Sedation in the ICU

Less is more …

Thomas Strøm

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Tutor: Palle Toft

Official opponents: Wesley Ely, Peter Sackey, Court Pedersen.

Correspondence: Department, Department of Anaesthesiology and Intensive Care, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark

E-mail: t.s@dadlnet.dk

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This PhD thesis is based on the following 4 papers that will be referred to by their roman numerals:

I. Strom T, Toft P. Time to wake up the patients in the ICU. A Crazy idea or common sense? Minerva Anestesiol 2011 Jan; 77(1):59-63.
II. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010 February 6;375(9713):475-80.
III. Strom, T., R. R. Johansen, J. O. Prahl, and P. Toft. 2011. Sedation and renal impairment in critically ill patients: a post hoc analysis of a randomized trial. Crit Care 15:R119.
IV. Strom T, Stylsvig M, Toft P. Long-term psychological effects of a no-sedation protocol in critically ill patients. Crit Care 2011 December 13; 15(6):R293.

List of abbreviations

APACHE II	**Acute Physiology and Chronic Health Evaluation**
ARDS	**Adult Respiratory Distress Syndrome**
CAM-ICU	**Confusion Assessment Method for the Intensive Care Unit**
CRRT	**Continuous Renal Replacement Therapy**
GFR	**Glomerular Filtration Rate**
LOS	**Length of Stay**
PTSD	**Post Traumatic Stress Disorder**
RASS	**Richmond Agitation-Sedation Scale**
RIFLE	**Acronym indicating Risk of renal dysfunction; Injury to the kidney; Failure of kidney function, Loss of kidney function and End-stage kidney disease**
SAPS II	**Simplified Acute Physiology Score**
SOFA	**Sequential Organ Failure Assessment**
VAP	**Ventilator Associated Pneumonia**

"….But what I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise."

Thomas L. Petty(1)

2. INTRODUCTION

For patients admitted to the Intensive care department undergoing mechanical ventilation, the golden standard of care has been to receive sedation [3-6]. However sedatives are not organ specific medications and much attention over the last decade has focused on the negative effects of sedatives. Medications administered to relieve suffering caused by critical illness might turn out to have the opposite effect; critically ill patients might become more ill because of the treatment with sedatives [7].

Background

In the early days of intensive care during the polio epidemic in Copenhagen in 1952, patients were dying because of mono organ failure: they lost the ability to breathe. Because of the infection the respiratory muscles were paralyzed and patients died from respiratory fatigue and inability to clear the airways. The anesthetist Bjørn Ibsen realized that patients were dying from a combination of hypoxia and hypercarpnia. The patients were therefore tracheostomized and breathing was supported by manual ventilation (figure 1). For the first time basic skills developed in the operation theater were used to save the lives of critically ill patients. Hands were few and medical students were summoned to help in this special situation. It proved to be a very effective treatment, and no treatment since in the history of intensive care has been able to reduce mortality from 90 % to 20 % as quickly and as effectively. The results were published in The Lancet and heralded the start of modern intensive care therapy [8-10].

During the polio epidemic learning from anesthesia proved to be very effective in treating patients. With the introduction of modern sedatives with acceptable half-lives, administered by infusion pumps, other skills migrated from anesthesia to intensive care and a new era began [11]. The earlier practice of hand ventilation by medical students was replaced by mechanical ventilators. Patients were put to sleep to accept the insensitive ventilators. Once again lessons from anesthesia were extended to intensive care but this time not necessarily to the benefit of the patients (se article I) [12].

Figure 1 : *Student ventilating and reading to a young polio patient. Copenhagen 1952 (Photo kindly provided by Dr. P. Bertelsen).*

Less is more…

A landmark was reached in 1998 with Kollef and Colleagues publication of a trial reporting an association between the continuous use of sedative infusion and the length of mechanical ventilation and intensive care length of stay [13]. The study was however retrospective and no causal relationship could be established. However this was established the year after in 1999, when the same group published a prospective randomized trial showing a beneficial effect of a nurse-driven sedation protocol [14]. Also the protocol's use of bolus doses instead of continuous infusion of sedatives proved beneficial. The group reported a shorter stay in mechanical ventilation, shorter stay in the intensive care department and shorter hospital length of stay. The beneficial effect was probably obtained through a continuous adjustment of the sedatives to meet the patient's needs, thus preventing unnecessary over sedation. The year after, in 2000, Kress and colleagues published a paper in NEJM which had a large impact [15]. 150 patients were randomized in two groups: an intervention group who, beside a sedation target of RAMSAY 3-4, received a daily interruption of sedative infusions. The control group received standard care with no target level of sedation, or interruption of the sedative infusions on a daily basis. The authors reported a significant reduction in time receiving mechanical ventilation of 2.5 days, a reduction in intensive care length of stay of 3.5 days. Another finding from the trial was that the need for CT and MR scans of cerebrum was significantly lower in the intervention group receiving a daily interruption of the sedatives. The database of patients from the study was retrospectively analyzed by investigators not directly involved in the study. They found a higher number of complications in the control group receiving continuous sedatives without interruption compared to the intervention group receiving a daily interruption of sedatives [16].

The logical and beneficial connection between weaning the patient from the ventilator and cessation of sedatives was the main intervention in Girard and Colleagues multicenter study published in the Lancet in 2009 randomizing 336 patients [17]. Earlier studies had shown a beneficial effect of a spontaneous breathing trial: by combining this with a daily interruption of sedatives, the authors could report a reduced time in mechanical ventilation, shorter intensive care and hospital length of stay [18]. Surprisingly the authors also reported lower one-year mortality in the intervention group compared to the control group.

Psychological consequences

Another rationale behind the use of sedation has been to relieve the patients from the suffering of critical illness. No one can doubt the suffering that critically ill patients experience while they fight to remain alive (figure 2).

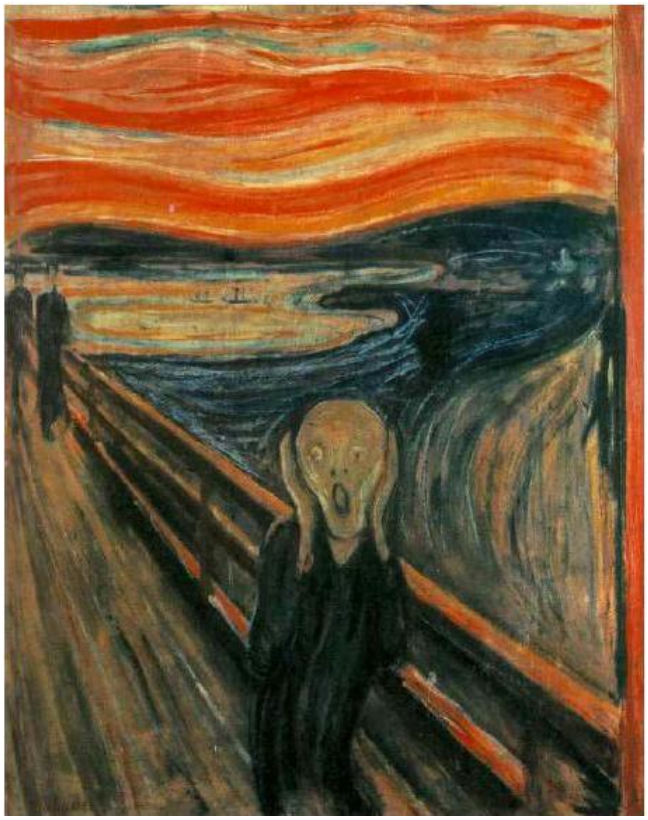

Figure 2: *The Scream by Edward Munch, 1893. The National Museum, Oslo*

However the pharmacological induction of a state of reduced consciousness does not necessarily eliminate the risk of psychological long term sequelae.

Jones and colleagues reported that patients with no real memory

of their intensive care stay had a higher risk of post-traumatic stress than patients with real or delusional memories [19]. This study was retrospective other causes than the use of sedation- such as severity of the disease, probably played an important role. The findings was however interesting.

Kress and colleagues conducted a psychological follow-up study on patients who had been through the same treatment modalities as in the authors' original study [20]. 32 patients were interviewed and the authors reported a lower risk of post-traumatic stress disorder (PTSD) in the intervention group with daily interruption of sedatives compared to the sedated control group. A daily interruption of sedatives did not increase the risk of a poor psychological outcome.

The same follow-up study was conducted with patients from the study by Girard and colleagues [21]. They did a three and twelve month's follow-up which involved 90 patients at three months and 63 patients at 12 months. Patient dropouts were mainly because of death. They reported a lower incidence of PTSD at 3 months follow-up in the group of patients from the intervention group who underwent both spontaneous breathing trials and daily interruption of sedation compared to the control group where patients only underwent spontaneous breathing trials. However at 12 months there was no longer any difference between the groups.

Treggiari and colleagues published a randomized prospective study including 137 patients comparing a strategy of light versus deep sedation [22]. They reported more ventilator-free days and ICU-free days with a strategy of light sedation. However their primary endpoint was psychological outcome and they showed a trend towards a lower PTSD score (P=0.07) with the use of light sedation compared to a strategy with deeper levels of sedation.

No sedation- is it possible?

A natural step in the evolution of critical care in terms of sedation practice would be to lower the use of sedatives to zero [3]. This approach was called for on several occasions in the literature [23-26]. As a natural consequence of modern ventilators and a demand for continuously monitoring of the CNS function, all routine sedative infusions were stopped in 1999 at the multidisciplinary intensive care department at Odense University hospital in Denmark (figure 3). For almost a decade, the department was like a foreign island, isolated alone with this practice. The impression was that patients were liberated earlier from mechanical ventilation and other measures such as length of stay in the intensive care department were also reduced with this no sedation strategy.

Before continuous renal replacement therapy (CRRT) was common in most ICU's, patients needing CRRT were referred from other departments in the region. Often patients were receiving a "battery" of medical infusions: sedatives, vasopressors, inotropes, and antiarrythmics. When the patients arrived, the strategy was to turn off sedation, often in the hallway before the patient had been transferred from the ambulance stretcher to the ICU bed. The other drugs could then be reduced quickly, if not completely turned off within hours. Another goal was to shift from controlled ventilation to pressure support ventilation as soon as the patients triggered the ventilator. Not infrequently the urine output returned after removing sedation, and CRRT was never employed. Although these stories abounded, and a strategy of no sedation was routine in the department, the final proof, a randomized controlled prospective study, was needed. Also concerns had been expressed about the long-term psychological effects of this strategy. It was perhaps possible to manage patients without sedation, but what was the risk of developing Post Traumatic Stress (PTSD) afterwards [27, 28]

We therefore took it upon us to conduct a randomized controlled prospective trial, investigating the effect of a no sedation strategy employed in critically ill patients in need of mechanical ventilation. The major endpoints were defined as length of mechanical ventilation, length of ICU and total hospital length of stay. The study investigating renal effects was conceived after finalizing randomization of patients to the main study, and designed as a post hoc analysis. Also we planned a psychological follow up trial, a prospective cohort study, with the primary endpoint being cognitive and psychological outcome at follow up.

Figure 3: *Awake and mobilized patient undergoing mechanical ventilation (with permission).*

"I have come gradually to realize two facts: the first that relief from pain is purchased always at a price, and the second that the price in both morbidity and mortality does not greatly differ whatever the agent or agents used."(2)

Ralph Milton Waters

3. METHODS

Design overview

In the main study the primary end point was to prove the effect of a no sedation strategy compared to a standard strategy with sedation and daily interruption of sedative infusions. The primary endpoints were the length of mechanical ventilation, length of ICU stay and total hospital length of stay. Secondary endpoints were the number of ventilator associated pneumonias (VAP), number of CT or MR scans of the cerebrum and number of accidental extubations. In the renal posthoc study we defined the renal effects in terms of urine output and RIFLE classification as the primary endpoints. Secondary endpoints were the mean arterial blood pressure, fluid balance and the use of vasoactive drugs between the two groups. For the psychological follow up

study the primary endpoint was the rate of PTSD between the groups. Other measures such as general health, rate of depression and recalls from the ICU were secondary outcomes.

Participants

Patients were recruited from the 18-bed general ICU at Odense University Hospital. Patients were considered eligible if the need for mechanical ventilation was expected to exceed 24 hours. Exclusion criteria was age below 18, pregnancy or increased intracranial pressure. Patients were randomized within 24 hours after intubation and initiation of mechanical ventilation. The study was approved by the local Ethics Scientific Committee. Informed consent was obtained from either the patients or their relatives.

Procedures

Patients were randomized to either our standard strategy with no sedation, with only bolus doses of morphine or haloperidol to be given if delirium was suspected (intervention group) (figure 4). The control group was randomized to the standard treatment described by Kress et al with sedative infusion to RAMSAY 3-4 and bolus doses of morphine and daily interruption of sedative infusion [15, 29]. The sedated control group received propofol as sedative for the first 48 hours, after which midazolam was administered to protect study patients from propofol infusion syndrome [30, 31]. If patients randomized to no sedation were unable to tolerate this despite thorough search for reversible causes, sedation would be implemented. They were given sedative infusion for a maximum of 6 hours and the sedative infusion was then stopped. If however sedatives were used 3 times, patients were treated as the control group with daily interruption of sedatives.

Data for the post hoc analysis of renal effects of a no sedation strategy was collected from the patients' ICU observational charts. Patients with a history of renal insufficiency: glomerular filtration rate (GFR) below 60 ml/min for more than 3 months or prior dependency on intermittent dialysis were excluded [33]. Daily mean arterial blood pressure 4 times a day, fluid infusion, urine output and use of vasoactive drugs were collected. Serum creatinine and blood gas analysis was collected for each patients ICU stay. Daily creatinine clearence and RIFLE score were calculated [34]. For further details please refer to article III [35].
In the psychological follow-up all surviving patients were contacted by telephone. Patients who presented with dementia or other severe neurological disorders that prevented them from participating in a psychological interview were excluded. Patients were interviewed by a neuropsychologist using the tests shown in table 1. The psychologist was blinded to the randomized treatment (No sedation vs. sedation). Aside from the psychological tests, seven questions were asked about the intensive care stay. These questions were a modification of the ICU memory tool [36]. The questions were: 1) whether patients recalled being admitted to intensive care, 2) remembered being awakened, 3) if they received sufficient rest, 4) whether they had nightmares, 5) if they had pain 6) whether they had trouble breathing and 7) whether they were still affected by their intensive care stay. For a full description please see the paper (article IV) [37]

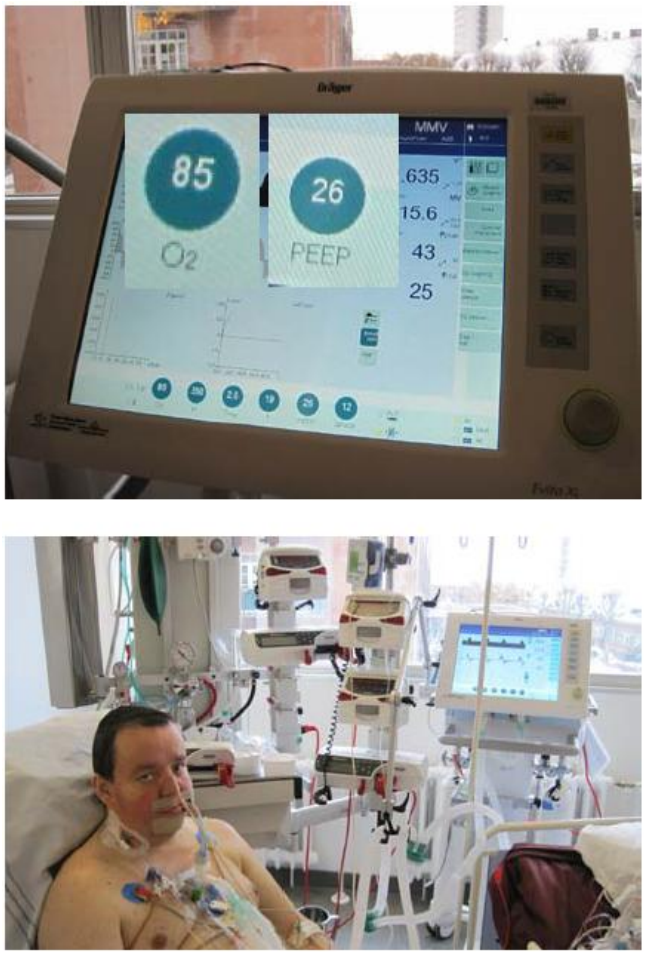

Figure 4: *Top: high ventilator settings (PEEP 26 and FiO2 85 %). Bottom: awake mobilized patient attached to the above ventilator (with permission).*

4. RESULTS

140 patients were randomized from April 2007 to December 2008. A priori it was defined that only patients receiving mechanical ventilation for more than 48 hours were included in the statistical analysis. Baseline data is presented in table 2. From the table it is seen that the median APACHE II value is 26. By the use of sedation the number of days without mechanical ventilation was decreased by 4.2 days (table 3). The ICU length of stay was increased by 9.7 days. Also the total hospital length of stay was increased; a difference of 24 days was seen between the two groups. Kaplan- Meier plots of Intensive Care and hospital length of stay can be seen in the paper II[32]. We observed no difference between the two groups with respect to known complications such as accidental extubation, Ventilator Associated Pneumonias or number of CT-scans of cerebrum (Table 3). 10 patients in the intervention group could not tolerate the no-sedation treatment and were subsequently sedated. This intolerance was mainly manifested in patients with severe ARDS. These patients were treated according to the control group with daily interruption of sedation. Data was treated according to randomization (intention-to-treat), no crossover was allowed. A member of staff, in addition to the patients nurse was needed on 14 occasions (11 times in the intervention group and 3 times in the control group)

but only for a mean time of 2.5 days.

	No sedation (n=55)	Sedation (n=58)
Age (years)	67 (54–74)	65 (54–74)
Women	13 (24%)	24 (41%)
Weight (kg)	80·0 (74·0–92·0)	78·5 (70·0–91·0)
APACHE II	26 (19–30)	26 (22–31)
SAPS II	46 (36–56)	50 (43–63)
SOFA (at day 1)	7·5 (5·0–11·0)	9·0 (5·5–11·0)
Diagnosis at admission to intensive care unit:		
Respiratory disorder	26 (47%)	27 (47%)
Sepsis	15 (27%)	19 (33%)
Pancreatitis	2 (4%)	3 (5%)
Peritonitis	0	1 (2%)
Gastro-intestinal bleeding	5 (9%)	0
Liver and biliary disease	2 (4%)	0
Trauma	2 (4%)	3 (5%)
Other	3 (5%)	5 (9%)

Table 2: *Baseline characteristics on admission to the intensive care unit. Data are in number (%) or median (IQR) .*

Test	Description	Area Measured	Scoring
Medical Outcome Study 36 item short-form health survey (SF-36)(38)	8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures	Generic quality of life	36 questions across 8 domains, range 0-100, with low scores indicating poor quality of life
Beck Depression Inventory 2 (BDI-II)(39)	Screening tool to assess severity of depression	Depression	21 questions ranging from 0-3 (total range 0-63). A score >10 suggestive of depression
State Anxiety Inventory scale (acute)(40)	Assess current anxiety	Anxiety	20 questions ranging from 0- (not at all) to 3 (very much so) (total range 0-60).
Revised Impact of Event Scale (IES-R) (41)	Assess current subjective distress for any specific life event	PTSD symptoms	22 questions ranging from 0 (not at all) to 4 (extremely) (total range 0-88). A score above 32 is suggestive of PTSD.
Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) (42)	Screening tool to assess the presence of PTSD symptoms	PTSD symptoms	10 questions ranging from 0-7 (total range 0-70). A score >35 suggestive of PTSD

Table 1. *Physiological tests performed at follow up*

10 patients were found to have a known renal impairment and were therefore not included in the retrospective analysis of the renal function. A total of 103 patients were included in this analysis of renal function. No difference was found with respect to blood pressure, fluid balance, vasopressors or number of patients receiving CRRT (table 4). However a significantly reduced urine output was found in the sedated control group compared to the awake intervention group (0.88 ml/kg/hour vs. 1.15ml/kg/hour, P=0.03). Also a higher RIFLE classification was found in the sedated control group compared to the awake intervention group (see figure 1). More patients from the sedated control group were classified with renal impairment (41 (76 %)) according to the RIFLE classification compared to the awake intervention group (25 (51 %), P=0.012) (figure 5 and table 3). S-creatinine was less important than urine output in determining the RIFLE class (paper III)[35].

	No sedation (n=55)	Sedation (n=58)	p value
Days without mechanical ventilation (from intubation to day 28)	13.8 (11.0); 18.0 (0–24.1)	9.6 (10.0); 6.9 (0–20.5)	0.0191
Length of stay (days)			
Intensive care unit	13.1 (5.7–··)	22.8 (11.7–··)	0.0316
Hospital	34 (17–65)	58 (33–85)	0.0039
Accidental extubation	7 (13%)	6 (10%)	0.69
VAP	6 (11%)	7 (12%)	0.85
Number of CT-scans of cerebrum	5 (9 %)	8 (15%)	0.43

Tabele 3: *Outcome data. Data are mean (SD), median (IQR), or number (%).*

A total of 43 patients were found to be eligible for psychological follow up. 5 patients did not respond or were not interested in psychological follow up. 7 patients changed their mind, 2 suffered from dementia and 3 died before the interview. Only 26 patients were interviewed. In this subgroup of patients APACHE II score was lower than seen in the original study (table 5). The number of days without mechanical ventilation was not significantly lower in the awake group compared to the sedated control group in this subgroup of patients (23 days vs 16 days, P=0.12). However the tendency in the use of drugs was similar in this subgroup of patients compared to the entire group of patients: no difference in the use of morpine and a higher use of sedatives (propofol and midazolam) in the sedated control group compared to the intervention group. The use of haloperidol was significantly higher in the awake intervention group compared to the sedated control group however the dose used was minimal (table 5). The time from randomization to interview was approximately 2 years with no difference between the two groups.

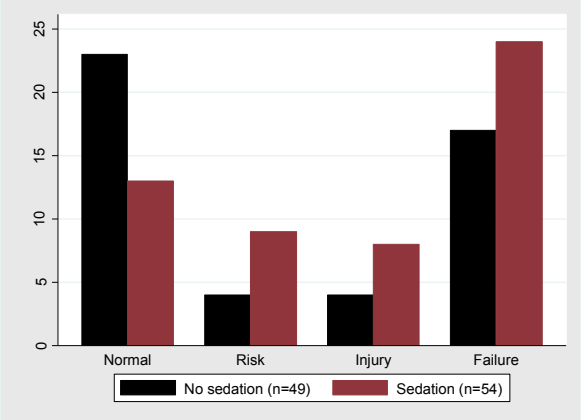

Figure 5: *The time from randomization to interview was approximately 2 years with no difference between the two groups.*

Table 6 shows the results from the psychological follow up. 2/3 of the patients from both groups remembered the ICU and remembered having nightmares. Very few patients from each group remembered pain or trouble breathing. No statistical difference was found with respect to depression or PTSD between the two groups.

	No Sedation (n=13)	Sedation (n=13)	P value
Age (years)	71 (58-74)	63 (56-67)	0.33
Female	9 (69 %)	8 (62%)	0.5
Weight (kg)	80 (75-90)	96 (70-103)	0.26
Apache II	20 (16-29)	25 (21-26)	0.20
SAPS II	41 (34-49)	46 (32-49)	0.63
SOFA (at day 1)	7 (5-9)	7 (5-10.5)	0.91
Ventilator free days (28 days)	23.15 (19.00-25.35)	16.13 (3.92-22.67)	0.12
Morphine (mg/kg/hr) *	0.0088 (0.0039-0.01676)	0.0047 (0.0030-0.0060)	0.24
Propofol (mg/kg/hr)*#	0 (0-1.2553)	1.3996 (0.5178-2.0408)	0.0127
Midazolam (mg/kg/hr)*	0 (0-0)	0.0135 (0-0.0405)	0.0029
Serenase (mg/kg/hr)*	0.0039 (0-0.0202)	0 (0-0)	0.0125
Time from randomization to psychological interview (years)	1.78 (1.46-2.10)	2.04 (1.55-2.29)	0.32
Time from hospital discharge to interview (years)	1.72 (1.42-2.05)	1.92 (1.47-2.20)	0.49

Table 5: *Baseline data. Data are in number (%) or median (IQR). APACHE II = acute physiology and chronic health evaluation. SAPS II = simplified acute physiology score. SOFA =sequential organ-failure assessment. *While receiving mechanical ventilation. # Dose during a maximum of 48 hours of treatment.*

	No sedation (n=13)	Sedation (n=13)	P value
SF-36			
Mental	58 (51-61)	52 (37-60)	0.46
Physical	39 (31-46)	40 (31-43)	0.85
BDI-II			
Overall score	3 (1-7)	3 (1-11)	0.61
Number being depressed (score>10)	1 (8 %)	4 (31%)	0.32
State Anxiety Inventory	28 (25-30)	30 (25-33)	0.58
Impact of Events Scale			
Overall score	4 (2-8)	2 (0-11)	0.41
Number of patients with PTSD (Score>32)	1 (8 %)	2 (15 %)	0.50
PTSS-10			
Nightmares	9 (69 %)	6 (46 %)	0.23
Anxiety and nightmares	3 (23 %)	4 (31 %)	1.00
Pain	1 (8 %)	0 (0 %)	1.00
Trouble breathing	2 (15 %)	5 (38 %)	0.37
Sum of B questions	3 (0-6.5)	10 (6-17)	0.09
Number of patients with PTSD (Score>35)	1 (8 %)	0 (0 %)	0.14
Modified ICU memory tool			
Remember ICU (yes)	9 (69%)	8 (62%)	0.68
Remember Wake up (yes)	2 (15 %)	5 (38 %)	0.37
Sufficient rest (yes)	12 (92%)	12 (92 %)	1.00
Nightmares (yes)	8 (62%)	8 (62%)	1.00
Pain (yes)	2 (15 %)	1 (8 %)	0.50
Trouble breathing (yes)	1 (8 %)	0 (0 %)	1.00
Still affected by ICU (yes)	3 (23 %)	1 (8 %)	0.29

Table 6: *Long term psychological outcomes. Data are in median (IQR) or number (%).*

5. DISCUSSION

Our studies presented in this thesis have severely questioned the routine use of sedatives to critically ill patients undergoing mechanical ventilation. We have shown that a strategy with "no sedation" is possible and is advantageous in terms of time spent in mechanical ventilation, time in ICU and total hospital length of stay. We observed no difference in adverse effects in terms of accidental extubations, VAP or number of CT and MR scans of cerebrum needed. Furthermore there might be a higher risk of AKI associated with the routine use of sedatives. Also the long term psychological effects seem to be unaffected by the use of no sedation.

The term "analgo-sedation" has become very popular, especially with the introduction of remifentanil, an opioid with a very short half-life. The elimination is independent of liver and kidneys and it does not accumulate in the body like other opioids. However no studies have proved remifentanil superior in terms of ventilator time or LOS [43, 44]. Much debate has arisen with the use of morphine in our study. One could fear that sedation was simply replaced by morphine and that it was just a study comparing analgo-sedation using morphine as the agent to standard care with sedative infusion. This was not the case, as shown in the article the cumulated morphine use was the same in both groups (II) [32]. This enforced the lessons learned in the prior studies by Kress and Girard and later shown in a study by Spies and Colleagues, that the sedative drug itself is less important, it is the way that the drugs is administered that determines outcome [45]. This is probably the reason why remifentanil has never have been shown to be superior to existing drugs. If the strategy with deep sedation remains unaltered, as was done in the study by Rozendaal et al, the outcome is also unaltered[43].

Dexmedetomidine, an alpha 2 adrenergic receptor agonist, has received much attention and some might say that this is the new "drug of choice" in terms of sedation. Some of the positive effects of using dexmedetomidine should be that the patients are les sedated, more awake and less delirious. One study by Riker and colleagues including 375 patients have shown less time in mechanical ventilation and more delirium free days with dexmedetomidine compared to midazolam [46]. A study by Pandharipande and Colleagues including 106 patients was unable to show any difference in length of ventilator free days and ICU length of stay in days comparing dexmedetomidine to lorazepam [47]. However there were more days without delirium seen when patients were sedated with dexmedetomidine compared to lorazepam. A recent metanalysis comparing dexmedetomidine with traditional sedative agents was unable to show an effect on length of mechanical ventilation, hospital length of stay or duration of delirium [48]. Dexmedetomidine significantly reduced intensive care length of stay but the authors of the metanalysis state that the included studies were very heterogeneous so the conclusions should be interpreted with caution. Two recent studies comparing propofol and midazolam to dexmedetomidine by Takala and colleaques were able to show a difference between dexmedetomidine and midazolam with respect to length of mechanical ventilation. However this difference could not be shown comparing dexmedetomidine to propofol [49]. The 2 studies included almost a thousand patients but were unable to show a clear benefit from dexmedetomidine compared to traditional sedatives. One important limitation with the Midex/Prodex studies was that the goal for sedation ranged very widely from RASS 0 to -3. Again this emphasizes that it is not the drug per se but the way it is administered that determines outcome [50].

A recent study published in NEJM by Papazian and Colleagues showed a mortality benefit with the use of neuromuscular blocking agents in severe ARDS [51]. This finding raises an important question: should respiratory insufficient patients in need of mechanical ventilation be deeply sedated and receive neuromuscular blocking agent? Does this study rule out our findings? We had 10 patients (18 %) from the control group who after randomization to no sedation needed sedative infusion. Data was kept in the assigned intervention group for the statistical analysis according to "Intention-to-treat". These patients mainly suffered from

severe ARDS and needed sedation to accept the high settings from the ventilator. Where they harmed by the initial efforts to keep them awake? Will a strategy with no sedation potentially harm some patients who may need higher settings on the ventilator? These questions cannot be answered by our data. However patients with severe ARDS, who would profit from deep sedation and neuromuscular blocking agents account for a relatively small group of patients compared to the number of patients in the ICU who undergo mechanical ventilation [52]. In the study by Papazian only ARDS patients with a PaO2/FiO2 ratio below 120 had a beneficial effect of receiving infusion of neuromuscular blocking agents. Even in a study including only ARDS patients, only a subset of patients was sick enough to benefit from the intervention. With this in mind most ICU patients, even with mild ARDS, will benefit from our intervention with no sedation to reduce the length of mechanical ventilation.

Our study has been criticized because we needed to sedate 10 patients; initially randomized to no sedation. This number needs to be put into perspective since 82 % of the patients randomized to no sedation could be managed according to the protocol with no sedation.

Comparing our results with results from Kress and Girard, our patients received mechanical ventilation and were admitted to ICU and hospital for a longer time than was the case in the other studies. In the study by Kress and colleagues the patients were recruited from the medical department and with APACHE II scores much lower than in our study (20-22 vs. 26) which could account for much of the difference [15]. Another difference was the management of "long stayers". In the study by Kress patients could be transferred to: "a facility equipped to provide long-term ventilation", and thereby leaving the study. In our department no such facilities exist, patients were managed in the ICU until weaned from the ventilator. Also long stayers in the hospital were recorded as admitted until discharged home. In the study by Girard the APACHE II scores were comparable to our study (26-26.5) [17]. However the longer stay could still be attributed to the above mentioned difference between Danish and American health care systems.

The large difference in length of stay between the two groups has also been the subject of speculation. In the editorial it is mentioned that the difference in disease severity might be a factor one should take in account [27]. There is a slight imbalance in the SAPS II score, with the control group having a higher score, however the difference is small and when tested not statistically significant (46 (36–56) vs. 50 (43–63), P=0.10). Article III [35] was one way to investigate a renal explanation for the huge difference between the two groups in terms of length of stay. The answer is probably multifactorial without any one thing providing the only explanation. We allowed both groups of patients to be mobilized on a daily basis, which is routine care in our department. However the sedated group was mainly mobilized during the wake up trial compared to the awake intervention group which could be mobilized more often. A recent randomized trial has shown the beneficial effect of early mobilization [53]. Another important factor to remember is the quality of care provided if the patient is awake or sedated/in coma. The ability for the caregivers to interact with the patients is very important. If one cannot interact with the patients, the patients are easily seen as objects and not living beings. Attention moves away from the patients towards things other than patient care. One just needs to recall how difficult "end of life" decisions are if the patients is awake compared to if the patients are comatose [54].

Limitations

Several limitations need to be addressed when interpreting our data. First of all the study was conducted as a single center study in a center with a routine in the no sedation strategy. However we believe that our control group tended to be less sedated than in centers with a routine use of sedatives and still we were able to demonstrate a difference which further highlights the risk of routine use of sedatives.

The 1:1 nurse: patient ratio has been criticized under the review process of the main article (II) [32] and later in response when presenting the work. The 1:1 ratio is becoming the standard of care in Danish ICUs and other Nordic countries. Also in the UK it is heavily debated whether it should be standard care with one nurse to each patient [55]. Of course the shortage of staff, which is the norm in many ICUs worldwide, is a limitation to the introduction of our method. However some of the results can still be incorporated in everyday patient care and with the use of as little sedatives as possible, enforcing that patients are not harmed as they are not sedated to RAMSAY 4. The use of an extra person to verbally comfort the patients has also been criticized. This was used in 14 patients (n=11 in Intervention group vs. n=3 in control group, p=0.0247, mean of 2.5 days). Whether the results would have been different if one had chosen to sedate these patients instead cannot be concluded from our data but it is unlikely considering the low numbers and short interval of time. Again it is worth emphasizing that we never used or use physical restraints [56].

Concerns have been raised about the switch from propofol to midazolam after 48 hours, that it might have prolonged the ventilation time and LOS because of midazolam's pharmacokinetic effects compared to propofol [57]. Kress and Colleagues could not demonstrate a difference; they "sub-randomized" patients to either midazolam or propofol but of course their patients were not as severely ill and where younger compared to the patients in our study [15]. However we decided a priori that it would be unethical to randomize patients to receive propofol for a prolonged period because of the risk of propofol infusion syndrome [31, 58-60].

Delirium was seen more often in the awake intervention group compared to the sedated control group. This is mentioned as one of the findings in the abstracts of paper II and has been a source of critique of the no sedation strategy [27, 61]. This is important since delirium has been shown to be a predictor of poor outcome [62-68]. As mentioned in the paper we only identified and registered agitated forms of delirium using DSM IV criteria [69]. Patients from the sedated control group who were restless during the daily interruption of sedative drugs had the sedatives restarted before they could be diagnosed as having delirium unless they were ready to be weaned (PEEP 5 cm H2O and FiO2 40 %). In this way we probably overlooked patients from the control group who might have had delirium, the method we employed was not ideal to detect this. A better and more sensitive way of diagnosing delirium would have been to use the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [70, 71]. This validated tool has the advantage of also diagnosing silent forms of

delirium which could be present in sedated patients. However sedation presented a dilemma in diagnosing delirium, is it simply because of sedation that the patient is diagnosed as having delirium, is delirium caused by the profound perhaps uncontrolled disease process that led the patient to the intensive care or is it caused by a combination? In the Girard study the CAM-ICU score was used, but they did not report any difference in the occurrence of delirium [17]. However in the sedated group one would suspect that diagnosing delirium would be postponed until reduction in the sedative infusion and a Richmond Agitation-Sedation Scale (RASS)>4 was reached [72].

Despite the search for an effect on the kidneys we did not find this as clear cut as described in the introduction. As discussed in the article this subgroup analysis has a very little sample size and a risk of a type 2 error is obvious (III) [35]. However our control group was at maximum sedated to RAMSAY 3-4, and probably not this deep all the time. At the introduction of this thesis we discussed patients in need of CRRT who were referred from centers where sedation is the standard care; these centers probably use much deeper levels of sedation. This can be suspected from Danish sedation surveys which document lack of sedation scales and lack of daily interruption of sedatives [4]. We suspect that our results would have shown a much larger difference between the groups with respect to kidney function if a strategy with deeper levels of sedation, as probably is common practice, was used in the control group. However this setup would have been unethical.

The statistical method used in the follow up study on the renal effects of a no sedation strategy could be questioned (III) [35]. The main problem with analyzing these data is the different follow-up time for each patient. Some patients were admitted for a few days and other patients more than 28 days. An analysis with repeated measurements assumes that exit of patients happens by chance and not as an effect of the intervention. We believe that a no sedation strategy reduces the time in mechanical ventilation and time in intensive care department and thereby that earlier exit does not happen by chance but because of the intervention. We therefore chose to use a summary measure for each patient but chose only to include up to 14 days, thereby minimizing the risk that data from fewer patients at risk after 14 days would be over-analyzed. No good statistical method to analyze longitudinal data exists. This is demonstrated in a recent study by the SAFE group analyzing the effects of albumin in critically ill patients [73]. They choose only to analyze the first 7 days in the intensive care department thereby minimizing the problem of exit of patients because of the intervention. The problem in our paper has also been addressed in a comment by Brummel and Girard [74]. However as stated in the comment the most important element of our finding is hypothesis generating. Renal impairment was not a predefined endpoint however the finding is suggestive and further highlights the need for further research in the area.

The psychological follow up study also holds several limitations. With the low number of patients one could fear that it is not representable with a high risk of a type II error. In table 7 the number of patients included in the mentioned studies is shown. It is seen that our study, like the studies by Kress and Girard, includes 1/5 of the randomized patients. Only the study by Treggiari includes more patients, but this study had psychological effects of sedation as the primary endpoint.

	Intervention	Patients interviewed (n)	Outcome
Kress et al (20)	Daily interruption of sedatives	32 of 150 randomized patients (21 %)	Less PTSD
Treggiari et al (22)	Light vs. deep sedation	102 of 132 randomized patients (77 %)	Tendency towards less PTSD (P=0.07)
Jackson (Girard) (21)	Daily interruption of sedatives and SBT vs. SBT alone	63 of 336 randomized patients (18 %)	Less PTSD at 3 month follow up. No difference at 12 month follow up.
Strom et al (IV) (37)	No sedation vs. sedation with daily interruption	26 of 140 randomized patients (19 %)	No difference between groups

Table 7: *Outline of the mentioned studies investigating the psychological long term effects of less sedation.*

Also there is a risk of selection bias since the patients interviewed were not as sick as the patients from the original study with respect to the lower APACHE II score. However this could not be done in any other way. All surviving patients were contacted and most of them were willing to participate. We might have increased the number of interviewed patients if the interview had been made earlier, whether this would have changed anything is impossible to predict. As mentioned earlier in the psychological follow up study by Girard and colleagues, the authors were able to demonstrate a difference in psychological long term effects after 3 month, but were unable to demonstrate a difference after 12 months. This might have been because of the same problem as we found in our study: patients in whom it would be possible to demonstrate a difference in psychological follow-up did not survive to the interview and a potential beneficial effect of the no sedation strategy was missed.

Future perspectives

Although our results from this randomized prospective single center study are promising further studies are needed before the method with no sedation can be widely accepted. As mentioned the limitation our department faced, was the use of the strategy of no sedation before the trial was initiated. A multicenter, or even better: a multinational trial with the same endpoint as the present study is warranted. Besides length of stay in ventilator, ICU and hospital, the study would also have to be powered to measure renal impairments, mortality and delirium evaluated with CAM-ICU [70, 71]. Whether departments with lower nurse: patient ratio should be included in the study is controversial. However it would be interesting to know the effect and feasibility of implementing a no sedation strategy in other facilities.

"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous"

Paracelsus

6. CONCLUSION

In this PhD thesis we have shown that a strategy with no sedation to critically ill patients in need of mechanical ventilation can be used and is feasible. By omitting the routine use of sedatives and only using bolus doses of morphine, we showed a reduction in both the time patients received mechanical ventilation, time spent in the ICU and total hospital length of stay. No change was seen in the frequency of adverse events: CT scans of cerebrum, VAP or accidental removal of tracheal tube with or without sedation. A posthoc analysis implies an increased risk of AKI with the use of sedation. At follow up no difference was seen between the two groups with respects to long term physiological sequelae (depression or PTSD).

7. ABSTRACT

Background: Standard treatment of critically ill patients undergoing mechanical ventilation is continuoicheus sedation. This standard treatment to all patients has been greatly challenged over the last decade. At the general intensive care department at Odense University hospital the standard treatment has been no sedation. The general impression has been that this reduces time in mechanical ventilation and reduces complications such as acute renal failure. It has not been the impression that this treatment increased the risk of long term psychological problems compared to standard treatment with sedation. The "no-sedation" method has however never been described in the literature or tested in a prospective randomized trial.

Hypothesis: The main hypothesis was that a no sedation strategy reduces the time patients receives mechanical ventilation, decrease intensive care and total length of hospital stay. Secondary endpoints were: a no sedation strategy would reduce secondary organ failure such as kidney injury and would not increase the risk of post-traumatic stress disorder after hospital discharge.

Methods: We randomized 140 critically ill patients in need of mechanical ventilation. The intervention group received only bolus doses of morphine or haloperidol if delirium was suspected. The control group received standard infusion of sedatives to RAMSAY 3-4 and sedatives were interrupted on a daily basis. Both groups received morphine as intravenous bolus doses (2.5 to 5 mg). The primary outcome was days without mechanical ventilation, days in the ICU and total length of hospital stay. We conducted a post-hoc analysis of the data with kidney function expressed in urine output and RIFLE classification as the primary outcome. After hospital discharge all patients were invited to an interview with a neuropsychologist to assess Post Traumatic Stress Disorder (PTSD), depression and general psychological and physical health.

Results: 27 patients died or were successfully weaned from mechanical ventilation within 48 hours and were excluded from further analysis. Patients from the awake intervention group (n=55) had 4.2 more days without mechanical ventilation compared to the sedated control group (n=58) (P=0.0191). Also ICU length of stay was reduced in the awake intervention group by 9.7 days (P=0.0316) and total hospital length of stay was reduced 24 days (P=0.0039) compared to the sedated control group. An increased urine output was seen in the group receiving no sedation compared to the sedated control group (1.15 ml/kg/hour vs. 0.88 ml/kg/hour, P=0.03), also more patients from the sedated control group was classified with renal impairment (41 (76 %)) according to the RIFLE classification compared to the awake intervention group (25 (51 %), P=0.012). 26 patients were interviewed approximately 2 years after randomization, 13 from each group. No difference was seen between the groups with respects to Post Traumatic Stress Disorder, depression and general psychological and physical health.

Conclusion: A strategy of no sedation to critically ill patients undergoing mechanical ventilation resulted in fewer days in mechanical ventilation, shorter ICU and hospital length of stay compared to a standard strategy with sedation. Also the risk of acute renal impairment seems to be reduced with the use of no sedation. The no sedation strategy does not seem to alter long term psychological outcome.

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