

Original Article

Effectiveness and safety of remimazolam sedation in the emergency department

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ABSTRACT

INTRODUCTION. The demand for procedural sedation in the emergency department (ED) has risen. This study aims to 1) investigate the safety of remimazolam as analgosedation, 2) evaluate amnesia and the quality of sedation and 3) determine whether the sedation was successful and effectively managed pain for procedures in the ED.

METHODS. This prospective clinical cohort study was performed by registered nurse anaesthetists in the ED at Aalborg University Hospital from February to May 2024. Outcome measures were 1) adverse effects of remimazolam, proportion of patients reporting 2) adequate sedation or amnesia post-procedure and 3) adequate pain or anxiety relief.

RESULTS. A total of 68 patients (median age 59, 58% female) were sedated by remimazolam with a median dose of 7.5 mg. Most patients (97% (n = 66)) had no or mild respiratory problems during sedation. Two patients had transient severe respiratory problems following sedation. Both patients had received large doses of opioids before remimazolam sedation. Patient satisfaction was 97% based on reports of procedural amnesia or satisfaction with sedation and pain control. Almost all (89%) joint reductions were successfully performed. In over half of patients who would have otherwise required general anaesthesia in an operating room (57%, n = 20/35), sedation with remimazolam was sufficient to perform the procedure in the ED.

CONCLUSIONS. The use of remimazolam in the ED was a safe and effective sedative treatment with high patient satisfaction levels.

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The requirement of procedural sedation for diagnostic or therapeutic purposes outside the operating room has led to an increase in the demand for both invasive and non-invasive procedures in the emergency department (ED) [1]. The goal of procedural sedation is to induce a state in which the patient can tolerate otherwise unpleasant procedures while maintaining cardiorespiratory function and protective airway reflexes [2]. Sedatives and analgesics like midazolam, propofol, ketamine, dexmedetomidine and remifentanyl are used by non-anaesthesiology physicians in the ED [1] or ambulatory settings that require brief and moderate sedation [3-6]. Remimazolam (RM) is a novel, yet well-established, ultra-short-acting benzodiazepine [4]. It is an ester-based benzodiazepine that can be rapidly hydrolysed into inactive metabolites by tissue esterases [7]. Its onset of action is approximately 1-3 min., and its half-life is 10 min. These qualities produce a moderate, brief sedation followed by rapid recovery [7, 8]. Recent studies comparing the use of RM with propofol and midazolam outside of the

operating room report no difference in sedation, but faster recovery and shorter hospital stays [7-9]. This observational clinical cohort study aimed to 1) investigate the safety of RM as analgosedation for procedures in the ED, 2) evaluate the proportion of patients experiencing amnesia and quality of sedation and 3) to establish whether the sedation was successful and effectively managed pain.

Methods

This prospective cohort study was conducted between 20 February and 31 May 2024 in the Emergency Department, Emergency and Trauma Centre, at Aalborg University Hospital, Denmark. The department receives and treats patients with all types of acute injuries and illnesses. Approximately 58,000 patients arrive at the ED annually (2023), and around 600 trauma calls and 1,200 emergency calls are handled annually. The team comprises approximately 85 nurses, 25 medical secretaries and 30 doctors.

Inclusion criteria were age ≥ 12 years, American Society of Anesthesiologists' physical status classification (ASA) score 1-3 and 4 if the on-call anaesthesiologist had sanctioned it, expected tolerance to benzodiazepines and opioids, and procedures that may cause pain or anxiety. Exclusion criteria were ABCDE instability before procedure, known intolerance to benzodiazepines, ASA score 4-5 or myasthenia gravis.

Outcome measures

Safety was measured as the percentage of patients receiving RM not requiring airway management, antidote or correction of other potentially life-endangering side effects observed by a registered nurse with anaesthetic training. Amnesia and sedative quality were measured as the percentage of patients reporting adequate sedation and amnesia following the procedure. Successful sedation and pain management were measured as the percentage of patients reporting adequate pain or anxiety alleviation, regardless of whether they remembered the procedure or not.

Data collection

Patients were included in the study when they met the eligibility criteria and when the relevant nurses were on duty and available to administer sedation. The sample size was based on feasibility.

Demographic and medical data were collected: age, gender, height, weight, BMI, ASA score and type of procedure (e.g., fracture manipulation, pleuracentesis). Dosage and administration of relevant drugs (RM, alfentanil, fentanyl or morphine) reported in mg or μg were registered.

Safety was measured by occurrence of respiratory problems graded as mild/moderate or severe (grade estimated by the required intervention to solve the respiratory problem). Data regarding amnesia and sedative quality: % of nurses' evaluation of the sedation as "a success" defined as 1) presence of antegrade amnesia, 2) an overall subjective feeling that it was a good experience for all involved, patient as well as staff, and 3) the planned procedure succeeded. Nurses evaluated pain by observing pain categorised as *mild*: frowning, making subtle noises, or briefly opening eyes during the most painful part of the procedure; *moderate*: moaning, expressing pain, tensing up or repeatedly opening eyes; or *severe*: undoubtedly expressing pain, attempting to evade the procedure or consistently keeping eyes open.

Procedure

Prior to sedation, each patient was evaluated according to: ASA score, presence of a large tongue, impaired mobility of the neck and jaw, obesity ($\text{BMI} > 30 \text{ kg/m}^2$), history of sleep apnea or prior difficult airway management according to the local guideline [10]. During sedation with RM, continuous monitoring comprised blood oxygen saturation, heart rate, respiratory rate and blood pressure every 5th min. Preoxygenation was

conducted using a nasal cannula with an oxygen flow of 3 l/min. Additionally, a functioning suction catheter, ventilation bag and antidotes (naloxone and flumazenil) were ensured to be readily available near the patient [11]. Depending on the present or the anticipated pain level during the procedure, opioids could be administered prior to or during the procedure. The initial dose of RM ranged from 2.5 to 7.5 mg, determined by patient biometrics, age, comorbidity and assessment of preprocedural pain [11]. Induction was performed via intravenous bolus of refractory doses followed by repeated doses of 2.5 mg administered every 30-60 sec. until the patient reached a state of sedation where the procedure was possible. The sedating nurse was responsible for monitoring the patient's vital signs and sedation level. Sedation level was assessed by evaluating the depth of sleep and the patient's response to pain, graded from mild to moderate-to-severe reaction. If the patient showed a moderate-to-severe pain reaction, additional doses of RM and/or alfentanil were administered. If the patient had a decrease in blood oxygen saturation during the sedation, the following interventions could be performed: verbal and physical contact, increase in oxygen flow, starting the painful procedure, basic airway manoeuvres, insertion of naso- or oropharyngeal airway, bag-mask ventilation or administration of an antidote. After completing the procedure, the sedating nurse monitored the patient until they were fully awake. Approximately 10 min. after awakening, patients were asked about their experience of pain during the procedure, satisfaction with the sedation and recollection of the procedure.

Statistical analyses

Descriptive statistics were reported as mean ($\pm$ standard deviation) for data following the normal distribution, and as median and interquartile range for non-normally distributed data. Proportions were calculated out of all participating patients unless otherwise stated. Data were collected and stored in REDCap, an electronic data capture software (REDCap, Version 9.5.6, Vanderbilt University) [12, 13]. The statistical software SAS enterprise was used for data analysis (SAS Institute Inc., Cary, NC, USA).

Trial registration: not relevant.

Results

A total of 68 patients were included (**Table 1**). Most procedures were either reductions of dislocated joints or fracture manipulations. We also administered RM to patients who were highly anxious or had mental disorders that made it difficult to carry out specific procedures due to their mental status.

TABLE 1 Patient characteristics.

Included patients, n	68
Age, median (IQR), yrs	59 (35-72)
Gender: women/men, %	58/42
<i>ASA score^a, % (n)</i>	
1	35 (24)
2	41 (28)
3	22 (15)
4	1.5 (1)
<i>Potential airway risks, % (n)</i>	
Large tongue	13 (9)
Decreased movement of jaw or neck	0
Obesity	21 (14)
Subtotal	21 (14)
<i>Procedures^b, % (n)</i>	
Reduction procedure of joint	53 (35)
Fracture manipulation	18 (12)
Lumbal puncture	5.9 (4)
Anxiety during of procedure	7.6 (5)
Pleura drainage	1.5 (1)
Other	14 (9)
Procedures normally done in the OP under anaesthesia but handled in the ED with remimazolam sedation, % of patients (n/N)	57 (20/35)

ASA = American Society of Anesthesiologists; ED = emergency department; IQR = interquartile range; OP = operating theatre.

a) ASA's physical status classification system score.

b) 66 patients.

Safety

Safety data and sedation doses for the 68 patients are shown in **Table 2** and **Figure 1**. Sedation was possible in 78% without respiratory challenges. Of the 22% (13 patients) where respiratory challenges developed, eleven were mild to moderate in character and could be solved by one of the following procedures: jaw lift, increasing oxygen or installing a naso-/ oropharyngeal airway for a short period of time. Only one patient was mask-ventilated and one was given an antidote for opioids. Both patients had been given large doses of opioids in the prehospital setting before the RM sedation. When RM was given, there were no respiratory problems until the procedure was finished. As soon as the painful stimuli were removed, the respiratory challenges arrived but

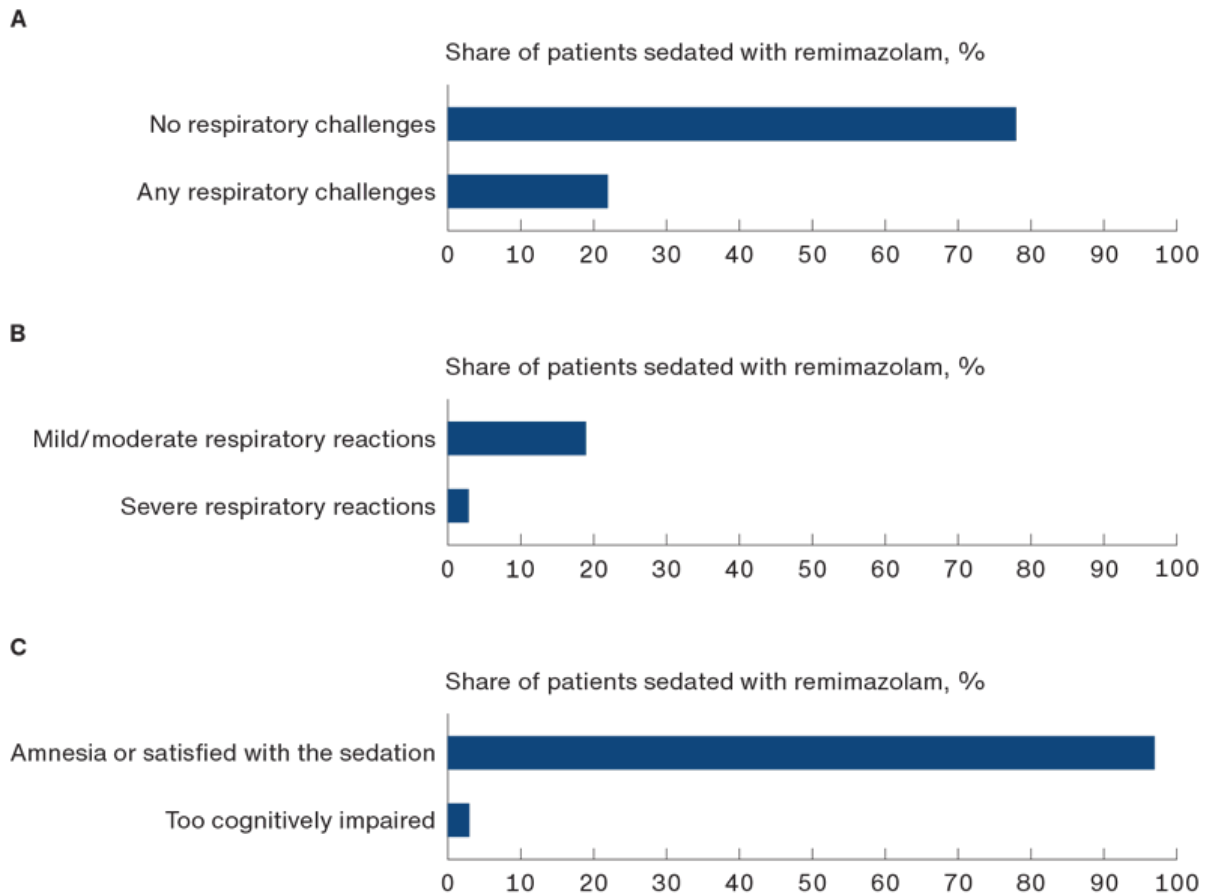
were short-lasting. Among the patients who did not receive an opioid, this was attributed to the use of RM as an anxiolytic agent, rather than the procedure being non-painful.

TABLE 2 Safety and medication given (N = 68).

<i>Safety, % (n)</i>	
Without any problems during sedation	78 (53)
With respiratory problems	22 (15)
Mild/moderate: solved with a max of 1 of the following:	19 (13)
O ₂ given by mask: 15 l/min.	2.9 (2)
With jaw lift	13 (9)
With naso- or oro-/pharyngeal airway	2.9 (2)
Severe: solved with a combination of actions:	2.9 (2)
Patient A: jaw lift, oxygen given by mask, and an opioid antidote	
Patient B: jaw lift, naso/pharyngeal airway, and mask ventilation	
<i>Medication</i>	
Remimazolam:	
Dose in total: % (n)	
1.25 mg	1.5 (1)
2.5 mg	12 (8)
5 mg	15 (10)
7.5 mg	33 (22)
10 mg	18 (12)
12.5 mg	3.0 (2)
15 mg	4.5 (3)
17.5 mg	4.5 (3)
20 mg	6.0 (4)
Other doses	3.0 (2)
Average dose, median (IQR), mg	7.5 (5-10)
<i>Opioids</i>	
Where opioids were given: any opioid, % (n)	82 (56)
Alfentanil, % (n)	80 (53)
Average doses alfentanil, median (IQR), mg	1 (1-1)
Fentanyl, % (n)	8.8 (6)
Average dose fentanyl, median (IQR), µg	50 (50-100)
Morphine, % (n)	7.4 (5)
Average dose morphine, median (IQR), mg	10 (10-10)

IQR = interquartile range.

FIGURE 1 Safety and patient satisfaction. **A.** Respiratory challenges. **B.** Respiratory reactions. **C.** Amnesia and satisfaction with the sedation.



Patient satisfaction

Most patients had amnesia for the event for which the RM sedation was performed. Among those who remembered the procedure, all were satisfied with the sedation (**Table 3**). Of the 35 joint reductions, 89% were successful in RM sedation, and 57% (20 of 35) of patients who would previously have been handled at the operating room under anaesthesia were successfully handled in the ED due to RM sedation.

TABLE 3 Effectiveness.

Joint reductions being successful, % (n/N)	89 (31/35)
Patients satisfied with the sedation or had amnesia ^a , n (%)	97 (66)
Nurses evaluating the sedation as <i>“a success” defined as this, because of the following, n (n/N)</i>	97 (65/67)
Antegrade amnesia in the patient, or An overall subjective feeling that "it was a good experience for all involved, patient as well as staff", and The planned procedure was a success	
<i>Nurses evaluating the patients as pain free, n (n/N)</i>	
“Yes”	82 (54/66)
“No”	12 (8/66)
Not possible to evaluate due to severe cognitive impairment	6.1 (4/66)
<i>Patients evaluated by the nurses to be in pain during the procedure^b, n (n/N)</i>	
Mild pain reaction	38 (3/8)
Moderate pain reaction	25 (2/8)
Severe pain reaction	38 (3/8)

a) 3% (n = 2) had severe cognitive impairment and could not answer.

b) 1 with a mild reaction had only partial amnesia, the rest had complete amnesia or were very satisfied with their relief despite their objectively observed pain reaction.

Effectiveness according to the remimazolam administering nurse

Overall, 97% of procedures were subjectively evaluated by the RM administering nurse as a “success for all involved”, even if the nurses registered insufficient pain treatment in 12% (n = 8) of patients. These patients showed objective pain reactions but did not remember them afterwards.

Discussion

This was a non-randomised, non-blinded quality improvement study of the use of RM as sedation for painful procedures in 68 patients in an ED. The sedation was provided by two registered nurses with anaesthetic training

working in the ED. No or mild respiratory problems during the sedation were observed in 97% of patients despite most of them having received large doses of opioids. All patients either reported satisfaction with the degree of relief or had antegrade amnesia. In 96% of patients, the nurse rated the sedation as sufficient.

Discussion of safety of remimazolam use in the emergency department

To the authors' knowledge, no studies have examined the safety of RM in an ED setting. The results of the present study demonstrate its safety when administered by registered nurses with anaesthetic training. This finding corroborates previous studies that assessed the safety of anaesthesia administered by trained advanced practice providers in the absence of anaesthesiologists, as well as a study comparing the safety of RM to propofol in patients undergoing colonoscopy [14, 15]. In the ED, some patients use benzodiazepines long-term or recreationally. This might necessitate a higher dose of RM and increase the risk of respiratory depression and hypotension during its administration [16]. However, as demonstrated in the present study, this did not compromise patient safety.

Discussion of patient satisfaction

In this study, 97% of patients experienced amnesia or were satisfied with the sedation. This finding supports an existing study that found that 97.5% of patients could not remember the procedure [6]. We did not differentiate between amnesia and satisfaction; both were measured on the same scale. Future studies should separate these metrics. Though cognitive function was not formally measured, nurses and doctors reported that patients quickly returned to their pre-sedation cognitive function.

RM can achieve a rapid offset unless an excessive dose is administered, making it suitable for short procedures such as fracture manipulation, a common procedure in the ED, where sedation ends as soon as the joint is repositioned [16]. Additionally, the orthopaedic surgeons found it practical that patients were deeply sedated, making joint reductions and fracture manipulations easier due to complete muscle relaxation in most cases. Using RM sedation was as quick as administering lidocaine into the fracture, but the manipulation was easier compared to when a large amount of local anaesthetic was present between the bone ends.

Discussions of effectiveness evaluated by the health professionals

This study found that approximately 20% of patients experienced respiratory challenges when sedated with RM, which is slightly higher than the 7.4% documented in the review by Tang et al. [8]. The difference might be explained by the fact that many patients in the ED had previously received opioids or were regular opioid users [17].

Only two patients experienced adverse events, which were managed with simple measures when they occurred.

Procedures were performed successfully, and several procedures, such as joint reductions, were performed in the ED that would otherwise need to be performed in the operating room due to the requirement of deep sedation with drugs such as propofol. While being sedated, most patients expressed low to moderate signs to pain, making the procedure easier to perform.

Some patients had low saturation while being sedated. However, this was solved rather simply by increasing oxygen flow and/or basic airway manipulation.

Strengths and limitations

Several limitations should be acknowledged. Patient satisfaction and other self-reported outcomes, such as amnesia and perceived sedation adequacy, are inherently subjective and may be influenced by contextual factors—for example, patients may feel reluctant to express concerns after being informed by a physician that a novel sedation method is being used. Similarly, administrator satisfaction and outcome assessments may be

prone to bias, as the sedation providers were also responsible for evaluating outcomes. No validated or objective tools were used for these assessments, which should be addressed in future research.

The sample size was based on feasibility considerations, given the exploratory nature of the study and limited prior data in this clinical context. This limits the generalisability of our findings and underscores the need for larger, controlled studies. Future research should aim to validate subjective outcomes with objective measures and consider additional patient-centred endpoints – such as complication rates – when comparing procedural sedation in the ED to general anaesthesia administered in the operating room.

Conclusions

The administration of RM by registered nurses with anaesthetic training in the ED proved to be safe and effective, leading to high patient satisfaction. The next logical step will be to evaluate whether nurses and doctors without specialised anaesthetic training but trained in the use of administering RM can achieve similarly positive patient responses.

Ethics approval and consent to participate

The study was registered and approved by the hospital administration as a quality study (ID 2017-011259). The data safety regulations approved the study under the ID K2024-039. All patients consented to being sedated with RM, and this was noted in their medical records. All laws relating to quality studies were followed. In Denmark, a quality study of a clinical treatment with an approved drug does not need written consent, only oral.

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