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# Dose-dependent side effects of prehospital analgesia with ketamine for winter sports injuries – an observational study

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## Abstract

**Background** Ketamine is one of the most used drugs in trauma patients after skiing accidents. However, the environmental conditions for these patients are often rough, with numerous unpleasant sensory impressions (e.g. noise from the helicopter, cold, wind, etc.), raising concerns about the adverse psychological side effects of ketamine. Moreover, it has not yet been established whether these side effects are dose-dependent, and the supplementary administration of benzodiazepines remains controversial. We analysed the subjective perception of side effects after administration of ketamine during helicopter emergency medical service missions involving trauma patients after ski accidents.

**Methods** In this retrospective observational study, data was collected from emergency services protocols and questionnaires filled out by patients. The primary outcome was defined as the patients' subjective perceptions of ketamine-associated side effects. The subjective intensity of twelve common classes of side effects was recorded on a five-point Likert scale. In addition, we conducted a linear regression analysis, with side effect intensity as the outcome and gender, age, type of injury, use of midazolam and fentanyl, ketamine dosage and relative pain reduction as covariates.

**Results** A total of 69 patients were identified who were treated with ketamine during the winter months of 2023/2024, after suffering trauma while doing alpine winter sports. Of these, 49 patients (71%) could be included. The side effects reported were mostly mild, with two-thirds of the patients describing them as “no [side effects]” or “mild”. Only 6% described them as “barely tolerable” or “unbearable”. No statistically significant association could be demonstrated between the ketamine dose and the total reported side effect score. The regression model identified the additional administration of midazolam as a significant covariate for fewer side effects. With regard to prehospital care, 85% of the patients stated that they had always felt safe, while two-thirds were satisfied with the prehospital pain therapy.

**Conclusion** Ketamine seems to be a suitable option for pain therapy in the case of injuries during alpine winter sport activities. Side effects reported by patients in this study were rare, not dose-dependent and described by most patients as subjectively well tolerable. The supplementary administration of midazolam could potentially further reduce these side effects.

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**Keywords** Ketamine, Emergency medicine, Trauma management, Prehospital analgesia

## Introduction

In prehospital emergency medicine, analgesia is an important intervention for initial treatment and patient comfort [1]. However, recent studies have shown that pain therapy is often inadequate in this setting and that there is significant patient dissatisfaction [2–4]. In addition to opioids, ketamine is also increasingly being used to treat severe trauma pain [5, 6].

In low doses, ketamine has an analgesic effect, while at higher doses, it causes dissociative anaesthesia. The transition from analgesia to anaesthesia depends, among other factors, on the dosage, concomitant medication and the patient's condition. Dysphoria, vivid hallucinations and even “emergence phenomena” (or agitation) are consistently reported side effects of ketamine use [7]. In addition to its analgesic potency, the side effects perceived by the patient are reported to play a crucial role in patient satisfaction [8]. However, most studies that have been conducted to date focus on the in-clinical application of ketamine, particularly in the context of balanced anaesthesia. As a result, the side effect profile and, in particular, the dose dependence of these side effects (especially hallucinations and nightmares) has not yet been thoroughly analysed in the prehospital setting. Moreover, it is unclear how stressful or unpleasant patients perceive these side effects to be. While it is assumed that a noisy or disruptive environment (with the sound of the helicopter, cold, wind, etc.) exacerbates these side effects, there is no clear evidence for this so far. In recent years, ketamine has also been recommended as a first-choice analgesic in military medicine and is explicitly covered in the Tactical Combat Casualty Care (TCCC) Guidelines [9]. Of course, patients treated under these conditions are also significantly exposed to the environmental factors mentioned above.

The patient group under consideration in this study was exposed to precisely these stimuli: trauma on the ski slope, immobilisation and the potential reduction of the injured extremity, the approach of the rescue helicopter and being loaded into the cabin. Several researchers have postulated that the psychological side effects occur particularly during the offset phase of ketamine [10–12]. At low doses (0.25–0.5 mg/kg body weight), this offset phase is likely to occur after just a few minutes, whereas at higher doses the time interval is significantly longer and the patient probably only enters the offset phase after handover to the target hospital (with warmth, rest, etc.), meaning that they are in a protected environment and thus subjected to fewer external stimuli.

The prophylactic administration of benzodiazepines continues to be controversial [5] and the hoped-for

effect has not yet been conclusively proven. In this study, we therefore aim to describe the relationship between the ketamine dosage and the occurrence and subjective severity of side effects. The influence of benzodiazepines will also be investigated in this context.

## Methods

In this observational cohort study, we examined data from patients who were injured on ski slopes in the Swiss Alps (canton of Valais) and transported to the hospital by helicopter emergency medical services (HEMS).

### Study design

Data collection took place between December 2023 and April 2024. Patients who were cared for by the local HEMS company (Air Zermatt) were screened. All trauma patients who had been injured during winter sport activities and who had been treated prehospitally with ketamine for analgesic therapy were included. Patients under 18 years old, seriously injured patients who had to be given emergency anaesthesia prehospitally and patients who could not be adequately informed (e.g. because of language barriers) were excluded. This study was purely observational and had no impact on the patients' treatment: the choice of pain therapy was entirely the responsibility of the treating emergency physician. The study was approved by the responsible ethics committee of the canton of Bern, Switzerland (reference number: 2023–02174).

### Data collection

The emergency service protocols were screened daily for the use of ketamine and a corresponding clinical research form (CRF) was created for each patient in the electronic data management system. Included patients were contacted as soon as possible following the injury: in the case of patients who were still in hospital, this was done in person on the ward. In the case of those who had already left the hospital, contact was made by phone. If the patient could not be reached by phone on the first attempt, further attempts were made in the following days. If the patient could not be contacted after a total of 10 days, the individual was excluded from the study. All the patients were then given the study documents (questionnaire and consent form) in paper form directly on the ward or by post. The questionnaire used was developed by the study team and is available in the appendix (Supplement 1).

The following data were recorded (data source given in brackets):

- Age (HEMS protocol).
- Injury pattern (HEMS protocol).
- Pain level [NRS] upon arrival of the HEMS team and handover at the hospital (HEMS protocol).
- Administered dosage of ketamine, midazolam and fentanyl (HEMS protocol).
- Subjective severity of pain on a numerical rating scale [NRS] and described in words (patient questionnaire).
- Satisfaction with pain therapy during prehospital treatment on a six-point Likert scale (“strongly agree” to “strongly disagree”, patient questionnaire).
- “Feeling safe” during prehospital treatment on a six-point Likert scale (“strongly agree” to “strongly disagree”, patient questionnaire).
- Subjective perception of side effects (nausea, vomiting, shortness of breath, rash/itching, palpitations, anxiety, dizziness, vivid positive dreams, nightmares, inner restlessness, physical restlessness, blurred vision) measured as “total side effect score, TSES” (see below) and a global assessment of side effects on a six-point scale (“no side effects”, “mild”, “relevant”, “well tolerable”, “barely tolerable”, “unbearable”) (patient questionnaire).

All data for this study were collected, recorded and stored using REDCap® (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee, United States). The total side effect score (TSES) was calculated by adding the recorded severity of the twelve side effect classes mentioned above. A scale between 0 (“no side effect”) and 5 (“unbearable side effect”) was used for each category. The TSES therefore gives a value between 0 and 60 points. This is not a validated assessment; the score was developed by the study team.

In this study, ketamine was administered exclusively via the intravenous route. The administered dosage of ketamine was given as mg/kg body weight (BW). A ketamine dosage of less than 0.5 mg/kg BW was categorised as “low”, 0.5–0.99 mg/kg BW as “moderate” and  $\geq 1.0$  mg/kg BW as “high”. This classification was implemented based on the generally accepted dosage recommendations: 0.25–0.5 mg/kg should be administered for analgesic therapy while maintaining spontaneous breathing and protective reflexes, while 1–2 mg/kg is recommended to induce general anaesthesia [13]. Absolute pain reduction was defined as the difference between the initial NRS and the NRS at handover in the hospital. The relative pain reduction was calculated by dividing the absolute pain reduction by the initial pain intensity.

### Statistical analysis

Patient demographics were presented in a table. Continuous variables were summarised by mean and standard

deviation, if normally distributed, or by median and interquartile range, if skewed. Categorical variables were summarised using counts and percentages for each level of variables. All statistical calculations were performed using “R” Version 4.4.1 [14].

In order to identify the factors influencing the occurrence of subjective side effects of ketamine, a multiple linear regression model plotting the TSES against the covariates gender, age, type of injury, use of midazolam and fentanyl, ketamine dosage and relative pain reduction was used. In addition, the correlation coefficient between ketamine dosage and TSES was calculated. The influence of ketamine dosage and midazolam use on the TSES was assessed using a likelihood ratio test comparing two linear regression models, with and without the corresponding covariate. In all the tests, a  $p$ -value  $< 0.05$  was considered statistically significant.

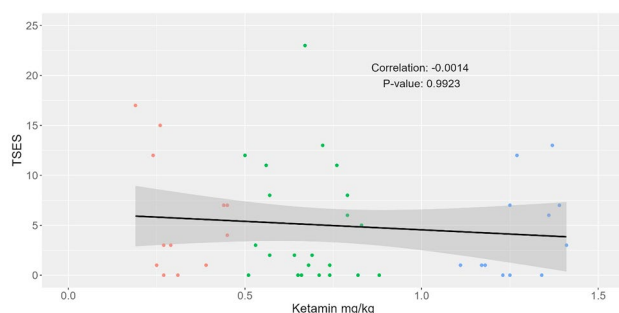
### Results

We identified 69 patients treated with ketamine prehospitally by the corresponding HEMS teams during the observed period. Patients under 18 years (9 cases) and those who did not respond to the request or did not return the questionnaire (11 cases) were excluded from the analysis. Ultimately, 49 patients (71%) were included in the analysis (51% male), with a mean age of 49 years (SD 14 years). The documented injuries affected the upper arm in 12 cases, the forearm in two cases, the femur/pelvis in 14 cases, the lower leg in 20 cases and the spine in one case. Furthermore, 12 patients received a low ketamine dosage based on body weight, 22 a moderate dosage and 15 a high dosage. The median dose was 50 mg ketamine [IQR 30–80 mg], i.e. 0.7 mg/kg BW [IQR 0.5–1.2 mg/kg BW]. In 21 cases (43%) midazolam [median 2 mg, IQR 2–3 mg] and in 42 cases (86%) fentanyl [median 100  $\mu$ g, IQR 100–200  $\mu$ g] was also administered. The initial pain score was a median of 8 points [IQR 8–9], the median absolute pain reduction was 5 points [IQR 4–7] and the mean relative pain reduction was 65% [IQR 57–78%]. The median TSES was 3 points out of a maximum of 60 points [IQR 1–8], and the reported side effects on the global six-point scale (0–5) exhibited a median of 1 point [IQR 0–2]. In this context, 69% of the individuals reported “no” or “mild” side effects and a further 25% “moderate” or “well tolerated” ones. Only 6% described the side effects as “barely tolerable” or “unbearable”. In 15 data sets, the NRS was not recorded at hospital handover, and thus pain reduction could not be calculated in these individuals. (Table 1, Supplement 2).

No statistically significant association was found between ketamine dosage and the reported total side effects (TSES) ( $p = 0.95$ , Fig. 1).

**Table 1** Baseline characteristics / main outcomes

Variable		N
<b>Total N = 49</b>		
<b>Baseline Characteristics</b>		
Age	49.1 (14.3)	49
Gender		49
Female	24 (49.0%)	
Male	25 (51.0%)	
Type of injury		49
Lower arm	2 (4.1%)	
Lower leg	20 (40.8%)	
Spine	1 (2.0%)	
Upper arm	12 (24.5%)	
Upper leg	14 (28.6%)	
Ketamin total [mg/kg BW]	0.7 [0.5;1.2]	49
Ketamin class		49
HIGH ( $\geq 1.0$ mg/kg BW)	15 (30.6%)	
LOW (0.5–0.99 mg/kg BW)	12 (24.5%)	
MID (< 0.5 mg/kg BW)	22 (44.9%)	
Midazolam		49
NO	28 (57.1%)	
YES	21 (42.9%)	
Fentanyl		49
NO	7 (14.3%)	
YES	42 (85.7%)	
<b>Main Outcomes</b>		
NRS start	8.0 [8.0;9.0]	39
NRS reduction	-5 [-7.0;-4.0]	34
NRS relative reduction	-0.65 [-0.57;-0.78]	34
Total Side Effect Score (TSES)	3.0 [1.0;8.0]	49

**Fig. 1** Dosage / TSES. Correlation between ketamine dosage and Total Side Effect Score (TSES). Dots: red = < 0.5 mg/kg BW, green = 0.5–0.99 mg/kg BW, blue =  $\geq 1$  mg/kg BW. The black line represents the linear regression line fitted to the data, while the surrounding grey area represents the confidence interval

A multiple regression analysis showed that gender, age, injury pattern and the additional administration of fentanyl were not associated with the occurrence of side effects. The adjusted midazolam administration suggests a lowering of the TSES by 4.8 points (SD 2.2 points;  $p = 0.04$ ). In addition, a lower TSES was found with a higher relative pain reduction ( $p = 0.03$ ) (Table 2). The likelihood ratio test comparing the models with and

**Table 2** Multivariate linear regression models on TSES

Characteristic	Beta	95% CI <sup>1</sup>	p-value
Gender			
Female	—	—	
Male	-2.3	-7.1, 2.5	0.3
Age	0.00	-0.17, 0.16	> 0.9
Type of injury			
Lower arm	—	—	
Lower leg	-0.40	-9.2, 8.4	> 0.9
Spine	0.48	-13, 14	> 0.9
Upper arm	-2.6	-12, 6.6	0.6
Upper leg	-2.9	-12, 5.8	0.5
Midazolam			
NO	—	—	
YES	-4.8	-9.5, -0.18	0.04
Fentanyl			
NO	—	—	
YES	-3.5	-10, 3.3	0.3
NRS relative reduction	-12	-22, -1.6	0.03
Ketamine tot [mg/kg BW]	-0.36	-6.5, 5.8	> 0.9

<sup>1</sup>CI = Confidence Interval**Table 3** Ketamine dosage categories

	LOW N = 12	MID N = 22	HIGH N = 15
Total Side Effect Score (TSES)	3.5 [1.0;8.25]	2.0 [0.0;8.0]	3.0 [1.0;8.5]
NRS start	8.0 [8.0;8.0]	8.5 [8.0;9.0]	8.0 [8.0;9.0]
NRS reduction	-5.6 (2.6)	-5.5 (1.5)	-5.1 (2.6)
NRS relative reduction	-0.72 (0.28)	-0.66 (0.10)	-0.60 (0.28)
Type of injury			
Lower arm	1 (8.3%)	1 (4.6%)	0 (0.0%)
Lower leg	5 (41.7%)	8 (36.4%)	7 (46.7%)
Spine	1 (8.3%)	0 (0.0%)	0 (0.0%)
Upper arm	2 (16.7%)	5 (22.7%)	5 (33.3%)
Upper leg	3 (25.0%)	8 (36.4%)	3 (20.0%)
Midazolam			
NO	12 (100%)	13 (59.1%)	3 (20.0%)
YES	0 (0.0%)	9 (40.9%)	12 (80.0%)
Fentanyl			
NO	0 (0.0%)	3 (13.6%)	4 (26.7%)
YES	12 (100%)	19 (86.4%)	11 (73.3%)

without the variable “midazolam” resulted in a p-value ( $\text{Pr(>Chi)}$ ) of 0.03, while the test comparing the models with and without the variable “relative pain reduction” resulted in a p-value ( $\text{Pr(>Chi)}$ ) of 0.01. This indicates that the inclusion of these two variables in the model significantly improves the fit of the model.

A comparison of the three classes of ketamine dosage showed comparable TSES, initial pain scores and injury patterns. Midazolam was administered significantly more frequently in the medium-dosage and high-dosage groups (Table 3). A higher ketamine dosage was not associated with a greater reduction in pain. The correlation coefficient of these two variables was only 0.15

with a  $p=0.4$  (Fig. 2). The TSES correlated well with the patients' global assessment of the side effects on a six-point scale (correlation coefficient 0.75, Fig. 3).

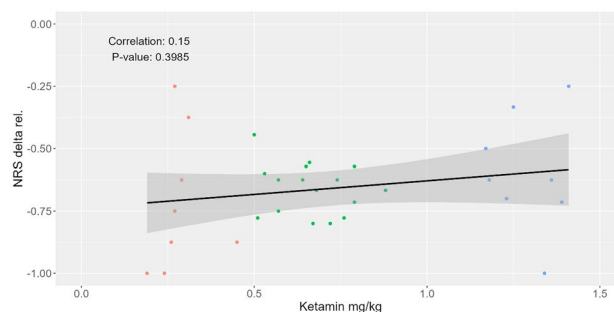
When the patients were asked whether they always “felt safe” during the treatment, 42 (86%) answered “strongly agree” or “agree” on a six-point Likert scale. Four patients (8%) could not remember. On the same scale, 36 patients (74%) rated their satisfaction with preclinical pain therapy as “strongly agree” or “agree”. Only two patients answered this question with “disagree” or “strongly disagree”. Three patients (6%) could not remember.

## Discussion

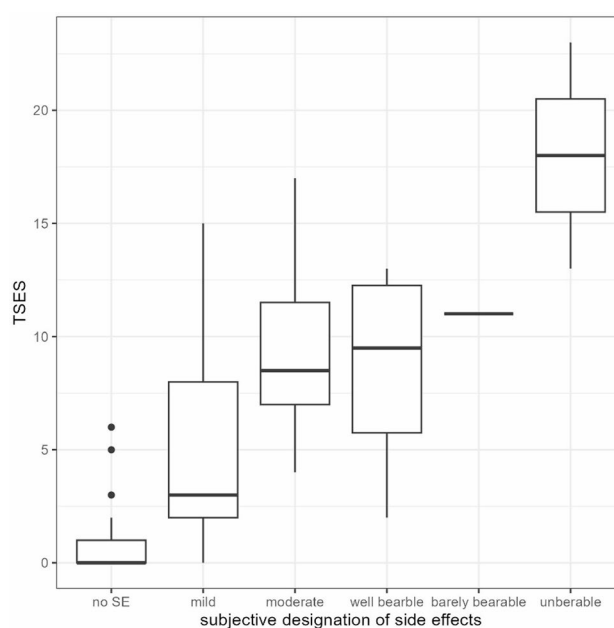
The focus of this study was on the assessment of subjective perceptions of ketamine-associated side effects when used during HEMS rescue on patients injured while doing winter sports activities. Unlike when ketamine is used in hospitals – e.g. during induction of anaesthesia or during procedural interventions in the emergency room – patients in this situation experience far more external stimuli from their immediate environment. The external meteorological conditions alone (cold, wind, snowfall, very bright and direct sunlight) make the situation significantly more stressful for the patient than when ketamine is used in hospital. Moreover, the initial medical assessment is often complicated by the situation (particularly the presence of sports equipment and winter clothing). As a result of the need to maintain warmth, it is often not possible to undress the patient, which can make it difficult to assess the consequences of the trauma and render careful splinting or immobilisation impossible. In any case, the patient must be transferred onto a rescue device (helicopter stretcher, rescue sled or evacuation using a rescue winch). Helicopter rescues add further specific stress factors such as extreme noise, downwash (and the resulting increased cold) and fear of flying. All these stimuli may exacerbate the psychogenic side effects of ketamine, potentially leading to intensified anxiety, hallucinations and nightmares [15].

The results of our study did not validate the concern that patients under ketamine analgesia in the context of a helicopter rescue following a winter sport accident suffer from increased psychogenic side effects. The vast majority of patients reported that the side effects were well tolerated and that they felt safe during prehospital care. Of course, it must be noted that the statistical power of this study is limited, particularly due to the limited sample size, and definitive conclusions cannot be drawn based solely on these results.

Nevertheless, these results are consistent with the findings of a study by Vanolli et al., in which emergency physicians who use ketamine in the prehospital setting were asked to assess its side effects (rather than assessing them from the patient's perspective, as in this study).



**Fig. 2** Dosage / relative pain reduction. Correlation between ketamine dosage and relative pain reduction. Dots: red = < 0.5 mg/kg BW, green = 0.5–0.99 mg/kg BW, blue = ≥ 1 mg/kg BW. The black line represents the linear regression line fitted to the data, while the surrounding grey area represents the confidence interval



**Fig. 3** Boxplot: subjective description of side effects. Boxplot of the subjective description of side effects by patients in words versus the Total Side Effects Scale (TSES)

The circumstances were identical, focusing on the use of ketamine in patients with trauma on the ski slope, who were treated and then transported to hospital by the HEMS crews for further treatment. All the participating physicians rated the use of ketamine as “fairly safe”, “safe” or “completely safe”. Although a large proportion of them stated that they had “already seen” psychiatric side effects, relevant neuropsychiatric side effects were described as rare. It should be noted that the recording of side effects in this study was not systematic, but based only on a survey of the experiences of the participating physicians [16].

In the patient group that received additional midazolam, side effects occurred less frequently. This effect was most pronounced in those patients who received a



medium dosage of ketamine. However, when administering midazolam, the known possible side effects of this benzodiazepine should be considered (in particular respiratory depression). A recent retrospective study describes exactly this dilemma, examining the use of ketamine sedation with and without midazolam in paediatric patients in the reduction of orthopaedic fractures. In contrast to our study, the authors found comparable side effects in both groups, but with more frequent hypoxia and prolonged sedation in the midazolam group [17]. Older studies in adult patients have shown that midazolam can sufficiently reduce psychiatric side effects during procedural sedation with ketamine and that even in relatively high doses of 0.07 mg/kg (5.6 mg  $\pm$  1.4 mg), midazolam led to respiratory depression in only 6% of cases, which was transient and easily controllable in all instances. By comparison, a median of 0.04 mg/kg BW [IQR 0.03–0.04 mg/kg BW] of midazolam was administered in our study [18].

It was not possible to demonstrate a linear relationship between the administered ketamine dose and the occurrence of side effects. Although patients in the various dosage categories did not differ in terms of their initial pain score, pain reduction and injury pattern, side effects occurred equally rarely in all groups. This result could be partly explained by the administration of midazolam: in the group with a low ketamine dose ( $<0.5$  mg/kg body weight), none of the patients received midazolam, while in the high-dose group ( $\geq 1$  mg/kg body weight), 80% received midazolam. We can only speculate as to why midazolam is administered more frequently at higher ketamine doses. One possibility is that the emergency physician is less concerned about the undesirable psychological side effects of low-dose ketamine, as is also the case in older literature [19]. This outlook could lead the treating emergency physicians to intentionally refrain from administering midazolam in this situation. On the other hand, the intention to administer midazolam with high doses of ketamine may be based on a conscious desire to achieve stronger sedation in the pain-stricken patient.

Nevertheless, it should be noted that concerns about the undesirable side effects of ketamine (emergence) or midazolam (particularly respiratory depression) can lead to underdosing of these drugs, and thus to insufficient analgesia and sedation in trauma patients. The inadequate analgesic treatment in half of the trauma patients described by Galinski et al. could possibly be attributed to these concerns [3]. However, this effect could not be observed in our study: three-quarters of the patients rated their satisfaction with the prehospital pain therapy as “agree” or “strongly agree”. Only two patients chose “disagree” or “strongly disagree”. Most patients described always feeling safe during the rescue and the side effects

were not perceived as seriously stressful. Thus, the fear of negative psychogenic side effects with possible traumatisation is probably unfounded in most cases. On the contrary, studies have shown that even a single dose of ketamine can have a positive modulating effect on the severity and duration of post-traumatic stress symptoms in accident victims [20].

A further result of our analysis was that it did not find any association between the ketamine dose and relative reduction in pain. In both the low-dose group and the high-dose group, the relative reduction in pain was the same. With comparable initial pain scores, the effect was tendentially even better with low doses than high doses. However, this finding was not statistically significant. Since the study was not designed to answer this question, this result can merely be regarded as an interesting incidental finding that requires further investigation for possible verification.

### Limitations

Naturally, our study has certain limitations. First, it is a purely observational study in which the individual treatment decision (the dosage of ketamine and the additional administration of midazolam) was always made by the treating emergency doctor. However, the group size was still uniform with regard to the selected dosage and the use of a benzodiazepine. Second, the pain values were recorded by the team that treated the patient and provided the indication for the use of ketamine. Suggestive influences may have distorted the assessment of the initial pain intensity and pain relief. However, the follow-up survey on the side effects and the patients' subjective feelings under the influence of ketamine was done by members of the study team who were not involved in patient treatment. This means that a distortion of the main aim of this study – i.e. to record the subjective side effects caused by ketamine – can largely be ruled out. Third, there was only a limited data set of 49 patients, which meant that some subgroups (e.g. injury patterns) were very small. Nevertheless, relevant subgroups (dosage classes and midazolam use) could be formed to evaluate the questions addressed in this study. A further differentiation into subgroups was deliberately avoided. For example, the relationship between dosage and relative pain reduction, as described in the discussion section, was not further explored. Fourth, the time to follow-up could not be strictly standardised. While some patients were interviewed directly during hospitalisation, most had to be consulted by telephone after discharge. This time span and the interim treatment may have caused them to forget the side effects. To capture this bias, patients were given the option to answer, “I cannot remember”. These response options were explicitly listed in the results section of the study under “satisfaction with

treatment” and “feeling safe.” Nevertheless, bias cannot be completely ruled out in this regard. From a statistical point of view, it is necessary to mention that the TSES is not a validated score, but was developed by the study team. Although the values for the initial pain score were skewed, we consciously decided to use a linear regression model anyway.

## Conclusion

The use of ketamine is a suitable option for pain therapy for injuries during alpine winter sports activities. The side effects reported by patients in this study were rare, not dose-dependent and described by most patients as subjectively well tolerable. The additional administration of midazolam could potentially further reduce these side effects.

## Abbreviations

BW	Body Weight
CI	Confidence Interval
CRF	Clinical Research Form
HEMS	Helicopter Emergency Medical Service
IQR	Interquartile Range
NRS	Numeric Rating Scale
SD	Standard Deviation
SE	Side Effect
TCCC	Tactical Combat Casualty Care
TSES	Total Side Effect Score

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12873-025-01252-6>.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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## Author contributions

R.S. and J.K. developed the original study protocol and wrote the draft manuscript. D.W. performed data collection and processing. R.S. and M.H. conducted the statistical analysis. All authors critically revised the manuscript and approved the final version.

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## Data availability

Rawdata is provided within the supplementary information files.

## Declarations

### Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Helsinki Declaration. Ethical approval was obtained from the responsible ethics committee of the canton of Bern, Switzerland (REF 2023–02174). Written informed consent to participate was obtained from all the participants

in the study. Participation was entirely voluntary, and participants had the right to withdraw from the study at any time.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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