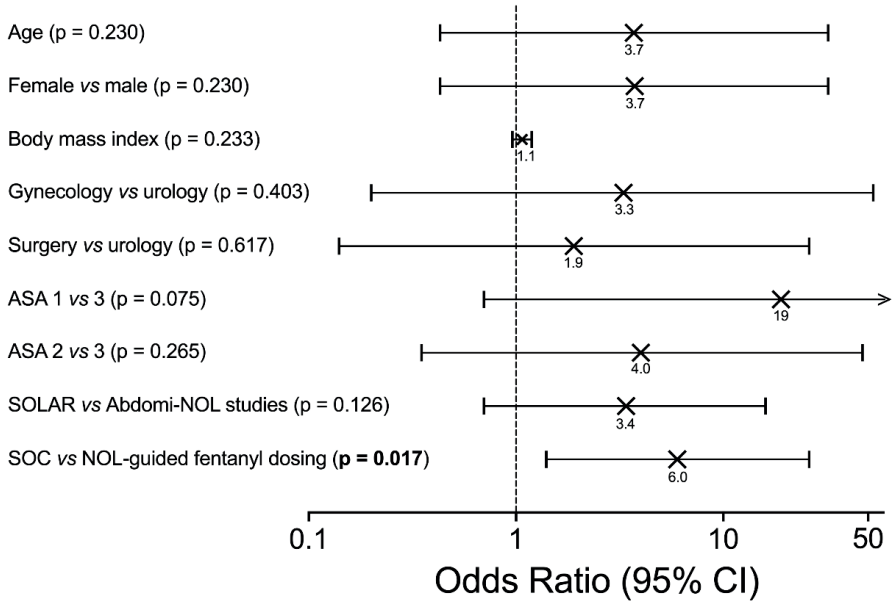

Figure 3. Logistic regression analysis identifying factors related to severe pain. The only significant factor associated with increased odds for severe pain was the standard of care approach for intraoperative fentanyl dosing compared to NOL-guided dosing.

In figure 4, the fentanyl consumption during surgery is plotted against the median pain scores in the PACU for all 125 patients. Analysis showed absence of correlation between opioid dosing and NRS.

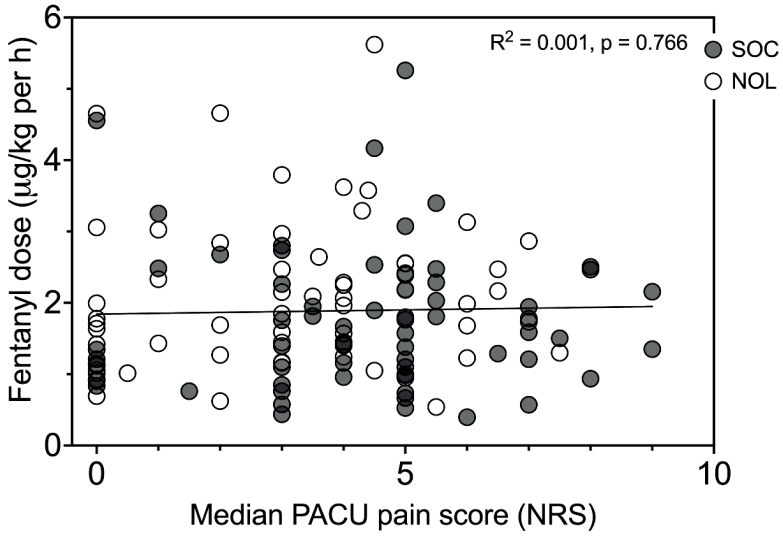

Figure 4. Intraoperative fentanyl dose *versus* median pain score in the PACU for Nociception Level (NOL)-guided patients (open symbols) and standard of care patients (SOC, closed symbols). Each dot is one patient. The line is the linear regression curve of the full data set. Pearson correlation: complete data set r^2 = 0.001, p = 0.766, NOL-guided patients r^2 = 0.022, p = 0.246, and SOC patients r^2 = 0.000, p = 0.891.

DISCUSSION

Appropriate prevention of high postoperative pain scores remains challenging and all available effective techniques should be utilized to prevent development of pain-related complications. These complications can range from anxiety and distress to prolonged hospital stay, unplanned 30-day readmission and the chronification of pain (4-7). Equally relevant is the observation that in some European countries but also in the US, patients are discharged with an opioid prescription for treatment of ongoing pain as a result of shorter hospital stays (8,16). Excessive prescribing of opioids for pain treatment after surgery has been identified as a public health problem and a potential contributor to patterns of opioid abuse and related harm (8).

In this publication, we present data on the use of a technology based on machine learning, the NOL monitor, to detect nociceptive events during surgery and treat them appropriately in order to reduce intraoperative nociception and prevent high pain scores in the PACU. In the pooled analysis of two controlled trials, we observed that titration of the fentanyl upon an intraoperative observation of an excessive nociceptive event resulted in significantly less PACU pain compared to the standard care with

opioid dosing based on intermittent hemodynamic measurements. PACU pain scores was reduced in the NOL-treated group by 1.5 NRS points or 30%, a clinically meaningful result (17-20). NOL-treatment reduced median highest pain scores in the PACU (from 6.2 to 4.5 NRS points) and the proportion of patients with severe pain by 70% (from n = 11 patients to 3 patients; Fig. 2). Despite multimodal pharmacotherapy, 17% of SOC patients suffered severe pain during their PACU stay; this number was reduced to 5% in patients who received intraoperative NOL-guided opioid dosing. This again is a significant observation and clinically relevant. Data from Cepeda et al. indicate that a clinically meaningful improvement in pain scores is more challenging to attain in patients with severe pain than in patients with moderate pain (17).

Interestingly, the largest benefit of NOL-guidance was demonstrated in patients undergoing urological surgery and patients with a body mass index >30 kg/m^2. Both of these groups had an difference in median PACU pain scores across treatment arms of more than 2 NRS points. Since a considerable proportion of patients in current clinical practice have a high body mass index, the value of using the NOL in particularly this population is of high clinical relevance.

In the NOL-guided group, fewer patients in the PACU experienced severe pain (Fig. 2). Similar observations were made for the maximal pains scores at any time in the PACU. If we focus on the pain scores that trigger pharmacological treatment in our medical centers (i.e. pain score of 4 NRS points or higher), we observed that intraoperative NOL-guided analgesia reduced the proportion of patients with pain scores > 4 (at any time in the PACU) from 90% in SOC patients to 66% following NOL-guided analgesia. This means that while 90% of SOC patients required a treatment for their pain postoperatively, this was true for just two-thirds of the NOL-guided patients; in other words, one-third of the NOL-guided patients did not require any opioid or any other pain medication in the PACU. Logistic regression analysis (Fig. 3) revealed further that intraoperative NOL-guided analgesia was the only variable that lowered the likelihood of experiencing severe pain in the PACU. These findings imply that disparities between groups in the number of patients reporting severe pain in the PACU are unrelated to patient or procedural variables.

One could reason that patients with severe pain in either treatment group received insufficient doses of fentanyl during surgery or that patients with mild or moderate pain were relatively overdosed. We determined, however, that pain scores were independent of fentanyl dose by plotting fentanyl consumption during surgery against the median pain scores in the PACU (Fig. 4). This is an important observation and indicates that other factors than the magnitude of total fentanyl dose are responsible for the disparate outcomes of the two treatments. One such factor is likely the timing

of fentanyl administration. We argue that when fentanyl was administered in response to a nociceptive event rather than triggered by an increase in blood pressure, the patient's nociceptive state was reduced throughout the surgical procedure, effectively resulting in less postoperative pain.

Combining individual data analysis from studies conducted at different sites into a pooled analysis requires uniformity in the patient population, surgical procedures, analgesic protocols, intervention and data collection (15,21). Since the Abdomi-Nol study was a replica of the SOLAR study to some extent and designed to independently corroborate the results of the SOLAR study, the two studies were sufficiently similar to permit data pooling. Still, there were some differences between studies, such as the use of a monitor to control anesthetic depth in the SOLAR study, while dependence on end-tidal volatile gas concentrations in the Abdomi-Nol study. Nevertheless, the two approaches are sufficiently comparable that they did not impact our current results. Nonetheless, pain sensitivity and attitudes toward pain scoring, may have been different in ethnically divergent Dutch and Israeli patient populations, despite the use of identical metrics (22,23). The comparable pain scores in the PACU between the two sites (Supplemental Digital Figure 1) imply that such differences were minor.

In conclusion, intraoperative machine-learning based NOL-guided dosing of fentanyl as opposed to dosing fentanyl based on blood pressure and heart rate, resulted in (1) improved PACU pain scores, (2) fewer patients with severe pain, (3) a greater proportion of patients who did not require any opioid treatment in the PACU compared to standard care; lastly, (4) our analysis showed that the predictor of less severe pain in the PACU was NOL-guided fentanyl dosing. These finding are pertinent and may aid in minimizing the prevalence of severe pain after surgery and all of its negative repercussions.

Relating to this last remark, it is important to reflect on the consequences of less PACU pain and a reduced number of patients that required opioid treatment in the PACU in light of the current opioid crisis. One of the causes of the opioid crisis, at least in the Netherlands, is the fact that hospital stay is currently relatively short and many patients are discharged from the hospital, while still in pain, with an opioid prescription (16). Although our study was not designed to study the long-term effects of less PACU pain and reduced PACU opioid requirements, we argue that this will assist in reducing long-term opioid consumption both in-house and possibly even after discharge. Further studies are needed to address this issue.

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Evaluating opioid dosing in the ICU using Nociception level Monitoring:

comparing COVID-19 and non-COVID-19 patients

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Submitted

Supplemental digital content of this article is available upon request

ABSTRACT

Background

During the COVID-19 pandemic, concerns grew about excessive opioid dosing in COVID-19 ICU patients. This study aimed to evaluate opioid dosing in the ICU by comparing objective (Nociception Level Monitor (NOL)) and subjective (Behavioral Pain Score (BPS)) pain measurement tools in COVID-19 and non-COVID-19 ICU patients.

Methods

This observational study included 40 sedated, mechanically ventilated ICU patients, of whom half were confirmed COVID-19. Measurements included NOL, BPS, Richmond Agitation Sedation Scale (RASS), Bispectral Index (BIS) and nurse questionnaires. NOL was categorized as <10 (possible excessive analgesia), 10-25 (adequate analgesia), and >25 (possible need for more analgesia). The Time Weighted Average (TWA) assessed duration of NOL >25 ($TWA_{NOL>25}$). Primary outcomes were NOL and BIS over time.

Results

COVID-19 patients received higher sufentanil (18 $\pm$ 9 µg/h versus 9 $\pm$ 6 µg/h) and propofol (307 $\pm$ 127 mg/h versus 277 $\pm$ 137 mg/h) doses (P<0.001). No significant differences were found in $TWA_{NOL>25}$ (P=0.78) or BPS (P=0.1). NOL values were <10 for 63% and 57% of the time in COVID-19 and non-COVID-19 patients. BIS (P<0.001) and RASS (P=0.02) were lower in COVID-19 patients.

Conclusions

While COVID-19 patients received significantly higher opioid doses, low NOL and BPS were seen in all patients, suggesting high analgesia in all patients. Therefore, based on our data, we cannot determine if COVID-19 patients required more opioids.

INTRODUCTION

Optimal pain management is crucial for ICU patients. Insufficient pain management can trigger a series of physiological responses, including elevated stress hormones, hypercoagulability and immune system dysfunction (1, 2). While sufficient analgesia is beneficial, excessive doses of opioids and sedatives negatively impact long term outcomes such as duration of ventilation and survival (3-5).

During the COVID-19 pandemic, concern grew regarding excessive opioid dosing in ICU COVID-19 patients (6). In some instances, COVID-19 patients required three times the opioid dose compared to a historical cohort of ICU patients (7). This raised questions on whether higher doses of opioids were required to achieve comparable levels of analgesia or if clinicians for some reason aimed at a higher level of analgesia in these patients.

Adequate dosing of analgesics in sedated ICU patients is challenging due to their inability to self-report on pain (8, 9). Current methods use vital signs or subjective tools such as the Behavioral Pain Score (BPS) or the Critical Care Pain Observation Tool (CPOT) (10, 11). Vital signs, however, can be affected by many physiological conditions (12), and the BPS and CPOT remain subjective measurements that can vary among health care professionals. Consequently, objective measures are needed to quantify pain in the ICU population.

In recent years, monitors like the Nociception Level (NOL) monitor (Medasense Biometrics Ltd. Ramat Gan, Israel) have been developed to objectively track nociception in sedated patients. Nociception is defined as the neural process of detection, transduction and transmission of noxious stimuli (13). It is assessed by the NOL monitor by combining heart rate, heart rate variability, peripheral vasoconstriction and skin conductance (14). Several studies in the operating room (OR) (14-21) demonstrate that NOL-guided analgesia reduces stress hormones and postoperative pain, and improves hemodynamics. Limited research on NOL in the ICU showed that NOL can identify nociceptive stimuli in ICU patients able to self-report (22, 23). However, further research is needed to assess efficacy of NOL in anesthetized ICU patients.

The aim of this exploratory observational study was to determine whether COVID-19 patients needed higher opioid doses by comparing subjective and objective measures to asses pain in sedated COVID-19 and non-COVID-19 ICU patients.

METHODS

This exploratory observational study was performed in the Leiden University Medical Center (LUMC) between October 6, 2020, and November 11, 2021. This two-phase study initially included 20 patients from October 6 to October 22, 2020. In order to also assess the depth of sedation, 20 additional patients with Bispectral Index (BIS) measurements were included from September 9 to November 11, 2021.

The first phase was registered on the Dutch Trial Register (NTR) (NL9159) (registration approval date: 17-12-2020). Because the NTR and the Central Committee on Research Involving Human Subjects (CCMO) register were merged, temporarily no protocol modifications were possible, leading to registration of the second phase on ClinicalTrials.gov (NCT05579106) (registration approval date:12-10-2022) . Both protocols received Institutional Review Board approval (Title: "Nociception Level Monitoring in the Intensive Care (NEMO)", approval number: A020-001, approval date: 04-09-2020; Title: "Nociception Level Monitoring in COVID-19 patients in the Intensive Care Unit", approval number: CoCo 2021-017, approval date: 08-06-2021. Principle investigator: A. Dahan). The requirement for informed consent was waived by the medical ethics committee. This study was conducted in accordance with the Declaration of Helsinki.

Patients

The study included 20 ICU patients with proven COVID-19 disease by PCR of nose- or airway sample, and 20 non-COVID-19 ICU patients. All patients aged 18 or older receiving mechanical ventilation were eligible. Exclusion criteria included aged 17 or younger. In the second phase the following exclusion criteria were added: severe peripheral edema, heart rate <35, veno-arterial (VA) and veno-venous (VV) extracorporeal membrane oxygenation (ECMO), and abdominal position. Non-COVID-19 ICU patients were randomly selected and were admitted to the ICU in the same period as the COVID-19 patients. The same exclusion criteria applied to this group.

The NOL Monitor

The NOL monitor by Medasense Biometrics Ltd. uses a finger probe to measure skin conductance, vasoconstriction, heart rate, heart rate variability and their time derivatives. These parameters are analyzed using a nonlinear Random Forest regression technique, calculating the NOL index which ranges from 0-100 (14). In the OR, NOL values between 10-25 suggests adequate analgesia, values <10 in the presence of noxious stimuli may suggest excessive analgesia, and >25 may indicate need for additional analgesia (15-17, 24). Only a NOL value above 25 for > 60 seconds during a

medical intervention is deemed indicative of pain. The NOL monitor received EU and health Canada certification, and U.S. Food and Drug Administration de novo grant.

Trial procedures

NOL was measured for 8 hours in all 40 patients. The finger probe was moved every 4 hours to prevent possible skin damage. In 20 patients, additional BIS measurements were done for 8 hours to assess sedation levels. Behavioral Pain Score (BPS) and the Richmond Agitation Sedation Scale (RASS) were documented at least once within the study period. There were no restrictions on types or doses of sedatives and analgesics used.

Nurses annotated clinical interventions such as change in patient position, airway management (e.g. endotracheal suctioning), and patient care (e.g. wound care, bathing) in the electronic medical record database. Subsequently, the type of event was matched with the corresponding NOL and BIS values at the same date and time. Standard care procedures were performed as usual, therefore if the patient needed to be transported for a scan or intervention, measurements were temporarily stopped and resumed as soon as possible.

For the 20 patients where both BIS and NOL were monitored (Supplemental digital content, appendix 1), an evaluation questionnaire was completed. This questionnaire included 7 closed-ended questions and three options to provide a textual response to the choice "other". The questionnaire included questions on the nurses' perception of patients' pain, moments when they believed the patient was in pain, signals that led them to suspect pain, actions taken based on the pain, and communication about their concerns with the attending physician. Results of pain-related questions were compared to the corresponding NOL values.

Data collection

Data was derived from three sources: 1. The NOL index monitor, 2. The BIS monitor, 3. The electronic medical record database (MetaVision). All monitors were time aligned before the start of the measurement. Hemodynamic parameters (heart rate, blood pressure) were extracted from MetaVision. Demographic data, medication, answers from the questionnaires, and annotation data were entered manually in an electronic case report form (eCRF) designed with Castor EDC (25).

Outcome measures

Primary outcomes were BIS and NOL values over time. Secondary outcomes were propofol and sufentanil dose, RASS and BPS, and feasibility of using NOL in the ICU. Feasibility of NOL was assessed in three ways, namely, the quality of the NOL signal, NOL's ability to identify a nociceptive event, and the alignment of nurses' responses to

pain-related questions and the corresponding NOL values.

Statistical analysis

NOL values over time were analyzed by calculating the Time Weighted Average when NOL exceeds 25 ($TWA_{NOL>25}$). The $TWA_{NOL>25}$ was calculated by dividing the accumulated area (AUC) of NOL values above 25 by the total time period ($TWA_{NOL>25}$ = (Area of NOL values above threshold)/(Total time (end-start)). A low $TWA_{NOL>25}$ shows minimal excursions above 25, while a higher $TWA_{NOL>25}$ shows more excursions above 25, which may indicate untreated nociceptive events. $TWA_{NOL>25}$ is presented as medians with interquartile ranges (IQR), and compared using the Mann-Whitney U test. BIS values over time were presented as mean with standard deviation (SD), and compared using an unpaired t-test.

For the secondary endpoints, continuous variables with a normal distribution were reported as means with SDs, whereas variables with a non-normal distribution were reported as medians with IQRs. Differences between groups were assessed using an unpaired t-test or a Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, and differences were analyzed using a chi-squared test.

NOL signal quality was categorized based on the percentage of occurrences where NOL indicated NaN. Signal quality categories were as follows: <10% = very good, 10-30% = good, 30-50% = moderate, 50-70% = poor, 70-90% = very poor. When NaN values exceeded 90% the patients were excluded from the analysis.

NOL responses before and after painful stimuli were calculated in a systemic approach. NOL before a painful stimulus was calculated as the average of NOL values in a 20 second window, which started 30 seconds before the stimulus annotation and lasted until 10 seconds before stimulus annotation. NOL post a painful stimulus was calculated as the average of NOL values in a 20 second window, which were calculated around the maximum NOL value between stimulus annotation and up to 90 seconds afterwards.

Statistical analyses were performed using MATLAB software (MathWorks, Natick, MA, USA) and R language and environment (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3). Statistical significance was defined as a P-value of <0.05 in a two-sided test.

Table 1. Baseline characteristics of patients.

Variables	COVID-19 ICU (N=20)	non-COVID-19 (N=20)
Age (median [IQR])	67 [61, 71]	65 [51, 71]
Sex = female (%)	16 (80)	13 (65)
BMI (mean (SD))	29 (5)	28 (5)
Day of ICU submission measurement took place (median [IQR])	3.5 [2, 7.25]	3.5 [2, 6.75]
Factors potentially influencing the NOL measurements		
Vasopressive/inotropic medication	14 (70)	15 (75)
Arrythmia	6 (30)	6 (30)
Hypertension	2 (10)	1 (5)
Hypotension	1 (5)	1 (5)
Hypothermia	4 (20)	1 (5)
Bradycardia	6 (30)	1 (5)
Tachycardia	2 (10)	8 (40)
Peripheral edema	3 (15)	9 (45)
VV-ECMO[a]	2 (10)	0 (0)
No influential circumstances	2 (10)	0 (0)
RASS (%)		
-5	9 (45)	8 (40)
-4	10 (50)	8 (40)
-3	1 (5)	4 (20)
BPS (%)		
3	16 (80)	15 (75)
4	3 (15)	4 (20)
5	1 (5)	1 (5)
Ventilation mode (%)		
PCMV	14 (70)	9 (45)
ASV	2 (10)	11 (55)
PSV	4 (20)	0 (0)
Rocuronium	3 (15)	0 (0)

BMI = Body Mass Index, VV-ECMO = Veno-Venous Extracorporeal Membrane Oxygenation, PCMV = Pressure control Continuous Mandatory
Ventilation, ASV = Adaptive Support Ventilation, PSV = Pressure Support Ventilation.
[a] These patients were included in the first phase of the study. VV-ECMO was added as an exclusion criteria in the second phase of the study.

RESULTS

Baseline characteristics can be observed in Table 1 and were similar between the two groups. Two patients were excluded from the analysis because in 98% and 100% NOL indicated NaN.

Primary outcomes

The total $TWA_{NOL>25}$ was 0.39 (IQR 0.09-0.82). No significant differences were observed

between the $TWA_{NOL>25}$ in the COVID-19 (0.33) and the non-COVID-19 group (0.46) (P=0.78) (Table 2). NOL was below 10 for 63% and 57% of the time, and between 10-25 for 22% and 33% of the time in the COVID-19 and non-COVID-19 group, respectively (Figure 1, Table 2). BIS values were 34±15 versus 47±17 in the COVID-19 and non-COVID-19 group (P<0.001) (Table 2).

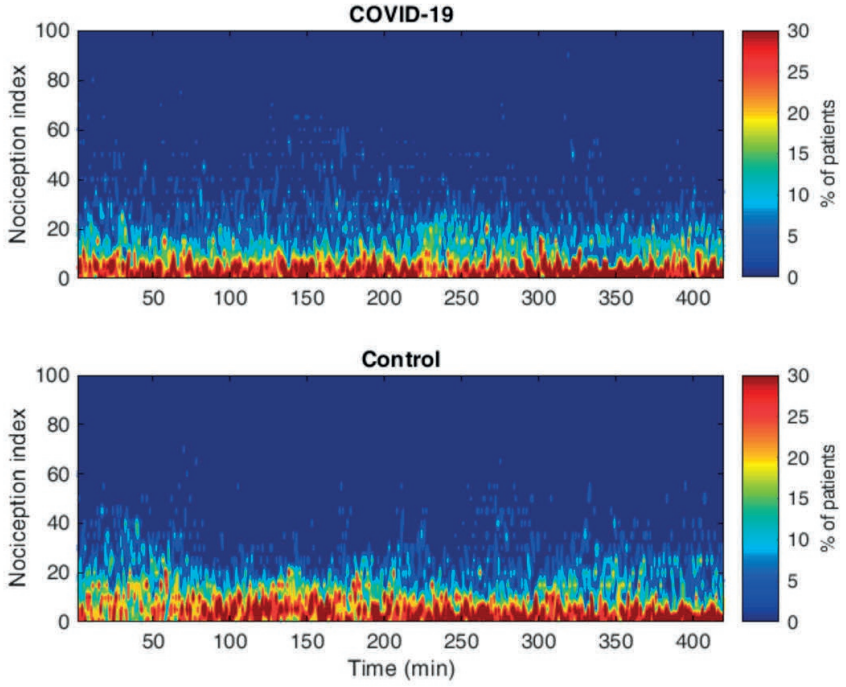

Figure 1. Fire plots of Nociception Level (NOL) index. Values are shown during 8 hours in COVID-19 and Control (non-COVID-19) patients. The colors reflect the percentage of subjects at any time point and range from 0% (dark blue) to 30% (dark red).

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Secondary outcomes

COVID-19 patients received higher doses of sufentanil compared to non-COVID-19 patients (18 ± 9 µg/h versus 9 ± 6 µg/h, P <0.001). Propofol was also dosed higher in COVID-19 patients (307 ± 127 mg/h) compared to non-COVID-19 patients (178 ± 140 mg/h) (P<0.001) (Table 2). Details on additional medication can be found in supplemental Table 1.

Table 2. Patient outcomes.

Variables	COVID-19 ICU	non-COVID-19	Total
NOL and BIS[a]	N=20	N=18	N=38
$TWA_{NOL>25}$ (median [IQR])	0.33 [0.12-0.83]	0.46 [0.06-0.81]	0.39 [0.09, 0.82]
NOL < 10 (%)	63	57	60
NOL 10-25 (%)	22	33	28
BIS (mean ± SD)	34±15	47±17	40±17
Medication[a]	N=20	N=18	N=38
Propofol (mg/h) (mean ± SD)	307 ± 127	178 ± 137	245±147
Sufentanil (µg/h) (mean ± SD)	18 ± 9	9 ± 6	13±9
Quality NOL signal	N=20	N=20	N=40
Very good, No. (%)	11 (55)	8 (40)	19 (48)
Good, No. (%)	6 (30)	5 (25)	11 (28)
Moderate, No. (%)	3 (15)	4 (20)	7 (18)
Poor, No. (%)	0 (0)	0 (0)	0 (0)
Very poor, No. (%)	0 (0)	1 (5)	1 (3)
Unusable , No. (%)	0 (0)	2 (1)	2 (5)
Annotations clinical intervention[a]			
All annotations [b]	N=39	N=39	N=78
Before (median [IQR])	3 [2-7]	4 [2-7]	4 [3-16]
After (median [IQR])	23 [16-32]	25 [14-34]	25 [13-41]
P-value	P<0.001	P<0.001	P<0.001
Airway management	N=20	N=21	N=41
Before (median [IQR])	4 [3-16]	3 [2-7]	4 [3-9]
After (median [IQR])	39[23-47]	26 [17-34]	32 [17-39]
P-value	P<0.001	P<0.001	P<0.001
Change of position	N=15	N=13	N=28
Before (median [IQR])	7 [4-15]	3 [2-5]	7 [4-15]
After (median [IQR])	22 [13-28]	18[12-26]	22 [13-28]
P-value	P=0.02	P<0.001	P<0.001
Patient care	N=3	N=4	N=7
NOL Before (median [IQR])	1 [1-8]	8 [4-14]	7 [1-19]
NOL After (median [IQR])	13 [13-18]	28 [22-31]	19 [15-29]
P-value	P=0.1	P=0.05	P=0.007

[a] Two patients were excluded from the analysis because the NOL signal was categorized as unusable. [b] More than one annotation of a clinical intervention could occur in the same patient.

BPS values were similar for both COVID-19 and non-COVID-19 patients, with scores of 3 (IQR 3-3.2) and 3 (IQR 3-3.5), respectively (p=0.1). RASS scores differed, with a median score of -4.5 (IQR -5 to -4) for COVID-19 and -4 (IQR -4.74 to -3.83) for non-COVID-19 patients (p=0.02). Table 3 shows BPS, BIS, RASS, sufentanil and propofol doses, categorized by mean NOL. Sufentanil levels were higher in COVID-19 patients across all categories, with higher propofol doses in COVID-19 patients when NOL was <10. Furthermore, BPS and RASS were lower in COVID-19 patients when NOL was 10-25.

NOL signal quality was mostly rated very good (48%), good (28%) or moderate (18%) (Table 2). Combining all NOL measurements, a significant difference was observed in the NOL measurement before (4, IQR 3-16) and after (25, IQR 13-41) interventions (P<0.001). During airway management, a median NOL of 4 (IQR 3-9) before and 32 (IQR 17-39) after was observed (P<0.001). When changing patients' position a median NOL value of 7 (IQR 4-15) before and 22 (IQR 13-28) after the intervention was observed (P<0.001). When receiving patient care a median NOL of 6.8 (IQR 1.0-19.3) before and 19 (IQR 15-29) after the intervention was observed (P=0.007). Comparing NOL values before and after interventions in COVID-19 and non-COVID-19 patients yielded similar results (Table 2).

Table 3. Categories based on mean NOL value.

Variables	COVID-19	non-COVID-19	p-value
NOL <10			
BPS (median [IQR])	3 [3, 3.5]	3 [3, 4]	0.5
BIS (median [IQR])	33 [18, 41]	46 [40, 52]	0.1
RASS (median [IQR])	-4.5 [-5, -4]	-4 [-4, -3.5]	0.2
Sufentanil µg/h (mean (SD))	16.4 (10)	10.5 (6)	0.08
Propofol mg/h (mean (SD))	334 (94)	233 (143)	0.08
NOL 10-25			
BPS (median [IQR])	3 [3, 3]	3.3 [3, 4]	0.08
BIS (median [IQR])	42 [36, 44]	48 [39, 62]	0.6
RASS (median [IQR])	-4.8 [-5, -4.5]	-3.8 [-4.6, -3]	0.03
Sufentanil µg/h (mean (SD))	20 (6.3)	8.8 (3.3)	0.005
Propofol mg/h (mean (SD))	311 (139)	233 (61)	0.3
NOL >25			
BPS (median [IQR])	3.5 [3.5, 3.5]	NA	NA
BIS (median [IQR])[a]	NA	NA	NA
RASS (median [IQR])	-4 [-4, -4]	NA	NA
Sufentanil µg/h (mean (SD))	20 (NA)[b]	NA	NA
Propofol mg/h (mean (SD))	250 (NA)[b]	NA	NA

BPS, BIS, and RASS values, and propofol and sufentanil doses when patients are categorized based on their mean NOL value. Two patients were excluded from this table because the NOL signal was categorized as unusable. [a]No BIS measurements were done in this patient. [b]A standard deviation could not be calculated because only one patient with a single measurement was assigned to this group.

Questionnaire

Table 4 shows details of responses to the questions. Most nurses (90%) found the pain medication the patient received "sufficient". Half (50%) of the nurses reported there were no signs of pain, 35% reported signs of pain "during interventions". When comparing NOL values in patients for whom nurses reported no pain (n=10), a median NOL value of 4 (IQR 2-8) before and 19 (IQR 14-27) after an intervention was observed. For those

thought to be in pain (n=10) a median NOL value of 5 (IQR 3-17) before and 30 (IQR 21-30) after an intervention was observed. Change in hemodynamics (60%) was the most frequently reported indicator of pain. In 66% additional actions were taken when patients showed signs of pain, and a bolus of pain medication was given in all cases. Concerns regarding the patients' pain were discussed with the attending physician in 3 out of 9 cases (33%), resulting in changes in the treatment plan in all cases. Questionnaire outcomes were similar between COVID-19 and non-COVID-19 groups (Table 4).

Table 4. Results evaluation questionnaire. It was possible to provide multiple answers for questions 2 and 5. Textual responses to "other" in question 2 were: "difficulty in assessment due to muscle relaxants" and "pain started after stopping/lowering the sedation/remifentanil". Textual responses to "other" in question 3 were: "breathing frequency", "desaturation in combination with drop in heart rate", and "coughing".

Questions		COVID-19 (N=10)	non-COVID-19 (N=10)	Total (N=20)
1.	**What is your general impression of the pain medication the patient has received today? (%)**			
	Sufficient	9 (90)	9 (90)	18 (90)
	Reasonable	1 (10)	1 (10)	2 (10)
	Insufficient	0 (0)	0 (0)	0 (0)
	Too much	0 (0)	0 (0)	0 (0)
2.	**What were moments when the patient gave the impression of experiencing pain?**			
	During interventions	3 (30)	4 (40)	7 (35)
	Throughout the whole day	0 (0)	0 (0)	0 (0)
	In intermittent episodes throughout the day	0 (0)	0 (0)	0 (0)
	Other	2 (20)	2 (20)	4 (20)
	The patient was comfortable and did not experience any pain	5 (50)	5 (50)	10 (50)
3.	**What signals gave you the impression that the patient was in pain? (%)**			
	Facial grimaces	0/5 (0)	1/5 (20)	1/10 (10)
	Higher blood pressure/heart rate	3/5 (60)	3/5 (60)	6/10 (60)
	Motor restlessness	1/5 (20)	0/5 (0)	1/10 (10)
	Other	1/5 (10)	1/5 (20)	2/10 (20)
4.	**Was any action taken when the patient gave the impression of being in pain? (%)**			
	Yes	3/4 (75)	3/5 (60)	6/9 (67)
	No	1/4 (25)	2/5 (40)	3/9 (33)
5.	**If yes, What actions were taken? (%)**			
	Bolus of pain medication	3/3 (100)	3/3 (100)	6/6 (100)
	Maintenance dose was increased	1/3 (25)	0/3 (0)	1/6 (17)
	Initiated new pain medication	0/3 (0)	0/3 (0)	0/6 (0)
	Other	0/3 (20)	0/3 (20)	0/6 (0)
6.	**Were concerns regarding the patients' pain communicated with the treating physician? (%)**			
	Yes	1/4 (25)	2/5 (40)	3/9 (33)
	No	3/4 (75)	3/5 (60)	6/9 (67)
7.	**Has this led to any changes in the treatment plan?**			
	Yes	1/1 (100)	2/2 (100)	3/3 (100)
	No	0/1 (0)	0/2 (0)	0/3 (0)

DISCUSSION

In this observational study, including 40 mechanically ventilated and sedated adult ICU patients, COVID-19 received higher sufentanil and propofol doses compared to non-COVID-19 patients. Both groups had low NOL and BPS values with lower BIS and RASS values in the COVID-19 group, suggesting high analgesia in both groups and deeper sedation in the COVID-19 group.

Most previous studies evaluated the use of NOL in the OR, showing potential benefits in reduced postoperative stress hormones, opioid use, and postoperative pain scores (15-21). Within an ICU setting, only two previous studies have been conducted (22, 23). These studies, including 15 and 54 patients, aimed to assess the ability of NOL to identify nociceptive stimuli in patients able to self-report. While both studies found that NOL could identify nociceptive stimuli, it is important to note that NOL is primarily validated in sedated patients. Therefore, an important added value of the current study is the focus on sedated ICU patients, offering new insights in using NOL in unresponsive ICU patients.

Our results show low NOL, BPS, RASS and BIS values in both groups. COVID-19 patients received higher doses of analgesia and sedation, however, NOL values were below 10 in more than 50% of the time in both groups, suggesting that in both groups greater amounts of analgesics were administered than required. However, before drawing this conclusion, several points should be considered. Firstly, it is important to note that the validation of NOL reference values was conducted in the OR (14, 17). Therefore, different reference values could be more appropriate for the ICU population, potentially misclassifying them as either under- or overdosed. Additionally, comparing NOL with subjective pain indicators like BPS and CPOT, is difficult as these measures are often biased by the feeling that the dosing of opioids is appropriate. Secondly, little is known about the influence of sedation on NOL. A previous study suggested that propofol had minimal effect on NOL, however, due to a small sample size this effect could not be properly investigated (17, 26). If the effect is present, this could be more pronounced in ICU patients due to longer periods of sedation compared to OR patients. Lastly, in the ICU, several indications, besides pain or discomfort, warrant higher doses of analgesics and sedatives. In COVID-19 patients, for example, higher doses of analgesics and sedatives were often required due to difficult mechanical ventilation and to subdue excitation (27, 28). All the above mentioned aspects require further investigation before ICU patients can be categorized as either under- or overdosed based on NOL values.

Our findings suggest that NOL has a good signal quality, has the ability to identify nociceptive stimuli, and has a reasonably well alignment with nurses' observations.

This suggests that the NOL monitor offers a valuable representation of pain levels. However, some observations need to be considered in the interpretation of the data. We observed that the NOL measurements may be impacted in the presence of factors such as tachycardia, peripheral edema and arrhythmias. Previous studies in the OR, where NOL showed to be of added value, mainly excluded patients under these conditions (14-21). The higher prevalence of these conditions in the ICU compared to the OR may reduce the added value of NOL. However, in our data we mostly observed a "good" or "very good" signal quality. Interestingly, COVID-19 patients seemed to have better signal quality, likely due to mono-organ dysfunction, compared to the non-COVID-19 group that had a higher incidence of conditions that could interfere with the NOL signal quality (e.g. tachycardia, peripheral edema). Hence, for a more conclusive statement on NOL reliability, further testing in a larger and more diverse ICU patient cohort is needed.

Since NOL measurements align reasonably well with nurses' observation, one may speculate whether we need a specific objective device to assess pain. In favor of the NOL is a previous study showing limited benefit of subjective pain assessment methods (CPOT and BPS) (29). In our data, we see a low BPS in both groups. A limitation of the BPS is when it is at its lowest (a value of 3), it is difficult to determine whether this low value is acceptable or if too much analgesics were administered. NOL might offer added value here, being a continuous monitor with a larger scale (between 0 and 100) and therefore could be better at making this distinction. Additionally, studies on NOL in the OR demonstrated a reduction in stress hormone levels when analgesia is guided by NOL (16). If NOL can effectively regulate pain and minimize stress hormone release in the ICU, it could have significant impact on both short- and long-term outcomes (3-5). Large-scale randomized controlled trials are needed to confirm these advantages.

Some limitations must be considered. Firstly, the small sample size limits robust statistical analysis. Nonetheless, it still remains one of the largest observational studies in this field. Secondly, half of the patients had COVID-19, allowing us to explore opioid administration in this subgroup, but impacting generalizability. Thirdly, in only half of the patients all measurements (BIS, NOL and evaluation questionnaire) were done. Replicating these findings in a larger patient cohort is therefore imperative. Also, the time gap between inclusion of the first and second 20 patients can influence outcomes due to changing COVID-19 protocols. However, when analyzing primary and secondary endpoints of both datasets separately, we obtained similar results.

In conclusion, COVID-19 patients received higher opioid doses compared to non-COVID-19 patients. Both groups had low NOL and BPS values with lower BIS and RASS values in the COVID-19 group, suggesting high analgesia in both groups and deeper

sedation in the COVID-19 group. Since all patients had low BPS and NOL values, we cannot determine whether COVID-19 patients needed more opioids. NOL shows promise for ICU use, however, further investigation is needed regarding reference values, medication effects, and specific ICU conditions on NOL measurements. Once these aspects are better understood, a randomized controlled trial is warranted to assess the impact of NOL-guided pain management on short- and long-term outcomes.

PART IV

SUMMARY & FUTURE PER-SPECTIVES

Summary, future perspectives and conclusions

SUMMARY

In the treatment of critically ill patients, several interventions are applied to stabilize vital functions and to restore homeostatic balance. Target ranges are used in various therapies in the intensive care unit (ICU) to administer interventions in the most effective way. In this thesis we aimed to improve the use of targeted intervention in three key areas, namely oxygenation, anticoagulant treatment, and pain management. Firstly, oxygen therapy is one of the most fundamental treatments in the ICU. Accurate oxygen administration is imperative, as too much and too little oxygen can do harm to the patient. Secondly, target ranges are also used in anticoagulation therapy, as excessive anticoagulation can lead to bleeding complications, whereas insufficient dosing may result in suboptimal therapy, potentially leading to fatal outcomes. Lastly, using target ranges for objective pain scores may avoid overuse of anesthetics while still achieving adequate pain management. It is well known that overuse of opioid anesthetics can prolong mechanical ventilation, while inadequate pain control can trigger stress responses and can negatively impact physiological processes and recovery. In the next section, more details are given of the targeted therapies that were studied, including future perspectives and conclusions.

In **Chapter 2**, data of the most recent trials comparing high (liberal) and low (conservative) oxygenation strategies in mechanically ventilated adult ICU patients were aggregated. Although previous systematic reviews provided guidance on oxygen administration, their results were unequivocal and new studies were published since. In this meta-analysis RCT's that compared high and low oxygenation strategies in adult mechanically ventilated ICU patients were included. Trials that solely focused on one specific subgroup (e.g. myocardial or cerebral infarction) were excluded, as well as animal studies, studies focusing on extracorporeal life support, or studies in the perioperative setting. The main outcome of interest was 90 day mortality. Other outcomes of interest were serious adverse events (SAE), support free days, and length of stay. In total, 9 RCTs including 5807 patients were included in the analysis. After data aggregation, no difference was found in 90 day mortality, support free days or length of stay. Conversely, a significant difference was found in the number of SAEs which was in favor of the low oxygenation group, suggesting a more beneficial outcome for patients in the low oxygenation group. However, the relatively small difference (10-25 mm Hg) between achieved oxygenation raised the question whether this contrast in achieved PaO2 was enough to yield meaningful differences in patient outcomes. Furthermore, variations in metrics used to monitor oxygenation levels (FiO_2, PaO_2 or SpO_2), variations in used target ranges and variations in used primary and secondary endpoints may have complicated our data aggregation. Consequently, future research should focus on adequately separating groups based on achieved oxygenation and on

the possible impact of important side effects of oxygen.

Chapter 3 discusses the ICONIC protocol, an international, multicenter study, that aimed to provide more insight in optimal oxygenation targets in the ICU. Adult patients with an expected mechanical ventilation duration of at least 24 hours were included. Most important exclusion criteria were acute respiratory distress syndrome (ARDS, PaO_2/FiO_2 < 150 mmHg), acute exacerbations of chronic obstructive pulmonary disease (COPD), and underlying diseases with an indication for hyperoxygenation. Eligible patients had to be randomized within 2 hours after intubation to either the low- (conservative) oxygenation group (PaO_2 55-80 mmHg) or the high- (liberal) oxygenation group (110-150 mmHg). Oxygenation targets were still pursued after extubation, namely, patients in the low-oxygenation group received no supplemental oxygen unless PaO_2 fell below 55 mmHg, and patients in the high-oxygenation group received a nasal cannula of 5L oxygen unless PaO_2 exceeded 150 mmHg. The intervention was continued until 28 days after randomization or ICU discharge, whichever came first. Due to the nature of the study intervention clinicians could not be blinded for the study intervention, however the data analysist remained blinded. The primary outcome was 28-day mortality. Secondary outcomes included the number of ventilator free days at day 28, ICU and hospital length of stay, ICU, hospital and 90-day mortality, and number of ischemic events. In order to assess patients' quality of life and patients' opinion on the use of deferred consent, the EQ5D questionnaire (after 6 and 12 months) and a deferred consent questionnaire (after 6 months) were used. A sample size of 1512 patients was required to detect a difference in mortality of 6% between the two study groups, with a two-sided α of 0.05 and a power of 80%. Statistical analysis was based on the intention to treat principle.

The results of the ICONIC trial, in which the effect of high- and low-oxygenation strategies on the 28-day mortality of mechanically ventilated ICU patients was evaluated, were described in **Chapter 4**. The original sample size was determined to be 1512 patients, but the study was stopped prematurely due to a significant delay caused by the COVID-19 pandemic. In total 882 patients were randomized to either the low-oxygenation group (PaO_2 55-80 mmHg) or the high-oxygenation group (110-150 mmHg) in 8 ICU in the Netherlands and 1 in Italy. In 664 patients informed consent could be obtained and these patients were included in the intention to treat analysis. The median achieved PaO_2 in the low-oxygenation group was 75 mmHg and in the high-oxygenation group 115 mmHg, with a median PaO_2 difference between the two groups of 40 mmHg. In total, 129 (38.5%) patients died within 28 days in the low-oxygenation group and 114 (34.7%) in the high oxygenation group (Risk Ratio 1.11, 95% Confidence Interval 0.9-1.4, P=0.30). The Kaplan Meijer survival curve showed no difference in mortality up to 28 days after randomization (P=0.4). No differences

were observed for ICU-, hospital- and 90-day mortality, ICU- and hospital length of stay, number of ventilator-free days at day 28, or ischemic events. Our data showed no reduction in 28-day mortality when using either a low- or a high-oxygenation strategy in mechanically ventilated ICU patients.

The follow-up study of the ICONIC trial assessed how patients reflect on participating in a study with deferred consent, and whether this opinion was dependent on their Quality of Life (QoL). Results of the follow-up study are described in **Chapter 5**. The study included patients proficient in Dutch and who were included in one of the Dutch ICUs by deferred consent (excluding those who gave consent before randomization). After verifying whether patients were alive after 6 months, patients received a questionnaire about deferred consent and QoL. The survey contained 12 closed-ended questions on whether they knew they had participated, on the deferred consent process, and the preferred decision-maker. In order to evaluate QoL the EQ-5D-5L questionnaire was used. To summarize the different health states of the EQ-5D-5L questionnaire the EQ-5D index was calculated, ranging from 0 (worst health) to 1 (full health). An ordinal regression analysis explored the relationship between deferred consent and QoL, considering EQ-5D-index, age and sex. Of the 664 ICONIC patients, 362 were eligible for this substudy, with 197 patients completing the questionnaire (54% response rate). Results indicated that while most patients were unaware of their participation (59%), they were generally positive towards the use of deferred consent. Patient with a higher QoL were more likely to be content (P=0.02). Our findings confirm that the deferred consent procedure is a suitable option for obtaining consent from ICU patients to participate in clinical studies.

In addition to standard metrics used for monitoring oxygen levels in ICU patients such as PaO_2 and SpO_2, **Chapter 6** explores whether the volume of oxygen administered during mechanical ventilation can be used as a direct parameter to assess oxygen exposure. The study hypothesized that this measure would be a more accurate and direct indicator of total oxygen exposure than previously used parameters. The volume of oxygen given during mechanical ventilation (MV) was calculated by estimating the area under the curve of FiO_2 and ventilatory minute volume over time (FiO_2 * ventilatory minute volume (L/min)* MV time (minutes)). The study retrospectively included 5017 eligible mechanically ventilated ICU patients. Findings revealed that the volume of oxygen administered during MV is independently associated with hospital mortality. Notably, in our data oxygen volume seemed to be more robust predictor of hospital mortality compared to existing oxygen exposure parameters like SpO_2, PaO_2 and the PaO_2/FiO_2 ratio. However, results were solely based on observational data. Therefore, future studies are needed to determine whether the volume of oxygen given during mechanical ventilation is relevant for patient outcomes.

Chapters 7 and 8 concern studies on coagulation. COVID-19 patients in the ICU often showed a prothrombotic state and venous and arterial thrombotic complications despite receiving adequate thromboprophylaxis. Unlike typical disseminated intravascular coagulation (DIC), COVID-19 patients showed high D-dimer levels (up to 20.000 ng/mL or higher), but generally normal platelet and coagulation test. As pathophysiology differed, questions were raised on whether conventional anticoagulant treatment was still effective. **Chapter 7** discusses the results of a clinical, radiological and laboratorial evaluation of pulmonary embolism (PE) in these patients. This study involved adult ICU patients diagnosed with COVID-19, who were mechanically ventilated and treated with unfractionated heparin (UFH) for PE which was confirmed by a CT scan. The thrombus load was assessed using the Qanadli obstruction index. The study defined its outcome measures across three categories: clinical outcomes, indicated by the absence of pulmonary embolism (PE) on follow-up CT scans or patient discharged alive from the ICU; radiological outcomes, assessed using the Qanadli index between baseline and follow-up CT scans; and laboratory outcomes, measured by comparing changes in D-dimers at baseline and day 2. The study included 19 patients, whose Qanadli index decreased significantly from baseline to follow-up ($p=0.03$), treatment was successful in 74% of the cases, and d-dimer levels decreasing with 17.9% and 14.6% in the first two days. These results suggest that standard therapeutic anticoagulant treatment is effective in managing PE in COVID-19 ICU patients.

In COVID-19 patients exceptionally high UFH doses were seen, often exceeding 35000 international units (IU) per 24 hours, to achieve activated partial thromboplastin time (APTT) levels within the therapeutic range. **Chapter 8** explores whether UFH doses were higher in COVID-19 ICU patients compared to a historical ICU cohort, and investigates potential factors causing these high doses. The study included COVID-19 patients treated with UFH for venous thromboembolism from March 15 to January 1, 2022, and non-COVID-19 patients treated with UFH for venous thromboembolism from January 1, 2014, to January 1, 2020. UFH was administered following a standard protocol, with a loading dose of 70 IU/kg (max 5000 IU) and a starting dose of 300 IU/kg/24 hours (max 30.000 IU/24 hours), aiming for an APTT between 60 and 80 seconds. In COVID-19 patients, anti-Xa levels were also measured daily. The study found that COVID-19 patients received higher doses (383 international units per kilogram per day (IU/kg/day)) than non-COVID-19 patients (308 IU/kg/day). Also, lower median APTT values were seen in COVID-19 patients compared to non-COVID-19 patients. Lower APTT values could not be explained by either BMI, CRP or AT levels. Other patient-related factors may have accounted for the differences in heparin administration.

Chapter 9 and 10 address studies on the Nociception Level (NOL) monitor. **Chapter 9** presents a pooled analysis of two randomized clinical trials that aimed to assess the

impact of intraoperative opioid dosing guided by the nociception level-index (NOL), a monitoring system that detects intraoperative nociceptive events using machine learning technology. The NOL-monitor assesses pain by combining heart rate, heart rate variability, peripheral vasoconstriction and skin conductance and translates this into an index ranging from 0 to 100. NOL values between 10-25 suggest adequate analgesia, values <10 in the presence of noxious stimuli may suggest excessive analgesia, and >25 may indicate need for additional analgesia. This study focused on evaluating the effect of NOL-guided analgesia on post-anesthesia care unit (PACU) pain in patients undergoing major abdominal surgery. The study involved 125 adult patients, with 61 receiving NOL-guided fentanyl dosing and 64 receiving standard care (fentanyl dosing based on hemodynamic parameters). The primary endpoint was the median pain score in the first 90 minutes in the PACU, collected on an 11-point Likert scale ranging from 0 to 10. The results showed that patients in the NOL group had significantly lower PACU pain scores (1.5 points lower) and a 70% reduction in the proportion of patients experiencing severe pain compared to the standard care group. Notably, the use of machine learning-based technology to guide opioid dosing during surgery led to decreased PACU pain scores and a reduced incidence of severe pain, highlighting its potential in improving postoperative pain management.

Chapter 10 investigates opioid use in the Intensive Care Unit (ICU) during the COVID-19 pandemic, particularly focusing on the potential overuse in COVID-19 patients. The study compares pain management in COVID-19 patients and non-COVID-19 patients using the Nociception Level (NOL) monitor and the Behavioral Pain Score (BPS). It involved 40 sedated and mechanically ventilated ICU patients, including 20 with confirmed COVID-19. Measurements taken included NOL, BPS, Richmond Agitation Sedation Scale (RASS), Bispectral Index (BIS) and nurse questionnaires. Primary outcomes were BIS and NOL values over time, along with secondary outcomes like propofol and sufentanil doses, RASS, BPS, and the feasibility of using NOL in the ICU. Results showed higher opioid doses in COVID-19 compared to non-COVID-19 patients (18 ± 9 µg/h versus 9 ± 6 µg/h, $p < 0.001$). Both groups had low NOL and BPS values with lower BIS and RASS values in the COVID-19 group, suggesting high analgesia in both groups and deeper sedation in the COVID-19 group. Since all patients had low BPS and NOL values, it could not be determined whether COVID-19 patients needed more opioids.

FUTURE PERSPECTIVES

When evaluation previous trials on oxygenation, concerns arose on whether the small differences between the two oxygenation groups ranging between 10-25 mm Hg, were large enough to yield meaningful differences in patient outcomes. In the ICONIC trial, a larger difference of 40 mmHg was found between the achieved higher and lower oxygenation target, but also no difference in 28 day mortality was seen. However it should be noted that in our trial, together with several previous trials, a small non-significant difference of 4% in favor of the high oxygenation target was seen, which is contrary to common beliefs based on lower oxygenation being more beneficial. One can wonder that if the study was not stopped prematurely whether a difference between the two groups would have been found. The small non-significant differences that were found may seem unimportant, but considering that supplemental oxygen is administered to hundreds of acutely ill patients daily, even small differences in mortality become of great significance. In future studies, large patient populations are needed to detect small mortality differences when comparing high and low oxygenation targets. Possibly, two ongoing trials, namely the UK-ROX and MEGA-ROX, including 16,500 and 40,000 patients, might provide us with a more definitive answer on which oxygen target to use in critically ill patients.

In addition to setting safe oxygen targets, it is crucial to determine whether we should continue searching for a one-fits-all approach, or to start to focus on an tailored approach for specific patient groups. In theory, a tailored approach for each patient group seems ideal, but up until now we do not have clear evidence as to which patients might benefit from higher or lower oxygenation strategies. It is plausible that if a difference is found for certain subgroups, it will likely be small, similar to when studying the entire ICU population. Therefore, I would not rule out a tailored approach and suggest conducting larger studies in specific patient groups in order to identify whether a tailored approach is more beneficial.

Another explanation of why an optimal oxygenation strategy has not yet been identified is the possibility that we are basing our research on the wrong parameters. Our oxygen-volume study showed that a novel parameter, namely the volume of oxygen administered, may be a stronger predicter of mortality and provide a more accurate reflection of oxygen exposure than established oxygen metrics. However, this conclusion was based solely on observational data and confounding is very likely since the most critically ill patients mostly have a higher minute ventilation, higher FiO_2 settings and were therefore exposed to a higher level of oxygen. Future studies, preferably randomized controlled trials, need to determine if this novel parameter is relevant for patient outcomes.

In the ICONIC study, informed consent was obtained using a deferred consent procedure. Our follow-up study revealed overall patient satisfaction with the deferred consent procedure, showing that patients with a higher QoL were more likely to be content. However, it should be noted that ICONIC participants reported a higher QoL compared to ICU patients in other studies. Therefore, in future research it would be interesting to explore whether this relationship still exists when patients with a lower QoL are also included in the analysis.

During the COVID-19 pandemic, the emergence of a hypercoagulable state and life-threatening pulmonary embolism (PE) urged for an evaluation of the efficacy of heparin in COVID-19 patients. We observed that, despite exceptionally high doses, standard therapeutic anticoagulant treatment is effective in managing PE in COVID-19 ICU patients. The higher UFH doses and lower APTT levels in COVID-19 patients could not be explained by the influence of AT, CRP, BMI, or additional anti-Xa monitoring. For the future, as many factors can potentially influence APTT measurements, using anti-Xa for UFH dosing instead may result in a more adequate dosing in ICU patients.

The use of machine-learning in the hospital is on the rise. A novel device, the Nociception Level (NOL) monitor, has been developed to guide pain management in sedated and ventilated patients. Combining two studies comparing NOL-guided analgesia with standard care in operating room (OR) showed a decrease in postoperative pain scores and fewer patients experiencing severe pain in the NOL-guided analgesia group. This could be useful in addressing the opioid crisis in the Netherlands, as improved pain regulation may lead to reduced opioid prescriptions upon discharge, potentially minimizing long-term opioid use. Further research is needed to explore this aspect.
The use of NOL in OR has been investigated in multiple studies, but its application in the ICU remains unexplored. While we could not definitively determine COVID-19 patients' opioid needs by using the NOL, we observed promising indications for the use of NOL in the ICU. Previous research has shown NOLs' ability to reduce stress hormones in OR patients. If similar reductions can be found in ICU patients, using NOL-guided analgesia can potentially have significant impact on both short- and long-term outcomes. However, large-scale randomized controlled trials are needed to confirm these benefits, also evaluating the cost-effectiveness of the NOL monitor.

CONCLUSIONS

The following conclusions can be drawn from this thesis:

- No reduction in 28-day mortality was seen when either using a low- or a high- oxygenation strategy in mechanically ventilated ICU patients.
- Patients generally found deferred consent an acceptable approach. Patients with a higher QoL were most likely to be content.
- Further research needs to be done on whether the novel parameter oxygen volume per minute administered during mechanical ventilation is relevant for patient outcomes.
- Standard anticoagulant treatment is effective in managing pulmonary embolism in COVID-19 ICU patients.
- COVID-19 patients received higher UFH doses compared to non-COVID-19 patients, a difference that could not be explained by CRP, BMI, AT, or additional anti-Xa monitoring.
- The use of machine learning-based technology to guide opioid dosing in the OR may lead to lower PACU pain scores and a lower incidence of severe pain.
- COVID-19 patients received higher opioid doses compared to non-COVID-19 patients. NOL could not identify whether COVID-19 patients needed higher doses of opioids.

PART V
APPENDICES

NEDERLANDSE SAMENVATTING

Bij de behandeling van ernstig zieke patiënten worden verschillende interventies toegepast om de vitale functies te stabiliseren en de homeostatische balans te herstellen. Op de intensive care (IC) worden hierbij in sommige gevallen streefwaarden gebruikt om de therapie op de meest effectieve manier toe te passen. Het doel van die proefschrift was om het gebruik van streefwaarden te verbeteren in drie kerngebieden, namelijk, oxygenatie, antistolling en pijnbestrijding. Zuurstof therapie is een van de meest fundamentele behandelingen op de IC. Het nauwkeurig toedienen van zuurstof is van belang omdat zowel te veel als te weinig zuurstof schadelijk kan zijn voor de patiënt. Streefwaarden worden op de IC tevens gebruikt bij het geven van antistollingsmedicatie. Overmatige antistolling kan namelijk leiden tot bloedingscomplicaties, terwijl een te lage dosering kan resulteren in een suboptimale therapie, welke potentieel fatale gevolgen kan hebben. Tot slot kan het gebruik van streefwaarden bij een objectieve pijnmeting het overmatig gebruik van opioïden voorkomen. Dit is van belang omdat overmatig gebruik van opioïden de duur van de beademing kan verlengen, en te weinig pijnbestrijding een stress reactie kan veroorzaken en een negatieve invloed kan hebben op verschillende fysiologische processen en het herstel van de patiënt.

Hoofdstuk 2 beschrijft een meta-analyse waarin de resultaten worden gecombineerd van de meest recente studies die hoge (liberale) en lage (conservatieve) zuurstof strategieën vergelijken bij beademde IC-patiënten. Hoewel eerdere onderzoeken en meta-analyses handvatten hebben geboden voor het toedienen van zuurstof in deze patiënten, waren de resultaten niet eenduidig en zijn sindsdien ook nieuwe studies gepubliceerd. In deze meta-analyse werden RCT's geïncludeerd die hoge en lage zuurstof strategieën vergeleken bij beademde en volwassen patiënten op de IC. Onderzoeken die zich uitsluitend op een specifieke subgroep richtten (bijv. patiënten met myocard of cerebrale ischemie) werden uitgesloten, evenals dierstudies, studies gericht op extra corporale ondersteuning of studies in de perioperatieve setting. De primaire uitkomstmaat was de mortaliteit na 90 dagen. Secundaire uitkomstmaten waren serious adverse events (SAE), het aantal beademings- en vasopressie- vrije dagen, en opnameduur. In de analyse werden negen randomized controlled trials (RCT) geïncludeerd met in totaal 5807 patiënten. Data aggregatie liet geen verschil zien in 90 dagen mortaliteit, beademings- en vasopressie- vrije dagen of opnameduur. Daarentegen werd er een significant verschil gevonden in het aantal SAE's, in het voordeel van de lage zuurstof groep, wat suggereert dat patiënten in de lage zuurstof groep een gunstiger resultaat hadden. Echter, het relatief kleine verschil dat werd gevonden tussen behaalde PaO_2 targets (10-25 mm Hg) van de twee oxygenatie groepen, riep de vraag op of het contrast tussen de groepen groot genoeg is om klinisch relevante resultaten te krijgen. Bovendien kan de data aggregatie beïnvloed zijn door de verschillende meetwaarden die gebruikt zijn voor het monitoren

van zuurstof niveaus in het bloed (FiO_2, PaO_2 of SpO_2), de verschillende streefwaarden en de verschillende gebruikte primaire en secundaire uitkomstmaten. Toekomstig onderzoek zou zich moeten richten op het creëren van een adequaat verschil in PaO_2 waarden tussen de twee verschillende interventiegroepen en de mogelijke impact van belangrijke bijwerkingen van zuurstof.

Hoofdstuk 3 bespreekt het ICONIC-protocol, een internationale, multicenter studie met als doel om meer inzicht te bieden in optimale zuurstoftargets op de IC. Volwassen patiënten met een verwachte beademingsduur van minstens 24 uur konden geïncludeerd worden in de studie. De belangrijkste exclusie criteria waren acuut respiratoir distressyndroom (ARDS, PaO_2/FiO_2 <150 mmHg), acute exacerbaties van chronische obstructieve longziekte (COPD) en onderliggende ziekten met een indicatie voor hyperoxygenatie. Volgens het protocol werden geschikte patiënten binnen twee uur na intubatie gerandomiseerd voor ofwel de lage (conservatieve) zuurstoftarget (PaO_2 55-80 mmHg) of de hoge (liberale) zuurstoftarget (110-150 mmHg). Zuurstoftargets werden ook na extubatie nagestreefd, namelijk, patiënten gerandomiseerd voor de lage zuurstoftarget kregen geen extra zuurstof tenzij een PaO_2 onder de 55mmHg werd gemeten, en patiënten gerandomiseerd voor de hoge zuurstoftarget kregen standaard een neusbril met 5L O_2 na extubatie, tenzij een PaO_2 boven de 150 mmHg werd gemeten. De interventie werd gecontinueerd tot 28-dagen na randomisatie of tot de patiënt van de IC werd ontslagen, afhankelijk van welk eindpunt eerst voorkwam. Vanwege de aard van de studie-interventie konden clinici niet geblindeerd worden voor de interventie, maar data-analisten bleven wel geblindeerd. De primaire uitkomstmaat was 28 dagen mortaliteit. Secundaire uitkomtmaten waren het aantal beademingsvrije dagen op dag 28, IC- en ziekenhuis-opnameduur, IC-, ziekenhuis- en 90-dagen mortaliteit, en het aantal ischemische events. Om de kwaliteit van leven van de patiënten en hun mening over het gebruik van deferred consent te beoordelen, werden de EQ5D-vragenlijst (na 12 en 6 maanden) en een vragenlijst over deferred consent (na 6 maanden) afgenomen. Om een absoluut verschil tussen de twee groepen van 6% aan de tonen, met een tweezijdige α van 0.05 en een power van 80%, was er een sample size van 1512 patiënten nodig. De statistische analyse zou worden uitgevoerd aan de hand van het intention-to-treat principe.

In **hoofdstuk 4** zijn de resultaten de ICONIC-studie beschreven, een studie waarin het effect van hoge- en lage zuurstoftargets op de 28-dagen mortaliteit van beademde IC-patiënten werd onderzocht. De oorspronkelijke sample size was vastgesteld op 1512 patiënten, maar de studie werd vroegtijdig gestopt vanwege een ernstige vertraging in de inclusie die werd veroorzaakt door de COVID-19-pandemie. In totaal werden in acht IC's in Nederland en één IC in Italië 882 patiënten gerandomiseerd voor de lage- (PaO_2 55-80 mmHg) of de hoge zuurstoftarget (110-150 mmHg). Uiteindelijk werden

er in totaal 664 patiënten, waarvan een getekend informed consent formulier aanwezig was, meegenomen in de intention-to-treat analyse. De mediane PaO_2 was 75 mmHg in de lage zuurstofgroep en 115 mmHg in de hoge zuurstofgroep, met een verschil in bereikte PaO_2 waardes van 40mmHg tussen de twee groepen. In totaal stierven 129 (38.5%) patiënten binnen 28 dagen in de lage zuurstofgroep en 114 (34.7%) in de hoge zuurstofgroep (Risk Ratio 1.11, 95% betrouwbaarheidsinterval 0.9-1.4, p=0.3). De Kaplan-Meijer survival curve liet geen verschil in mortaliteit zien (p=0.4). Er werden tevens geen verschillen waargenomen in IC-, ziekenhuis- en 90-dagen mortaliteit, IC en ziekenhuis opnameduur, aantal beademingsvrije dagen op dag 28, of ischemische events. Concluderend liet onze data geen lagere 28-dagen mortaliteit zien bij gebruik van een lage- of hoge zuurstoftarget.

De follow-up studie van de ICONIC-studie onderzocht hoe patiënten terugkijken op deelname aan een studie waarbij informed consent werd verkregen door deferred consent, en of deze mening beïnvloed werd door hun kwaliteit van leven (QoL). De resultaten van de follow-up studie worden geschreven in **hoofdstuk 5**. De studie includeerde patiënten die de Nederlandse taal beheersten en in een van de Nederlandse IC's waren geïncludeerd met behulp van deferred consent (met uitzondering van degenen die toestemming gaven vóór randomisatie). Nadat werd geverifieerd of patiënten na 6 maanden nog in leven waren, ontvingen zij een vragenlijst over deferred consent en kwaliteit van leven. De enquête bevatte 12 gesloten vragen over of patiënten wisten van hun deelname, over het proces van deferred consent en over welke persoon zij prefereerden om toestemming voor hen te geven als zij daar zelf niet toe in staat waren. Om de kwaliteit van leven te evalueren werd de EQ-5D-5L vragenlijst gebruikt. Om de verschillende gezondheidsniveaus van de EQ-5D-5L vragenlijst samen te vatten werd de EQ-5D index berekend, variërend van 0 (slechtste gezondheid) tot 1 (volledige gezondheid). Een ordinale regressie analyse werd gebruikt om de relatie tussen deferred consent en kwaliteit van leven te onderzoeken, waarbij rekening werd gehouden met de EQ-5D-index, leeftijd en geslacht. Van de 664 ICONIC-patiënten kwamen er 362 in aanmerking om deel te nemen aan de studie. In totaal vulden 197 van de 362 patiënten de vragenlijsten in (54%). De resultaten toonden aan dat hoewel de meeste patiënten zich niet bewust waren van hun deelname aan de studie (59%), ze over het algemeen positief waren over het gebruik van deferred consent. Patiënten met een hogere kwaliteit van leven hadden een hogere mate van tevredenheid (p=0.02). Onze data liet zien dat deferred consent een geschikte optie is voor het verkrijgen van toestemming van patiënten op de IC als ze daar zelf niet toe in staat zijn.

Naast de standaard meetmethoden die worden gebruik voor het monitoren van het zuurstofniveau bij IC-patiënten, zoals PaO_2 en SpO_2, onderzoekt **hoofdstuk 6** of het volume van toegediende zuurstof tijdens mechanische beademing kan worden

gebruikt als een directe parameter om de hoeveelheid zuurstof waaraan patiënten worden blootgesteld te meten. De studie stelt de hypothese dat deze parameter een zorgvuldigere en directere parameter is van de totale zuurstofblootstelling in tegenstelling tot eerdere gebruikte parameters. Het volume van toegediende zuurstof tijdens mechanische beademing (MV) werd berekend door een inschatting te maken van de area under the curve van FiO_2 vermenigvuldigt met het ademminuutvolume gedurende de beademingstijd (FiO^2 * ventilatory minute volume (L/min) * beademingstijd (minutes)). In totaal werden er retrospectief 5017 patiënten geïncludeerd. Onze data liet een onafhankelijke associatie zien van MV met ziekenhuissterfte. Opvallend was dat in onze gegevens het zuurstofvolume een robuustere voorspeller van ziekenhuissterfte leek te zijn vergeleken met bestaande parameters zoals SpO_2, PaO_2 en de PaO_2/FiO_2 ratio. Echter, de resultaten zijn uitsluitend gebaseerd op observationele gegevens. Daarom zijn toekomstige studies nodig om te bepalen of het volume van toegediende zuurstof tijdens mechanische beademing klinisch relevant is voor patiënten.

In **hoofdstuk 7 en 8** worden studies over antistolling bij COVID-19 patiënten op de IC besproken. COVID-19 patiënten op de IC hadden, ondanks dat adequate tromboprofylaxe, vaak een verhoogde stollingsneiging met bijbehorende veneuze en arteriële trombotische complicaties. In tegenstelling tot diffuus intravasale stolling (DIS), toonden COVID-19 patiënten hoge D-dimeerwaarden (tot 20.000 ng/mL of hoger), maar geen trombocytopenie of afwijkende stollingstesten. Omdat er sprake was van een andere pathofysiologie, vroeg men zich af of de behandeling met conventionele anticoagulantia wel effectief was in deze patiënten groep. **Hoofdstuk 7** bespreekt de resultaten van een studie die de behandeling van longembolieën met ongefractioneerde heparine (UFH) in COVID-19 patiënten evalueert aan de hand van klinische, radiologische, en bloeduitslagen. Deze studie includeerde beademde volwassen IC-patiënten met COVID-19, waarbij longembolieën waren vastgesteld middels een CT-scan en die behandeld werden met UFH. De mate van obstructie van de trombus werd berekend door middel van de Qanadli index. Uitkomstmaten werden opgedeeld in drie categorieën: klinische uitkomsten, gedefinieerd als de afwezigheid van longembolieën op de follow-up CT-scans of een patiënt die levend werd ontslagen van de IC; radiologische uitkomsten, gedefinieerd als het verschil van de Qanadli-index tussen baseline en follow-up CT-scan; en aan de hand van bloeduitslagen, gedefinieerd als de verandering in D-dimeerwaarden op dag 0 en dag 2. De studie includeerde 19 patiënten, waarvan de Qanadli-index significant daalde ($p=0.03$), de behandeling succesvol was in 74% van de gevallen, en de D-dimeerwaarden daalden met 17.9% en 14.6% in de eerste twee dagen. Onze resultaten laten zien dat behandeling van longembolieën van COVID-19 patiënten op de IC met standaard anticoagulantia effectief zijn.

COVID-19 patiënten hadden uitzonderlijke hoge doses UFH nodig, vaak meer dan 35.000 internationale eenheden (IE), om een therapeutische APTT te bereiken. **Hoofdstuk 8** onderzoekt of UFH-doseringen op de IC hoger waren bij COVID-19 patiënten vergeleken met reguliere IC patiënten. Bij een eventuele hogere dosering werd er ook gekeken naar factoren die hierbij mogelijk een rol speelden. De studie includeerde COVID-19-patienten die behandeld werden met UFH voor een veneuze trombo-embolie en werden opgenomen tussen 15 maart 2020 en 1 januari 2022. In het historische cohort werden patiënten geïncludeerd die opgenomen waren tussen 1 januari 2014 en 1 januari 2020. UFH werd toegediend volgens een standaardprotocol, met een oplaaddosis van 70 IE/kg (maximaal 5000 IE) en een startdosis van 300 IE/kg/24 uur (maximaal 30.000 IE/24 uur), waarbij een APTT tussen de 60 en 80 seconden werd nagestreefd. Bij COVID-19 patiënten werd ook dagelijks een anti-Xa spiegel gemeten. Onze data liet een hogere dosis UFH zien voor COVID-19 patiënten (383 internationale eenheden per kilogram per dag (IE/kg/dag)) vergeleken met de patiënten in het historische cohort (308 IE/kg/dag). Ook werden lagere mediane APTT-waarden gezien bij COVID-19 patiënten, welke niet verklaard konden worden door BMI, CRP of AT. Andere patiënt gerelateerde factoren spelen mogelijk een rol bij de hogere UFH dosering in COVID-19 patiënten.

In **hoofdstuk 9 en 10** worden studies over de Nociception level (NOL) monitor besproken. **Hoofdstuk 9** laat de resultaten zien van een gepoolde analyse van twee RCT's die hebben gekeken naar de invloed van het gebruik van de NOL-monitor voor het sturen van de pijnstilling op de postoperatieve pijnscores op de verkoever. De NOL-monitor is een apparaat die intra-operatieve nociceptieve events kan herkennen. Er wordt een inschatting gemaakt van de pijn door hartslag, hartslagvariabiliteit, perifere vasoconstrictie en geleiding van de huid te combineren en te vertalen naar een index tussen de 0 de 100. NOL-waarden tussen de 10-25 suggereren adequate analgesie, waarden <10 geven aan dat er mogelijk teveel pijnstilling is gegeven, en waarden >25 geven aan dat er mogelijk te weinig pijnstilling wordt gegeven. Deze studie richtte zich voornamelijk op de invloed van NOL-gestuurde analgesie op de pijnscores van patiënten na een grote buikchirurgie. In deze studie werden 125 volwassen patiënten geïncludeerd, waarvan 61 patiënten pijnstilling kregen op basis van NOL-waarden, en 64 patiënten de standaard behandeling kregen (fentanyl gedoseerd op basis van hemodynamische parameters). Het primaire eindpunt was de mediane pijn score in de eerste 90 minuten op de PACU, die werd gescoord op basis van een 11-punts Likert schaal tussen 0 en 10. De resultaten lieten een significant lagere pijnscore (1.5 punten lager) zien en een reductie van 70% in het aantal patiënten met ernstige postoperatieve pijn in de NOL-groep vergeleken met de standaard behandeling. Concluderend zorgde het gebruik van de NOL-monitor ervoor dat patiënten lagere pijnscores hadden en een lagere incidentie van ernstige postoperatieve pijn. Mogelijk kan het gebruik van de

NOL op grotere schaal postoperatieve pijn verminderen.

Hoofdstuk 10 onderzoekt het gebruik van opioïden op de IC tijdens de COVID-19 pandemie. De studie vergelijkt pijnmanagement bij COVID-19 patiënten en niet-COVID-19 patiënten met behulp van de Nociception Level (NOL) monitor en de Behavioral Pain Score (BPS). In totaal werden 40 gesedeerde en beademde IC-patiënten geïncludeerd, waarvan 20 een bewezen COVID-19 infectie hadden. Van bovengenoemde patiëntengroepen werd data verzameld over de NOL-waarden, BPS, Richmond Agitation Sedation Scale (RASS), Bispectral Index (BIS) en een vragenlijst over de inschatting van pijn bij gesedeerde patiënten die werd afgenomen onder verpleegkundigen. Primaire uitkomstmaten waren BIS- en NOL-waarden gedurende 8 uur. Secundaire uitkomstmaten waren de dosering van propofol en sufentanil, RASS en BPS waarden, en er werd gekeken of het gebruik van de NOL monitor een toegevoegde waarde heeft op de IC. De resultaten lieten een hogere ipioïd-dosering bij COVID-19 patiënten zien vergeleken met de controle groep (18 $\pm$ 9 µg/h versus 9 $\pm$ 6 µg/h, p <0.001). Beide groepen hadden lage NOL- en BPS-waarden, met lagere BIS- en RASS-waarden in de COVID-19 groep, wat wijst op hoge analgesie in beiden groepen en diepere sedatie in de COVID-19 groep. Aangezien alle patiënten lage BPS- en NOL-waarden hadden, kon niet worden vastgesteld of COVID-19 patiënten meer opioïden nodig hadden dan niet-COVID-19 patiënten.

Toekomstperspectieven

De kleine verschillen tussen de twee oxygenatiegroepen die gevonden zijn in eerdere onderzoeken, variërend tussen de 10-25 mmHg, riepen vragen op of de verschillen tussen de twee oxygenatiegroepen groot genoeg waren om uitkomsten te geven die klinisch relevant zijn voor patiënten. In de ICONIC-studie werd een groter verschil van 40 mmHg gevonden tussen de hoge en de lage zuurstof targets, maar ook hier werd geen verschil in 28 dagen mortaliteit gevonden. Echter, in de ICONIC studie werd, net als in andere eerdere studies naar dit onderwerp, een klein niet-significant verschil gevonden van 4% in het voordeel van de hoge zuurstof target gezien, wat in tegenspraak is met de gangbare opvatting dat lagere zuurstoftargets gunstiger zouden zijn. Men kan zich afvragen of, als de studie niet voortijdig gestopt was, er een significant verschil tussen de twee groepen gevonden zou zijn. De kleine niet-significante verschillen die werden gevonden lijken niet belangrijk, maar aangezien zuurstof dagelijks gegeven wordt aan honderden acuut zieke patiënten zijn ook kleine verschillen in mortaliteit van groot belang. In toekomstige studies naar hoge en lage zuurstoftargets zijn grotere aantallen patiënten nodig om kleine verschillen in mortaliteit aan te kunnen tonen. Mogelijk kunnen twee lopende studies, namelijk de UK-ROX en de MEGA-ROX, met respectievelijk 16.500 en 40.000 patiënten, ons een definitief antwoord geven over welke zuurstof target het beste is bij acuut zieke en beademde patiënten.

Naast het vaststellen of een zuurstof target veilig is, is het van cruciaal belang om te bepalen of we moeten blijven zoeken naar een universele benadering, of dat we ons gaan richten op een gepersonaliseerde benadering voor specifieke patiënten groepen. Theoretisch lijkt een gepersonaliseerde benadering beter, maar tot op heden hebben we geen duidelijk bewijs welke patiënten zouden kunnen profiteren van hoge of lage zuurstof targets. Het is aannemelijk dat als er een verschil gevonden wordt voor specifieke patiënten groepen dat dit, net als in de gehele IC populatie, een klein verschil zal zijn. Een gepersonaliseerde benadering per patiënten groep moet zeker niet uitgesloten worden, maar waarschijnlijk zijn hier ook grotere studies nodig om te bepalen of een gepersonaliseerde benadering voordelen voor de patiënt oplevert.

Een andere verklaring waarom het nog niet gelukt is om een optimale zuurstof strategie te vinden is de mogelijkheid dat we ons onderzoek baseren op de verkeerde parameters. Onze Oxygen-volume studie liet zien dat een nieuwe parameter, namelijk de hoeveelheid toegediende zuurstof per minuut, mogelijk een betere voorspeller is voor de mortaliteit dan de huidige zuurstof parameters. Hoe meer zuurstof er werd toegediend per minuut, hoe hoger de mortaliteit. Deze conclusie was echter uitsluitend gebaseerd op observationele data en de invloed van confounding is zeer waarschijnlijk aangezien de meest zieke patiënten meestal een hogere minuutventilatie en hogere FiO_2 instellingen hebben en daardoor aan een hoger zuurstofniveau worden blootgesteld. Toekomstige studies, bij voorkeur RCT's, moeten bepalen of het gebruik van deze nieuwe parameter ook relevant kan zijn voor de klinische uitkomsten van de patiënt.

In de ICONIC studie werd toestemming verkregen via een uitgestelde toestemmingsprocedure, ofwel deferred consent. Onze follow-up studie van de ICONIC toonde aan dat patiënten over het algemeen tevreden waren over de deferred consent procedure, waarbij patiënten met een hogere kwaliteit van leven (QoL) het meest tevreden waren. Het moet echter worden opgemerkt dat de ICONIC-deelnemers over het algemeen een hogere QoL rapporteerden dan IC-patiënten in eerdere studies naar QoL. Daarom zou het in de toekomst erg interessant zijn om te onderzoeken of deze correlatie nog steeds bestaat in een studie die ook patiënten includeert met een lagere QoL.

Tijdens de COVID-19-pandemie zorgde een verhoogde stollingsactiviteit in combinatie met levensbedreigende longembolieën ervoor dat de behandeling en effectiviteit van ongefractioneerde heparine (UFH) opnieuw werd geëvalueerd. In onze data zagen we dat, ondanks uitzonderlijk hoge doseringen, UFH effectief is in het behandelen van longembolieën bij COVID-19 patiënten op de IC. De hogere UFH doseringen en lagere APTT-waarden bij COVID-19 patiënten konden niet worden verklaard door de invloed van AT, CRP, BMI of extra anti-Xa monitoring. Aangezien veel factoren APTT-metingen

kunnen beïnvloeden, kan het gebruik van anti-Xa monitoring voor het sturen van de UFH dosis in de toekomst zorgen voor een adequatere dosering bij IC-patiënten.

Het gebruik van machine learning in het ziekenhuis neemt steeds meer toe. Een nieuw apparaat, de Nociception Level (NOL) monitor, is ontwikkeld om het geven van pijnstilling beter te titreren in gesedeerde en beademde patiënten. Een gepoolde data analyse van twee studies die het sturen van analgetica met behulp van de NOL monitor vergeleken met de standaard behandeling liet een afname zien van de postoperatieve pijnscores en ernstige postoperatieve pijn in de NOL-gestuurde analgesie groep. Deze resultaten kunnen nuttig zijn bij het aanpakken van de Opioïdencrisis in Nederland, aangezien betere regulatie van pijn ervoor kan zorgen dat er minder opiaten worden voorgeschreven bij ontslag. Dit kan mogelijk langdurig opiaatgebruik verminderen. Er is meer onderzoek nodig om aan te tonen dat het gebruik van de NOL ook daadwerkelijk tot een vermindering van het opioïd gebruik zal leiden.

Het gebruik van NOL op de OK is in meerdere studies onderzocht, maar de toepassing ervan op de IC blijft onduidelijk. Hoewel we niet definitief konden vaststellen wat de opiaatbehoefte van COVID-19-patienten is met behulp van de NOL, concludeerden we dat het gebruik van de NOL wel van toegevoegde waarde kan zijn op de IC. Eerder onderzoek heeft aangetoond dat NOL in staat is om stresshormonen te verminderen bij patiënten op de OK. Als vergelijkbare reducties in stresshormonen ook bij IC-patiënten worden gezien, kan het gebruik van NOL-gestuurde analgesie mogelijk een grote impact hebben op zowel korte-als lange termijn uitkomsten. Grootschalige RCT's zijn echter nodig om deze voordelen te bevestigen, waarbij ook de kosteneffectiviteit van de NOL-monitor moet worden geëvalueerd.

Conclusies

- Er werd geen lagere 28-dagen mortaliteit gezien bij beademde IC-patiënten wanneer er een lage- of hoge-zuurstof strategie werd gebruikt.
- Patiënten vonden het over het algemeen acceptabel als toestemming voor wetenschappelijk onderzoek werd verkregen door middel van deferred consent. Patiënten met een hogere kwaliteit van leven waren het meest tevreden over de procedure.
- Er is meer onderzoek nodig om te bepalen of de hoeveelheid toegediende zuurstof per minuut tijdens beademing klinisch relevant is voor de uitkomsten van de patiënt.
- De standaard behandeling van longembolieën met UFH bij COVID-19 patiënten op de IC is effectief.
- COVID-19 patiënten kregen hogere UFH doseringen in vergelijking met niet-COVID-19-patienten, een verschil dat niet verklaard kon worden door CRP,

BMI, AT of extra anti-Xa monitoring.

- Het gebruik van de NOL om pijnstilling op de OK te doseren kan voor lagere PACU-pijnscores en een lagere incidentie van ernstige postoperatieve pijn zorgen.
- COVID-19-patienten kregen een hogere dosering opiaten in vergelijking met niet-COVID-19 patiënten. De NOL-monitor kan niet vaststellen of COVID-19 patiënten deze hogere dosering ook daadwerkelijk nodig hadden.

CURRICULUM VITAE

Lea Imeen van der Wal werd geboren op 24 november 1992 in Gendringen, Nederland, en groeide op in Ulft samen met haar ouders, zus en broer. Na het behalen van haar VWO-diploma in 2011 startte zij dat jaar met de studie Farmacie aan de Rijksuniversiteit Groningen. Na het succesvol afronden van haar propedeuse van de studie Farmacie in 2012 maakte zij de overstap naar de Engelstalige variant van de Geneeskunde studie in Groningen, de International Bachelor Medicine Groningen (IBMG), met een speciale focus op global health. Haar co-schappen deed ze in het Martini ziekenhuis, het Deventer Ziekenhuis en het Diakonessenhuis in Utrecht en haar masterscriptie schreef ze aan de Universiteit van Amsterdam. Ook deed ze een deel van haar co-schappen in het Louis Filipe Moncada Hospital in San Carlos, Nicaragua. In december 2018 behaalde zij haar Master Geneeskude aan de Rijksuniversiteit Groningen.

Om ervaring op te doen als beginnend arts werkte zij als arts niet in opleiding tot specialist binnen de medisch-oncologische disciplines in het Antoni van Leeuwenhoek Ziekenhuis in Amsterdam. Gedreven door haar interesse voor de Intensive Care en Anesthesiologie maakte ze in februari 2020 de overstap naar de Intensive Care van het Leids Universitair Medisch Centrum (LUMC), waarna ze in juni 2020 begon aan haar promotieonderzoek op diezelfde afdeling. In januari 2024 startte zij met de opleiding tot anesthesioloog in het LUMC.

In haar vrije tijd houdt ze van reizen, hardlopen en lekker eten met vrienden en familie. Op dit moment woon ze in Utrecht met haar man Cas de Jongh.

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