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Research Article

The Effect of Non-Sedation Compared to Sedation on Renal Function in Mechanically Ventilated Critically Ill Patients. A Substudy of the NONSEDA Trial

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Abstract

Background: Acute kidney injury is associated with increased morbidity and mortality. In the NONSEDA trial 700 mechanically ventilated patients were randomized to non-sedation or light sedation with a wake-up trial. The purpose of this post hoc sub-study is to present the effect of non-sedation on renal function, especially the need for renal replacement therapy (RRT)

Methods: The primary endpoint was mortality at 90 days. The secondary endpoints were thromboembolic events, coma or delirium free days, ventilator free days and acute kidney injury. Every day Risk, Injury, Failure, Loss of kidney function, Endstage kidney disease (RIFLE) and the need for CRRT were registered. In addition fluid balance, weight, mean arterial and systolic blood pressure and noradrenaline infusion were registered.

Results: The percentage of patients treated with continuous renal replacement therapy (CRRT) was 28% in the non-sedated compared to 40% in the sedated group (p=0.04). Need for CRRT at discharge was 5% in the non-sedated compared to 11% in the sedated group (p=0.02). The number of days in the RIFLE category renal failure was 1365 in the non-sedated compared to 1678 in the sedated group (p=0.01). In the sedated group, the mean blood pressure was 79.8 mmHg compared to 81.8 in the non-sedated group (p=0.05). Days with noradrenaline was 4.2 in the sedated compared to 3.7 in the non-sedated group (p=0.01). There was no difference in fluid balance.

Conclusion: The kidney function might be better preserved in the non-sedation group compared to light sedation with a wake-up trial. Clinicaltrials.gov (NCT01967680)2013-10-18.

Keywords: Acute kidney injury; CRRT; Non-Sedation; Sedation.

INTRODUCTION

In recent years, there has been a trend towards minimizing sedation in critically ill patients. By introducing, a daily wake-up trial heavy sedation might be minimized [1]. Our group performed a single center RCT comparing non-sedation with sedation and a daily wake-up trial [2]. The non-sedated group had a significantly shorter time on the ventilator and significantly shorter time in the ICU and in hospital. In our recently published multicenter study [3], we were not able to report any effect of non-sedation on mortality. In the non-sedated group, there were more coma and delirium free days, less thromboembolic events and a beneficial effect on physical function at extubation and ICU discharge [4]. A post hoc analysis of our single center study by Stroem et al., showed that the highest RIFLE score within the first 14 days was significantly higher in the sedated group compared to the non-sedated group [5]. In our multicenter study by Olsen et al, only the highest RIFLE score within the observation period has been published [3]. As earlier reported there was no difference in the highest measured RIFLE score [3]. Several other parameters of renal function especially the need for RRT were however prospectively registered on a daily basis in our database. These data have never been published. Our single center study [5], and our multicenter study [3], are the only studies where the impact of sedation on renal function compared to non-sedation has been investigated The purpose of the present sub-study is to investigate the impact of sedation compared to non-sedation on renal function especially the need for RRT.

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MATERIALS AND METHODS

The present study is a sub-study to the NONSEDA trial which was a Scandinavian multicenter trial [3]. In the NONSEDA trial 700 patients 18 years or older who were intubated within 24 hours and expected to receive mechanical ventilation for more than 24 hours were included (Figure 1). Patients with a medical reason for sedation such as status epilepticus were excluded. Patients were randomized to non-sedation or light sedation with a daily wake-up trial. Both groups received bolus doses of morphine as needed. Patients in the sedated group were sedated to a Richmond Agitation Scale (RASS) of on average -2. Propofol was used for the first 48 hours followed by midazolam to avoid the development of propofol infusion syndrome. Due to the nature of the study, it was not possibly to blind the intervention as described in the study protocol [6]. The non-sedated group received only bolus doses of morphine and were not sedated with propofol or midazolam.

Every day after inclusion in the daytime, we prospectively registered if the patient had normal renal function, Risk of renal injury, Injury and Failure of renal function (RIFLE score). The RIFLE score Risk, Injury and Failure are nearly identical to the Kidney Disease Improvement Global Outcomes (KDIGO) stage 1, 2 and 3 respectively. Patients were hospitalized acutely why complete loss of renal function for > 4 weeks or end stage renal disease could not be registered. In this way the highest RIFLE score was failure of renal function. Patients with stage 3 AKI were treated with CRRT. The proportion of stage 1 and 2 AKI were nearly identical in the

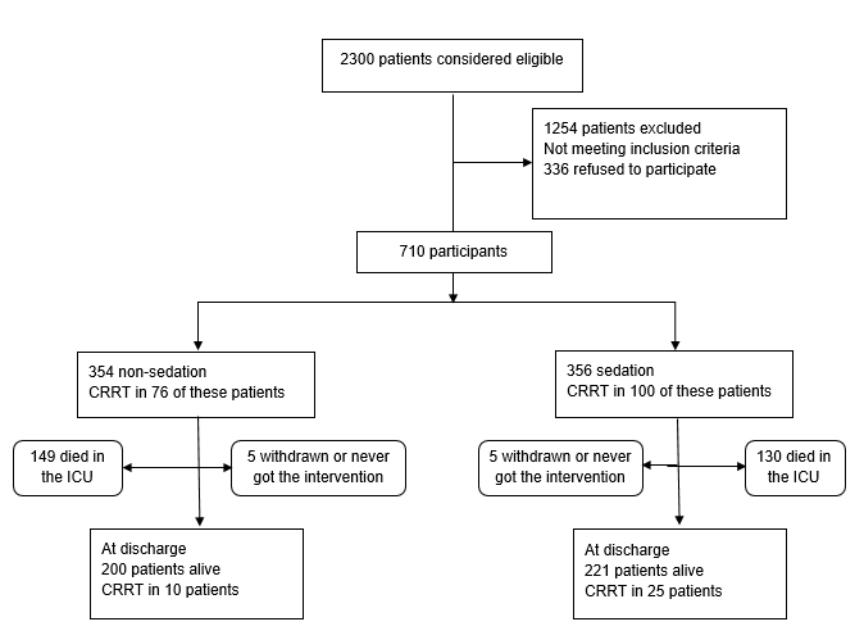

Figure 1: Study flow chart

two groups. The RIFLE score was as the KDIGO score based on changes in creatinine or urinary output depending on which of these measurements first deteriorated. Development of acute kidney injury with the need for CRRT was registered prospectively. The kidney function was followed for 90 days as illustrated in Figure 4. The decision to treat the patients with CRRT was at the discretion of the attending physician and not the investigators. The weight of the patient and the amounts of fluids given were prospectively registered on a daily basis. In addition, the average Mean Arterial Pressure (MAP), the lowest Systolic Blood Pressure (SBP) and the use of noradrenaline infusion were prospectively registered on a daily basis. MAP and SBP were continuously monitored electronically. Based on stored curves for 24 hours the MAP and lowest SBP were measured. Fluid therapy, planned fluid balance and the decision to treat the patients with noradrenalin was likewise at the discretion of the attending physician and not the investigators. Only isotonic crystalloids were used. The weight was nearly identical in the two groups (See results). The fluid balance was calculated including all administered fluids, dilutions for medication, insensible losses etc. Informed consent was obtained from all subjects or their legal guardian by signing a form. The NONSEDA trial was approved by the local ethics committee (23/10/2013, ID: 20130025) and was registered at clinicaltrials.gov (NCT01967680) 2013-10-18.

STATISTICAL ANALYSIS

The data are presented in mean ± standard deviation unless the distribution was skewed. In this case, data were presented as medians with interquartile ranges. As this is a sub-study of the NONSEDA trial no power calculation was performed. Wilcoxon rank-sum test, student´s t test or Chi^2 test were performed as appropriate .In the Kaplan Meier Curve a Log-Rank test was performed. $P< 0.05$ was considered statistically significant. No correction for multiple comparisons was done.

RESULTS

In the NONSEDA, trial 700 patients were randomized to non-sedation or light sedation with a daily wake-up trial. The characteristics of the patients at baseline was balanced except for a 1 point higher Acute Physiology and Chronic Health Evaluation (APACHE) II score in the non-sedation group [3]. The non-sedated group was in other words more severely ill when the study was initiated. There were no difference in age, sex, height, weight, type of admission, chronic kidney injury and diagnosis at baseline. The most common reason for ICU admission were pneumonia or ARDS, Sepsis, exacerbation of COPD, gastrointestinal bleeding, trauma, cardiac failure, severe acute asthma or postoperative complications. The median ICU stay for survivors were 7.5 days.

The mean weight increased slightly in both groups during the first 7 days but the increase was nearly identical in the 2 groups. On day one the mean weight was 81.8 kg in the non-sedated group compared to 81.7 kg in the sedated group (NS). At day, seven the mean weight was 84.6 (±18.9) kg in the non-sedated group compared to 83.6 (±20.8) kg in the sedated group (NS).

There was no difference neither in the daily fluid balance nor in the cumulative fluid balance between the 2 groups (NS). As shown in Table 1 and Figure 2 the daily fluid balance was positive for the first 2 days and negative for the following 5 days. The cumulative fluid balance was positive for the first 6 days but nearly neutral on day 7 (Table 1, Figure. 3)

The number of days in the RIFLE category renal failure (identical to KDIGO stage 3) was however significantly higher in the sedated group ($p=0.01$) (Table 1).The total number of patients including survivors as well as non-survivors who needed treatment with CRRT was significantly higher in the sedated group($p=0.04$) (Table 2). Among patients, who survived the ICU the use of CRRT was also significantly more frequent in the sedated group ($p= 0.001$) (Table 2). More patients in the sedated group were dependent on CRRT treatment at discharge from the ICU ($p=0.02$) (Table 2, Figure 4). At discharge from the ICU the SOFA score was also significantly higher in the sedated group mainly due to the development of AKI ($p= 0.03$) (Table 1).There was no difference in the use of contrast between the groups. Intermittent haemodialysis was not used in this trial.

The mean± SD of MAP was 81.8 ± 12.8 mmHg in the non-sedated group compared to 79.8 ± 11.8 mmHg in the sedated group ($p=0.05$) (Table 1). The lowest SBP in the non-sedated group was 104.3 ± 19.4

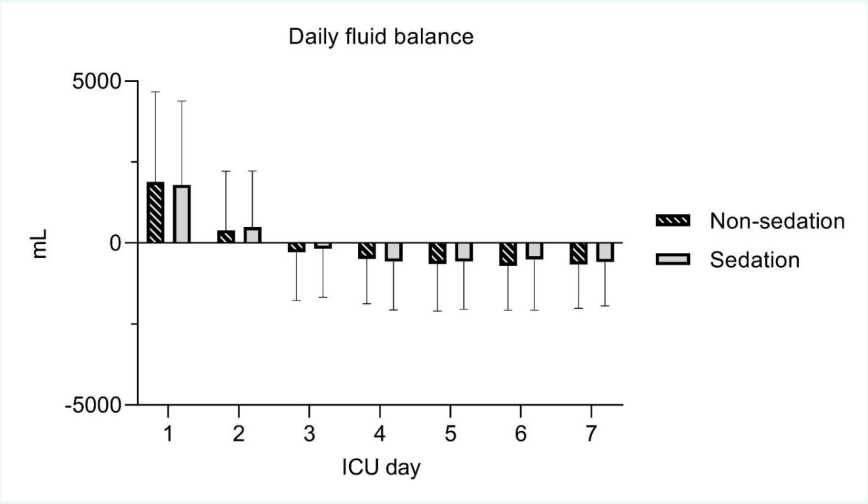

Figure 2: Daily fluid balance.

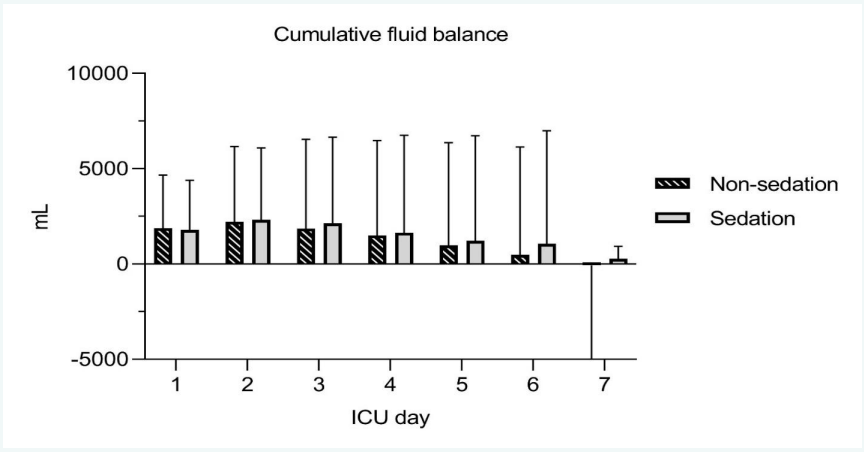

Figure 3: Cumulative fluid balance.

mmHg compared to 102.8 ± 17.9 in the sedated group (p =0.12). The average number of days the patients were treated with noradrenaline was significantly lower in the non-sedated group (p =0.01) (Table 1). No other vasopressors were used.

Significantly, more propofol and midazolam were used in the sedated group. Day 1-2 0.84 mg/kg/hour was used in the sedated group compared to 0.22 mg/kg/hour in the non-sedated group. Day 2-28 0.00019 mg/kg/hour of midazolam was given in the sedated group compared to 0 in the non-sedated group. Day 1-7 0.0045 mg/kg/hour of morphine was used in the sedated group compared to 0.0051 mg/kg/hour in the non-sedated group (NS).

DISCUSSION

The main finding in the present sub- study was that days with highest RIFLE score, the number of patients treated with CRRT and the number of patients who needed CRRT at discharge from the ICU were significantly higher in the sedated group. In the sedated group a significantly more pronounced use of noradrenaline was observed though the APACHE score at baseline was higher in the non-seated group [3].

In the present study there was a tendency towards lower values of MAP as well as SBP in the sedated group. The difference did not achieve a statistical significance with p=0.05 and p=0.12 respectively. Continuous intravenous sedation affect blood pressure by reducing the tension of the venous system, the cardiac preload and cardiac output [7]. The sedated group had a higher frequency of acute kidney injury (Table 1,2). An association between lower blood pressure and increased frequency of acute kidney injury has been demonstrated in several studies. In a cohort study Salmasie et al. [8], demonstrated that intraoperative low MAP was associated with increased frequency of acute kidney injury. Acute kidney injury was more pronounced at lower threshold and when hypotension was prolonged. Also in a retrospective cohort study, Smischney et al. [9], showed that in surgical patients without intraoperative hypotension postoperative hypotension was associated with increased risk of acute kidney injury. Several retrospective studies have shown that a low MAP is a risk factor for development of acute kidney injury in the intensive care unit. In a single center study Izawa et al. [10], found that the time spend below recommended MAP of 70 - and 65 - mm Hg was associated with acute kidney injury. This is in accordance with a study by Poukkanen et al. [11], who observed that hypotensive episodes were associated with increased risk of acute kidney injury. In another retrospective study with data from 110 intensive care units, Maheshwari et al. [12], observed

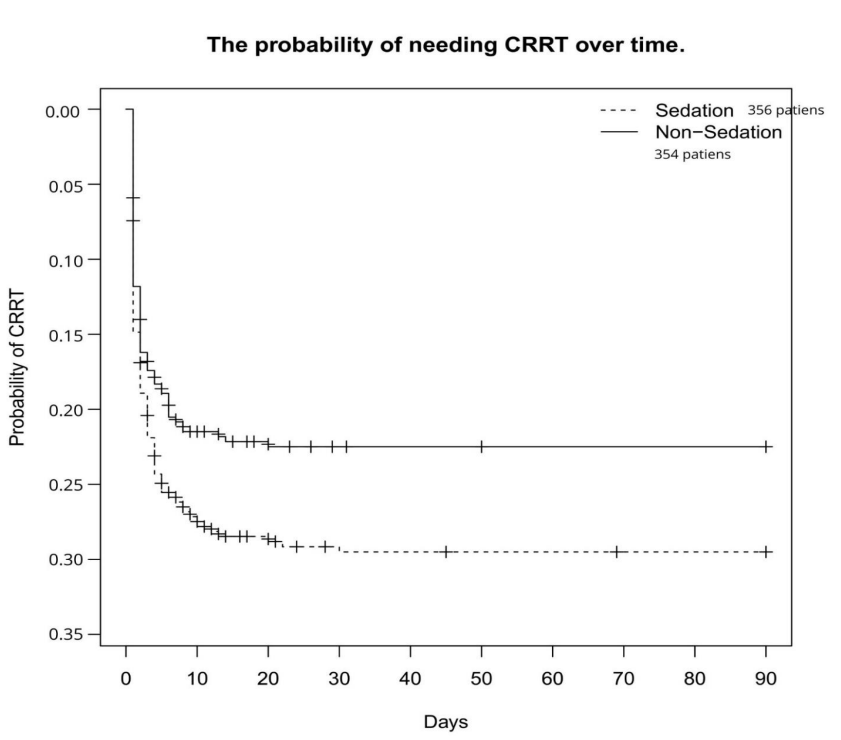

Figure 4: The probability of needing CRRT over time. All patients were censored at death while patients discharged were censored atn90 days (p< 0.05).

Table 1: Fluid balance, haemodynamic and renal parameters

Daily fluid balance					
	Non-sedation		Sedation		
day	mean	sd	mean	sd	p-value
1	1885.4	2783.8	1795.5	2593.6	Ns
2	397.1	1824.6	499.4	1730.6	Ns
3	-286.8	1480.4	-176.4	1497.0	Ns
4	-487.7	1384.5	-571.7	1491.9	Ns
5	-647.7	1446.9	-566.7	1472.4	Ns
6	-707.8	1359.1	-506.9	1564.2	Ns
7	-658.4	1357.3	-587.6	1348.1	Ns
Cumulative fluid balance					
	Non-sedation		Sedation		
day	mean	sd	mean	sd	p-value
1	1885.4	2783.8	1795.5	2593.6	Ns
2	2213.5	3950.3	2316.1	3778.1	Ns
3	1855.1	4686.7	2127.7	4528.5	Ns
4	1494.6	4991.8	1648.1	5113.5	Ns
5	985.9	5380,2	1222.5	5505.4	Ns
6	481.6	5657.0	1058.1	5931.0	Ns
7	-68.9	5840.8	273.8	661.4	Ns
Haemodynamic and renal parameters during the stay in the ICU					
	Non-sedation		Sedation		
	mean	sd	mean	sd	p-value
Mean Arterial Pressure	81.8	± 12.8	79.8	± 11.8	= 0.05
Lowest systolic blood pressure	104.3	± 19.4	102.8	± 17.9	= 0.12
Days with noradrenaline	3.67	± 5.0	4.69	± 5	=0.01
SOFA at discharge	3.7	± 2.5	4.2	± 2.6	= 0.03
Days in the KDIGO Stage 3	1365		1678		= 0.01

ICU (Intensive Care Unit)
KDIGO (Kidney Disease Improving global outcomes)
SOFA (Sequential Organ Failure Assessment score)

Table 2: Treatment with CRRT during the stay in the ICU

		CRRT No	CRRT Yes	CRRT in %	p-value
Total no of patients (Survivors+non-survivors)	Non-sed	273	76	28 %	0.04
	Sed	250	100	40%	
Patients who survived ICU	Non-sed	169	31	18 %	0.001
	Sed	163	58	36 %	
Need RRT when discharged from ICU	Non-sed	0	10	5 %	0.02
	Sed	0	25	11 %	

that the risk for acute kidney injury progressively worsened at lower thresholds of MAP. It is possibly that the lower MAP observed in the present study might play a major role in the development of the higher frequency of acute kidney injury in the sedated group.

As sedation decreases blood pressure in critically ill patients vasoactive agents such as noradrenaline are commonly used [7]. In the present study, significantly more patients were treated with noradrenaline infusion in the sedated group. In healthy volunteers, infusion of noradrenalin can harm the kidney function [13]. In patients with vasodilatory shock a too low dose of noradrenalin might result in a MAP below the kidneys autoregulation. Panwar et al. [14], showed that in critically ill patients requiring vasopressors a lower perfusion pressure resulted in a higher frequency of acute kidney injury. In a study by Redfors et al. [13], they increased MAP from 60 to 75 mmHg in patients with noradrenalin dependent vasodilatory shock. This increase in MAP resulted in an increase in glomerular filtration rate, oxygen delivery and urine flow while oxygen extraction was lower. When MAP was increased further to 90 mmHg, the renal variables did not improve further. Similarly in a study by Asfar et al. [15], increasing MAP to 80-85 mmHg compared to 65-70 mmHg did not improve renal function unless the patients had chronic hypertension. It has been recommended to use noradrenalin to maintain MAP between 60 and 65 mmHg in patients with vasodilatory shock to avoid the development of acute kidney injury [16]. In the present study, the infusion of noradrenalin has probably been used to fulfill these recommendations. Watchorn et al. [17], suggested a differential effect of noradrenaline on pre and post glomerular arterioles which in turn might reduce glomerular filtration rate. Sedation induces a lower blood pressure. Not only the magnitude of the low blood pressure but also the duration of the low blood pressure have a detrimental effect on renal function. We only registered the low blood pressure but not the duration. This is a limitation. The sedation was given as a continuous infusion and the effect on the blood pressure is probably also continuous. A persistent lower blood pressure and an increased use of the vasoconstrictor noradrenaline might explain the harmfull effect on renal function.

In the study by Lassnigg et al. [18], the lack of a renoprotective effect of furosemide infusion was demonstrated. Luckraz et al. [19], demonstrated that when forced diuresis with furosemide along with administration of intravenous fluids in a rate that is matched to the urine output was administered, it improved the renal function. So the detrimental effect on renal function was not due to the administration of furosemide but due to dehydration. In the present study, the higher frequency of acute kidney injury in the sedated group was not due to dehydration as the fluid balance as well as the accumulated fluid balance after a week was nearly identical in the two groups.

The effect of long-term use of sedative medication on renal function has only been investigated sparingly. The results from randomized controlled trials (RCT) on the effect of sedation with dexmedetomidine on renal function has been contradictory. One RCT [20], showed a better preserved renal function when the patients were sedated with dexmedetomidine as compared to propofol sedation. In the other RCT [21], there was no difference on renal parameters between the group sedated with dexmedetomidine and the control group. In our newly published RCT on non-sedation [3], the control group was lightly sedated with propofol for the first 48 hours and then switched to midazolam to avoid the propofol infusion syndrome of which kidney failure is a part. In a cohort study Leite et al. [22], observed a higher incidence of acute kidney injury in patients sedated with midazolam as compared to propofol. The effect on the kidney function might be an effect of a decrease in the microcirculation of the kidney induced by sedation [23].

The strength of this sub-study is the large number of patients, the multicenter design with few exclusion criteria providing a high external validity. Our population resembles the general mixed ICU population. There are some limitations that need to be addressed. First of all this is a sub-study to the NONSEDA trial where the sample size was calculated based on mortality and not renal function. The data in this sub-study was collected prospectively on a daily basis but the analysis was not a priori defined.

CONCLUSION

In conclusion the kidney function might be better preserved in the non-sedation group compared to the group treated with light sedation. Further studies are required to build on the findings of this substudy.

DECLARATIONS

Ethics approval and consent to participate

Approval was obtained from the local Ethics Committees (S-20130025). De Videnskabsetiske komiteer, Region Syddanmark, Damhaven 12, 7100 Vejle. All included patients gave informed consent to participate by signing a form.

AVAILABILITY OF DATA AND MATERIAL

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request

FUNDING

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AUTHORS CONTRIBUTION

All authors have made substantial contributions to the conception, design of the work, the acquisition and analysis or interpretation of data. All authors read and approved the final manuscript.

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