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The Effect of Sedation on Renal Function in ICU Patients: A Systematic Review

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Abstract

Sedatives are administered to the majority of critically ill patients in the ICU. Sedatives are important to diminish agitated delirium and anxiety. The use of sedatives might however harm organ function. Kidney injury is one of the most common causes of mortality in the ICU. We present a systematic literature review aimed to summarize the existing evidence of the effect of sedatives on renal function. Dexmedetomidine appears to have no, or maybe a positive effect on renal function. Concerns regarding the increased plasma levels of inorganic fluoride during sevoflurane sedation and its negative effect on renal function seem to be of irrelevancy. A higher incidence of renal impairment is observed following midazolam sedation compared to propofol. Further studies are required to decide if non-sedation is associated with a better renal function.

Keywords: Critically ill; Renal function; Non-sedation; sedation

Introduction

Sedative medications are administered to the majority of patients in the Intensive Care Unit (ICU). However, there are increasing attempts to minimize the use of sedatives through non-sedation and light sedation [1]. Sedatives are important to diminish agitated delirium and anxiety. The use of sedation might harm organ function. A post hoc analysis of a RCT with sedation compared to non-sedation shows decreased urine output and increased likelihood of renal impairment [1].

The most common sedative medications used are propofol, dexmedetomidine, and benzodiazepines. They are administrated *via* infusions, and volatile sedatives *via* inhalation [2]. Propofol is a short-acting sedative that is usually given as a bolus injection of 40 mg to 100 mg followed by an infusion of 25 μg/kg/min to 75 μg/kg/min [2]. Dexmedetomidine, an alpha-2 receptor agonist, is usually initiated with a bolus of 1 μg/kg over 10 to 20 min, followed by an infusion of 0.2 μg/kg/h to 0.7 μg/kg/h [2]. Dexmedetomidine compared to propofol and midazolam might contribute to the protection of renal function in critically ill patients, in particular those with sepsis [3]. Benzodiazepines are GABA agonists and have been used for sedation in the ICU for many years. The use of benzodiazepines is limited by their prolonged half-life [4]. Sedation with volatile anesthetics is relatively new but their use in the ICU setting has been limited due to their more complicated administration technique. In addition, doubts remain about safe levels of inorganic fluoride and their renal effects [2].

Renal impairment is a serious and common complication in ICU patients and is associated with an increase in mortality and length of stay in ICU [5]. It is important to acknowledge the risk factors for developing acute kidney injury and find out which preventive measures are available. This systematic literature review aims to summarize the existing evidence of the effect of sedation on renal function. With kidney injury being a common cause of mortality in the ICU [2] it is of great importance to optimize sedation strategies to preserve kidney function.

Method

This literature review was performed according to PRISMA guidelines [6]. Two data bases were searched; Medline and Embase. The final search was conducted on the November 2nd, 2021, on both databases. The search strategy involved crossing relevant terms concerning renal impairment in sedated patients in the ICU. Search strings were constructed; by using a broad random search of keywords, finding keywords from three control articles provided by our instructor (P. Toft), reviewing titles and abstracts of similar articles, and consulting with our Ph.D. student instructor (L. Abildgren). Relevant controlled keywords were identified *via* the MeSH database and the EMTREE thesaurus, which were then combined with free-text words and proximity searches. Search terms are

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Regarding the selection of data, Covidence [7] was used. Both authors (RLÚ and GL) performed independent title-abstract screening in advance of the full-text screening. Conflicts were resolved by discussion, and if needed, instructors (Abildgren. L and P. Toft) were consulted. When searching we included all study designs, all age groups, and no limitation was used in the year of publication, the only limits were set to humans. No attempts were made to identify unpublished studies. When screening, the following criteria were used:

Inclusion criteria:

- All age groups
- Humans
- Studies published in English, Danish, Norwegian, and Icelandic
- Patients sedated in the ICU
- Measurement of renal values reported

Exclusion criteria:

- Animal studies
- Studies reporting on anesthesia
- Nephrogenic diabetes insipidus
- Propofol infusion syndrome
- Reviews

Reviews were excluded unless the main focus was on the effect of sedation on renal function; in that case, the reference list was searched manually. For assessment of the risk of bias "Cochrane Risk of Bias Tool" [8] was used for the evaluation of randomized controlled trials. The ROBINS-I quality assessment scale [9] was used for case-control and cohort studies.

Results

This systematic literature search identified a total of 5.098 titles, 642 of them through Medline and 4.456 through Embase. After removing duplicates, 4.666 articles were screened of which 66 were full-text read and assessed for eligibility. Forty-seven studies did not meet the inclusion criteria and three duplicates were further identified. Various reasons for exclusions are summarized in Figure 1. One reviewer (RLÚ) screened a reference list of detected systematic reviews focusing solely on the effect of sedation on kidney function, further identifying one study meeting the inclusion criteria.

Thirteen articles were included in this review, including one case report, six randomized controlled trials, and six observational studies and post hoc analysis. All studies were conducted within the last 20 years and the majority within the last 10 years. The included studies, except the case report, had a relatively homogenous group of participants with comparable disease severity, fairly even age distribution, and multiple comorbidities. The characteristics and main findings of included studies are summarized in Tables 1-3.

When assessing the risk of bias, included studies were assessed to be of adequate quality. Two of the included randomized controlled trials were assessed to be of high quality while four were of moderate quality. When the method by which randomization was achieved was not clearly defined, studies were assessed of moderate quality. Three studies were considered to have an unclear way of randomization. Blinding of personnel was difficult to achieve when the sedative administration was different between drugs, it is though not assumed to affect the quality of the study. Furthermore, outcomes were evaluated *via* measured laboratory values, so the risk of outcome assessment bias is low. Findings are listed in Table 4, 5.

For the observational studies and post hoc analysis, most were assessed to be of high quality, with some domains having a moderate risk of bias. One cohort study [10], where sequentially selected patients were alternatively assigned to the study groups, was considered to have a moderate selection risk of bias. Included subgroup analytical studies [1,11] were also considered to have a moderate risk of bias in selection, because of the nature of the study design.

The included studies were divided into four categories based on the sedatives assessed; 1) dexmedetomidine 2) sevoflurane 3) propofol and midazolam and 4) non-sedation.

For dexmedetomidine, two randomized controlled trials [5,12] and one post hoc subgroup analysis [3] involving adult patients were included, along with a single center matched cohort study involving 102 pediatric patients [13]. The RCT trial by Jingquan et al. [5] indicated a lower incidence of acute kidney injury in patients who received dexmedetomidine compared to patients who received propofol at a loading dose of 1 μg/kg/10 min, followed by 0.2 μg/kg/h to 0.3 μg/kg/h for 5 days. Similar results were found in a post hoc analysis of patients with severe sepsis, carried out by Nakashima et al. [3]. The patients were sedated with dexmedetomidine at a dose of 0.1 μg/kg/h to 0.7 μg/kg/h, and low doses of propofol and midazolam for seven days. The dexmedetomidine group had lower serum creatinine values (p=0.04) than patients who only received propofol and midazolam. In contrast, Goksedef et al. [12] in a RCT found no major effects on renal parameters between the control group and dexmedetomidine group. However, in a subgroup analysis, if the total amount of dexmedetomidine exceeded 110 μg the creatinine clearance values were significantly better (p=0.04) compared with the control group. A cohort study with 102 pediatric patients [13] was included. At a dose of 0.3 μg/kg/h to 0.5 μg/kg/h of dexmedetomidine, higher values of creatinine clearance (p=0.09) and lower values of serum creatinine (p=0.05) were found compared with patients sedated. The authors did not mention what kind of sedation was used in the control group.

For sevoflurane, three randomized controlled trials, one cohort study, and one case report were included. Angela et al. [14] conducted a trial involving 60 participants, randomized in 2:1 to receive inhaled isoflurane or standard intravenous sedation with the median sedation length of 114 h. Outcomes showed no correlation between glomerular filtration rate and plasma inorganic fluoride levels, which often exceeded 50 μmol/l.

In 2009, Rohm et al. [15] published a trial where 125 ICU patients were randomized into two groups, 61 patients were sedated with propofol and 64 patients with sevoflurane. In the sevoflurane group, plasma fluoride levels exceeded the 50 μmol/l thresholds in up to 43% of patients, but serum creatinine levels and urine output remained unchanged. Renal function was observed up to 48 h after cessation of sedation and it remained unchanged. Similarly, Mesnil et al. [16] observed that no renal toxicity occurred during sevoflurane sedation, despite mean plasma inorganic fluoride levels being 82 μmol/l (range 12 μmol/l to 220 μmol/l). In a postoperative cohort

Table 1: Dexmedetomidine.

Study ID: First author Year of publication	Study design	Number of patients (n=)	Patient age	Compared interventions	Dose Length of sedation	Renal outcomes	Physical status and relevant comorbidities	Key findings
Nakashima T 2020	Post hoc analysis of RCT	n=104	71 ± 14 years	Sedation with dexmedetomidine, propofol and midazolam *vs.* sedation with propofol and midazolam	0.1 µg/kg/h to 0.7 µg/kg/h of dexmedetomidine 7 days	sCr was lower in dexmedetomidine group (p=0.04). No statistical effect on urine output.	APACHE II ≥ 23	Dexmedetomidine was associated with improved renal function among patients with severe sepsis.
Kwiatkowski DM 2016	Cohort	n=102	25 ± 22 months	Sedation with dexmedetomidine *vs.* unregistered sedation	0.3 µg/kg/h to 0.5 µg/kg/h of dexmedetomidine 24 h	sCr was lower in dexmedetomidine group (p=0.05). cCr was higher in dexmedetomidine group (p=0.09).	APACHE II=22-37	Dexmedetomidine was associated with lower incidence of AKI.
Liu J 2020	RCT	n=200	51 ± 20 years	Sedation with dexmedetomidine *vs.* sedation with propofol	0.2 µg/kg/h to 0.3 µg/kg/h of dexmedetomidine and 3 mg/kg/h of propofol 120 h	sCr and BUN were lower in dexmedetomidine group (p<0.05). cCr was higher in the dexmedetomidine group (p<0.05). Renal injury markers were lower in dexmedetomidine group (p<0.05).	Mean APACHE II=29	Dexmedetomidine was associated with lower incidence of AKI according to the KDIGO criteria.
Goksedef D 2010	RCT	n=86	61 ± 11 years	Sedation with dexmedetomidine *vs.* unregistered sedation	0.04 µg/kg/h to 0.5 µg/kg/h of dexmedetomidine and 0.04 µg/kg/h to 0.5µg/kg/h of placebo 5 days	No statistical effect on sCr, urine output and BUN values. cCr values were significantly better dexmedetomidine group on postoperative day one (p=0.04).	Post op CABG patients	No major effects on renal parameters. If the total amount of dexmedetomidine exceeded 110 µg, the creatinine clearance values were significantly better (p=0.04) compared with the placebo group.

Table 2: Sevoflurane.

Study ID: First author Year of publication	Study design	Number of patients (n=)	Patient age	Compared interventions	Levels of plasma inorganic fluoride	Renal outcomes	Physical status and relevant	Length of sedation	Key findings
Maussion E 2019	Case report	n=1	34 years	Sedation with sevoflurane	Plasma inorganic fluoride peaked at 137.9 µmol/l	sCr 104 mmol, urine output 2.3 ml/kg/h, BUN 9.8 mmol, plasma osmolality 333 mOsm, and urinary osmolality 37 mOsm-62 mOsm.	Multiple trauma patient	48 h (from day 6-8)	Polyuria and hypernatremia, with marked accumulation of plasma inorganic fluoride. Resolved with cessation of sevoflurane.
Rohm KD 2009	RCT	n=125	67 ± 10 years	Sedation with sevoflurane *via* ACD vs. sedation with propofol in fusion	39 ± 25 µmol/l	No statistical effect on sCr, cCr and urine output.	Post major abdominal, vascular or thoracic surgery patients	Sevoflurane group: 9.2 h ± 4.3 h. Propofol group: 9.3 h ± 4.7 h.	Post operative short term sedation with sevoflurane *via* ACD and propofol infusion did not negatively affect renal function.
Marcos JM 2012	Cohort	n=129	69 ± 11 years	Sedation with sevoflurane via ACD *vs.* sedation with propofol infusion	Not measured	No statistical effect on sCr, CK or CK/MB.	Post cardiac surgery patients	292 min ± 142 min	Post operative sedation with sevoflurane did not negatively affect renal function.
Mesnil M 2011	RCT	n=47	46 ± 15 years	Sedation with sevoflurane *via* ACD *vs.* edation with propofol and/or midazolam infusion	Mean value of 82 µmol/l	No statistical effect on sCr and urea.	Mean APACHE II=21-28	24 h to 96 h	No renal toxicity due to sevoflurane was observed, even though plasma fluoride levels often exceeded 50 µmol/l.

Jerath A 2020	RCT	n=60	58 ± 13 years	Sedation with inhaled isoflurane *vs.* sedation with propofol and/or midazolam infusion	Mean value of 15 µmol/l in volatile group. Mean value of 2 µmol/l in infusion group.	sCR was higher in volatile group (p=0.02). GFR was higher in infusion group (p=0.34).	Mean APACHE II=31-34	Median of 114 h and 88 h	Serum fluoride levels rose with the duration of isoflurane sedation but were not associated with altered renal function.
Bazin JE 2014	Observational study	n=12	57 ± 23 years	Sedation with inhaled sevoflurane *via* ACD	Mean value of 0.7 µmol/l ± 0.7 µmol/l at day 0, and 51.7 µmol/l ± 7.5 µmol/l and 68.1 µmol/l ± 7.4 µmol/l on days 1 and 2	No statistical effect on urea sCr decreased. No kidney injury was detected.	mean SAPS II=44	48 h	Long term sedation with sevoflurane did not negatively affect renal function.

Table 3: Propofol, midazolam and non-sedation.

Study ID: First author Year of publication	Study design	Number of patients (n=)	Patient age	Compared intervention	Dosage of sedative Length of sedation	Renal outcomes	Physical status and relevant comorbidities
Olsen HT 2020	RCT	n=700	71 ± 9 years	Non-sedation *vs.* Light sedation with daily interruption	Dose according to Danish guidelines. Propofol for 48 h, then midazolam. 7 days.	Only the highest measured RIFLE score was reported	APACHE II= 21-30
Leite TT 2015	Cohort	n=1396	64 ± 19 years	Sedation with propofol *vs.* Sedation with midazolam	Mean dose of 35.5 µg/kg/min of propofol. Mean dose of 0.8 µg/kg/min of midazolam. 6 h-48 h.	AKI by KDIGO criteria	Non-specific
Strøm T 2011	Post hoc analysis	n=103	65 ± 10 years	Non-sedation *vs.* sedation with daily interruption	Dose according to Danish guidelines. Propofol for 48 h, then midazolam. 14 days.	Increased urine output in non-sedated group (p=0.03). Lower RIFLE score in non-sedated group (p=0.0012).	APACHE II= 19-30

RCT: Randomized Control Trial; ACD: Anesthetic Conserving Device; sCr: serum Creatinine; cCr: creatinine Clearance; BUN: Blood Urine Nitrogen; CK: Creatinine Kinase; CK/MB: Creatinine Kinase/Myocardial Band; GFR: Glomerular Filtration Rate; APACHE II: The Acute Physiology and Chronic Health Evaluation; SAPSII: Simplified Acute Physiology Score; h: Hour; RIFLE score: Risk Injury Failure Loss End-Stage Kidney Disease; AKI: Acute Kidney Injury

Table 4: Cochrane risk of bias tool, a summary of risk of bias in the six randomized control trial studies included.

Study	Random sequence generation (selection bias)	Allocation concealment (selection of bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Liu J 2020	Unclear	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Olsen HT 2020	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Rohm KD 2009	Unclear	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Goksedef D 2010	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Jerath A 2020	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Mesnil M 2011	Unclear	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	Low risk of bias

study, including 129 patients, Marcos et al. [10] found no difference in serum creatinine levels between groups receiving propofol (n=62) or sevoflurane (n=67).

In contrast, the included case report [17], suggested the onset of polyuria and hypernatremia with an increase of plasma inorganic fluoride levels, which then improved when sevoflurane sedation was changed to sedation with intravenous midazolam and sufentanil. Here, the plasma in organic fluoride levels reached as high as 137.9 µmol/l and the patient received sevoflurane for about 48 h.

For midazolam and propofol, included studies varied both in design and in the way they analyzed those two medicaments. In a cohort study from Leite et al. [11] in 2015, patients were sedated with either propofol or midazolam in a 1:1 ratio. Renal outcomes were observed during the first seven days in the ICU. With acute kidney injury defined by the KDIGO criteria, a higher incidence was observed in patients sedated with midazolam.

Furthermore, patients receiving propofol had oliguria less frequently (p=0.001) and diuretics prescribed less frequently (p=0.001).

In the latest RCT [18], 700 patients were included and divided into two groups in a 1:1 ratio. One group received non-sedation and the other group light sedation with a daily interruption. The control group was sedated with propofol for the first 48 h, continuing with midazolam. Only the highest measured RIFLE score within 28 days after randomization was reported in this article. No difference was observed in the highest RIFLE score between groups. In contrast, a post hoc analysis of a single-center trial with 140 patients randomized to non-sedation or light sedation with a wake-up trial [1], showed that non-sedation increased urine output (p=0.03) and resulted in a lower RIFLE score (p=0.0012). In this trial, the control group was also

Table 5: ROBINS-I risks of bias tool, a summary of the risk of bias in the six cohort studies included.

Study	Domain 1 confounding	Domain 2 selection	Domain 3 classification of intervention	Domain 4 deviation from interventions	Domain 5 missing data	Domain 6 measurement of outcomes	Domain 7 selection of reported results
Nakashim T 2020	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Moderate risk of bias
Leite TT 2015	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Strøm T 2011	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Bazin JE 2014	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Kwiatkowski DM 2016	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias
Marcos JM 2012	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

sedated with propofol for the first 48 h followed by midazolam.

Discussion

This systematic review aimed at creating an overview of the current evidence on non-sedation and the most commonly used sedatives in the ICU and their effect on renal function. When searching for literature it became clear that only spare research has been made in this area.

We identified and included four studies [3,5,12,13] describing the effect of dexmedetomidine on renal function. Two of those studies were RCTs [5,12]. One of them indicated a lower incidence of renal impairment in patients sedated with dexmedetomidine [5]. The other RCT by Goksedef et al. [12], however, showed no effect of sedation with dexmedetomidine on renal function. The two other studies reported a lower serum creatinine and higher creatinine clearance with the dexmedetomidine sedation [3,13]. Further studies are required to show a clinical effect of dexmedetomidine on renal function.

Regarding sevoflurane, we included three trials and one observational study that all resulted in renal function remaining unchanged in patients receiving sevoflurane or isoflurane [14-16,19]. The elevation of plasma fluoride levels has been of primary concern when sedating patients with volatile anesthetics and its accumulation has been thought to lead to renal toxicity [14]. However, our findings suggest that sevoflurane can be safely used in the ICU setting. Patients in included studies had plasma fluoride levels rising as high as 220 µmol/l without it resulting in renal toxicity [16]. In contrast, one case report was included that suggests renal failure caused by increased plasma fluoride levels which then improved when sedation was stopped [17]. Because of the nature of that study design, this could be an incidental finding.

Regarding propofol and midazolam, there was only one trial that met our inclusion criteria. In this cohort study, the effect of propofol and midazolam on renal function was compared [11]. The study showed that midazolam causes a higher incidence of renal injury compared to propofol. Propofol is widely used in intensive care settings and its use is often combined with midazolam [2] which was the case in several of our included studies.

Two randomized control trials investigated the effect of non-sedation on renal function. The post-hoc analysis of the first RCT of non-sedation showed a rather encouraging beneficial effect of non-sedation on renal failure [1]. The larger and later RCT on non-sedation could not demonstrate a beneficial effect on the highest measured RIFLE score. In this RCT other parameters of renal function were prospectively registered. Publication of further studies is required to decide the effect of non-sedation on renal function.

Limitations

There were some limitations to this review. Firstly, only two databases were searched and no attempt was made to identify unpublished studies. Secondly, this is a broad topic, including different types of sedatives, often mixed and in different ways between institutions. We observed that only spare literature exists concerning the effect of sedation on renal function. Included in the review are therefore different types of studies. Some of the included studies were judged to have some risk of bias, listed in Table 4, 5. Study samples varied greatly regarding types of included patients.

Conclusion

This review suggests that sedation can have different effects on renal function in critically ill patients, depending on the medication administered. Dexmedetomidine appears to have no, or maybe a positive effect on renal function in ICU patients. Concerns regarding the elevation of plasma in organic fluoride levels during sevoflurane sedation and its negative effects on renal function seem to be of irrelevancy. A higher incidence of renal impairment is observed following midazolam sedation compared to propofol. Publications of further studies are required to decide if non-sedation is associated with a better renal function.

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