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Rectal ketamine during paediatric burn wound dressing procedures: a randomised dose-finding study

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ABSTRACT

Background: Worldwide, ketamine is used during paediatric procedures, but no recommendations are available regarding a suitable dose for rectal administration during procedures involving high levels of pain and/or anxiety such as burn wound dressing change.
Methods: We evaluated three different single doses of rectally administered racemic ketamine mixed with a fixed dose of 0.5 mg/kg of midazolam. In total, 90 children – aged 6 months to 4 years – were randomised 1:1:1 to receive 4 mg/kg (K-4 group), 6 mg/kg (K-6 group) or 8 mg/kg (K-8 group) of racemic ketamine for a maximum of three consecutive procedures. Primary outcome measure was procedural pain evaluated by Face, Legs, Activity, Cry, Consolability (FLACC) behavioural scale. Secondary outcome included feasibility and recovery time. Patient safety was evaluated using surrogate outcomes.
Results: In total, 201 procedures in 90 children aged 19 ± 8 months were completed. The median maximum pain was FLACC 0 in all groups ($p = 0.141$). The feasibility was better for groups K-6 ($p = 0.049$) and K-8 ($p = 0.027$) compared with K-4, and the mean recovery time was the longest for group K-8 (36 ± 22 min) compared with groups K-4 (25 ± 15 min; $p = 0.003$) and K-6 (27 ± 20 min; $p = 0.025$). Median maximum sedation measured by the University of Michigan Sedation Scale (UMSS) was higher in group K-8 compared with group K-4 ($p < 0.0001$) and K-6 ($p = 0.023$). One child in group K-8 had a study drug-related serious adverse event — laryngospasm/airway obstruction. No rescue analgosedative medication was administered for group K-6.
Conclusions: A rectally administered mixture of racemic ketamine (6 mg/kg) and midazolam (0.5 mg/kg) during paediatric burn dressing procedures with a duration of approximately 30 min provides optimal conditions regarding pain relief, feasibility, recovery time and patient safety, with no need for rescue analgosedative medication.

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1. Introduction

Paediatric procedural sedation is a multidimensional field that involves the child, the guardian(s) and healthcare staff. A safe and successful sedation results in the optimal situation of a cooperative, relaxed and pain-free child who can quickly return to everyday life after the procedure. A frightening and/or painful experience with the procedure may have a long-term psychological impact on the child and the guardian(s), affecting future relationships with healthcare [1,2]. Placing an intravenous (i.v.) line in young children requires special skills, is often time-consuming and is sometimes painful. The possibility of inducing sedation by routes other than i.v. is thus valuable, especially in repeated procedures.

Ketamine provides sedation, analgesia and amnesia. It can be administered through various routes, including i.v., intramuscular, intranasal, oral or rectal. Ketamine has been well documented during the procedural analgosedation of children and is considered safe and effective [3–6]. To reduce the known adverse effects of ketamine (such as agitation and dysphoria), concurrent benzodiazepines have traditionally been administered [7,8] but its use has been disputed [9].

Studies show a broad variation of the routes of administration and different dosages of ketamine, either by itself or combined with other drugs [3,10,11]. To the best of our knowledge, there is a lack of consensus on the guidelines regarding the suitable dose of ketamine when combined with benzodiazepines for rectal administration during the analgosedation of young children for painful procedures such as burn wound dressing.

The current study objectives were to evaluate three different single doses of rectal ketamine combined with a fixed single dose of midazolam on their effects on pain relief, procedure feasibility, recovery time and patient safety for children between 6 months and 4 years during burn wound care.

2. Material and methods

2.1. Trial design

This prospective, double-blinded randomised controlled trial with parallel groups was conducted in accordance with the amended Declaration of Helsinki and followed the CONSORT guidelines. The study was approved by the Regional Ethics Review Board (#2013/326-31) and written informed consent was obtained from guardians for all subjects participating in the study. The study was registered prior to patient enrolment at clinicaltrialsregister.eu (#2013-002012-27, Principal investigator: Folke Sjöberg, Date of registration: 2013-10-30), and it was monitored independently by Forum Östergötland, Sweden.

2.2. Participants

Children (0.5–4 years and 7–38 kg on weight) scheduled for a minimum of three procedures for burn wound care were assessed for eligibility during their first visit to the clinic. The exclusion criteria were rectal/anal pathology, ongoing intensive care and contraindication for the study drugs.

2.3. Study setting

National Burn Centre, Department of Hand and Plastic Surgery, Linköping University Hospital, Sweden.

2.4. Interventions

On the day of the burn care procedure, the children were randomised consecutively into three groups (1:1:1) as follows: K-4 group — 4 mg/kg of racemic ketamine (Ketalar® 50 mg/ml, Pfizer AB, Sollentuna, Sweden) and 0.5 mg/kg of midazolam (Midazolam Accord, Accord Healthcare AB, Solna, Sweden), K-6 group — 6 mg/kg of racemic ketamine and 0.5 mg/kg of midazolam and K-8 group — 8 mg/kg of racemic ketamine and 0.5 mg/kg of midazolam. The randomised dose was repeated during all wound care procedures for each child. A designated nurse not involved in sedation or wound care mixed the ketamine and midazolam doses with sodium chloride (Natriumklorid Baxter, Baxter Medical AB, Kista, Sweden) to obtain a total volume of 5 ml (<20 kg) or 10 ml (≥20 kg). The syringe was prepared with a rectal nozzle.

All children followed the European anaesthetic guidelines for preoperative fasting [12]. The procedure started with the rectal administration of the mixture. Analgosedation was carried out by an experienced nurse anaesthetist, and an anaesthesiologist was immediately available; wound care was performed by a wound care nurse. When nystagmus occurred (approximately 15 min after the rectal administration), wound care was initiated. The procedure was considered complete when wound care was completed. Parents were present until start of procedure and post-procedural during recovery.

If sedation or pain relief on clinical grounds was insufficient, an i.v. catheter was inserted, supplementary oxygen was administered, and analgosedation was deepened stepwise by using a mixture of nitrous oxide (N_2O)/oxygen (O_2) (50/50%) (Medicinsk Lustgas Air Liquide, Air Liquide Gas AB, Malmö, Sweden), sevoflurane (increasing up to 3% end-tidal concentration) (Sevorane®, AbbVie AB, Solna, Sweden) and propofol (Recofol 10 mg/ml, Algol Pharma AB, Kista, Sweden).

2.4.1. Vital sign monitoring

The nurse anaesthetist monitored oxygen saturation (SpO_2), heart rate (HR) and respiratory rate (RR) during and after the procedure. The values were recorded every 5 min until the child was assessed as being recovered. Hypoxemia was defined as $SpO_2 < 90\%$; bradycardia as HR < 80 (6–12 months), <70 (1–3 years) beats/min; tachycardia as >20% [13] increase from the baseline HR and 5 min after rectal administration of ketamine; and respiratory depression as RR < 25 (6–12 months), <20 (1–3 years) breaths/min [14]. Supplementary oxygen was not routinely administered. During episodes of a semiobstructed or obstructed airway, appropriate interventions were undertaken and recorded.

2.4.2. Pain assessment

The nurse anaesthetist assessed pain using the Face, Legs, Activity, Cry, Consolability (FLACC) behavioural scale [15,16] every 5 min per- and postprocedurally. The instrument has five categories, with each category scored on a scale of 0–2,

resulting in a total score of 0-10; the higher the score, the greater the pain. The scale had been used frequently and routinely by the two experienced nurse anaesthetists involved in the study. Also, a pre-study training session was held for these nurse anaesthetists to ensure consensus and equivalent assessments of pain.

2.4.3. *Sedation level assessment*

The nurse anaesthetist assessed the sedation level every 5 min per- and postprocedurally according to the University of Michigan Sedation Scale (UMSS) [17]. The scores were as follows: 'awake and alert' (0); 'minimally sedated — tired/sleepy, appropriate response to verbal conversation and/or sound' (1); 'moderately sedated — somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command' (2); 'deeply sedated — deep sleep, arousable only with significant physical stimulation' (3); and 'unarousable' (4).

2.4.4. *Recovery assessment*

The recovery time was assessed by nurse anaesthetist and defined as the time between completion of the procedure until UMSS=0 and cardiovascular and respiratory stability.

2.4.5. *Procedure feasibility assessment*

After the completion of the procedure, the nurse anaesthetist and the wound care nurse assessed procedure feasibility using a study specific scoring. The scores were as follows: 'can perform the procedure without any limitation in access' (1); 'can perform the procedure with partly affected access' (2); 'can perform the procedure with markedly affected access and great effort' (3); and 'failure to complete the procedure satisfactorily' (4).

2.4.6. *Side effects*

The presence of the known side effects found in the summary of the product characteristics were not considered adverse events but was reported in accordance with the consensus-based recommendations for procedural sedation and analgesia in children [18].

2.5. *Outcomes*

The primary outcome was pain during the procedure, as measured by the FLACC behavioural scale [15,16]. The secondary outcomes were procedure feasibility and recovery time. Furthermore, patient safety was assessed using the surrogate outcomes, comprising sedation level measured by UMSS [17], vital signs, side effects and adverse events.

2.6. *Sample size*

For sample size calculation we used G*Power version 3.1.9.3 (Heinrich-Heine-Universität Düsseldorf, Germany). For the primary outcome we estimated the sample size, power of 80% and $p < 0.05$, to 30 children for each group (90 children in total). Sample size calculation was based on FLACC scores from clinical data for group K-6 and K-8, and an estimation for group K-4. Mean FLACC scores was set to 1 for group K-4, 0.5 for group K-6 and 0.15 for group K-8, all groups with a standard deviation of 1. Results for total sample size was rounded up. The total sample size was considered also to be sufficient to address the secondary outcomes.

2.7. *Randomisation*

On the day of the burn care procedure, the children were randomised consecutively into three groups (1:1:1) by a designated nurse not involved in sedation or wound care using sealed opaque envelopes (made by third-party with a block size of 6).

2.8. *Blinding*

The study was blinded to study participants including their parents, care providers and those assessing outcome. A designated nurse not involved in sedation or wound care prepared the study drugs. The opened envelopes were kept in a safe for exclusive access by the nurses who were preparing the mixture. The code was broken after finishing data collection.

2.9. *Prior to the current study — preliminary dose-finding experiments*

A decade prior to the present study, rectal ketamine was already being used parallel with the intramuscular route because it was found to work properly. It was also being administered in conjunction with the acetaminophen dose that nurse anaesthetists administered rectally as routine prior to the change-of-dressing procedure. Initially, doses in line with the intramuscular recommendation were used. However, these doses were gradually being reduced to shorten the duration of the postprocedural sedation, which was found to be unnecessarily long. In clinical praxis for the routine dressing procedure, we then reached a dose level of 6-8 mg/kg, which we considered relevant for scientific evaluation. For the final and current study, we also chose a level that was possibly less than optimal to discover if the final outcome would be properly evaluated.

2.10. *Statistical methods*

We used GraphPad Prism version 7 (GraphPad Software, La Jolla, USA) and IBM© SPSS© Statistics version 25 (International Business Machines Corp., New York, USA) to aid us with statistical analysis. Linear mixed model analysis was used for repeated measures. The significance of differences between continuous variables was assessed with analysis of variance (ANOVA) and *posthoc* Holm–Sidak. Kruskal–Wallis test followed by *posthoc* test Dunn's test was used to assess the significance of differences among data that were not normally distributed. A chi-square test or Fischer's exact test was used for categorical data. Data are presented as the mean (±standard deviation), median (interquartile range) or number of patients/procedures (%).

3. Results

Of the 224 children screened for inclusion, 90 were randomised between December 2013 and September 2017 following a 1:1:1 ratio into the three groups (Fig. 1) without any dropouts. The demographics showed differences in age, height and sex

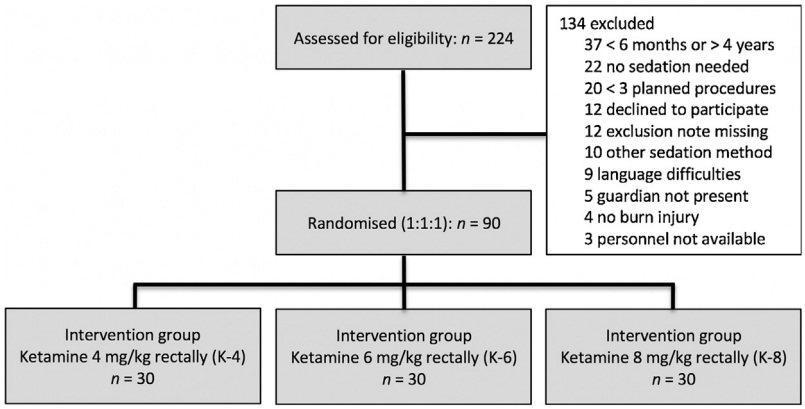

Fig. 1 – Flowchart figures denote number of children. *Abbreviations*: K-4=ketamine 4mg/kg; K-6=ketamine 6mg/kg; K-8=ketamine 8mg/kg.

distribution between the children in groups K-4 and K-6, but all three groups were equal in the remaining demographics and their procedural characteristics. Forty children completed three consecutive procedures during the study period, but those who were completely healed or needed no further procedural analgosedation underwent one or two consecutive study procedures (Table 1). No children complained about using the rectal route for administration.

No significant differences in maximum pain were found among the three groups (Table 2). The procedure feasibility was more affected for group K-4 compared with K-6 ($p=0.049$) and K-8 ($p=0.027$), respectively (Table 2).

The recovery time was longest for group K-8 compared with groups K-4 ($p=0.003$) and K-6 ($p=0.025$). After the first procedure, the greatest difference was observed between K-8 (45 ± 27 min) and K-4 (27 ± 15 min) ($p=0.015$). The maximum level of sedation was deeper for group K-8 (all procedures) compared with K-4 ($p<0.0001$) and K-6 ($p=0.023$).

Group K-8 had significantly more hypersalivation ($p=0.038$) compared with groups K-4 and K-6. No differences in other vital signs were noted among the three groups (Fig. 2). One event with laryngospasm/airway obstruction without desaturation occurred in group K-8.

The rescue medication for suboptimal analgesia and/or sedation was administered in five of the 201 procedures (2%) and only in groups K-4 and K-8; no statistical differences among the three groups were found. Dressing time was significantly longer for the children receiving rescue medication in group K-8 (46 ± 7 min) compared with those who did not need it in the same group (30 ± 1 min) ($p<0.0001$). The recovery time was not affected for the children receiving rescue medication compared with those who had no need for it (data not shown). Furthermore, no differences could be found, regardless of group, between the children with or without the need for rescue medication and episodes of tachycardia.

4. Discussion

The results show that rectal administration of a single dose of ketamine and midazolam during painful procedures, such as paediatric burn wound care, resulted in effective sedation and analgesia with negligible need for additional drugs. Recovery time was dose related and prolonged by using a higher dose of ketamine. Compared with the lower and higher doses, 6mg/kg of ketamine showed significantly less affected vital signs and side effects. In contrast to earlier studies showing a great variation in bioavailability [19], we found that rectal administration gave clinically very stable conditions. The findings from the current study add new and valuable knowledge to the field of burn wound dressing sedation and support an increased use of the rectal route of administration.

A strength is the study's design, with three parallel groups that were strictly randomised and double blinded. It was chosen to compare different doses of ketamine. Because of the possibility that multiple variables, such as total burned surface area, total healed surface area and former hospital experience, might influence the outcome measurements, we decided to repeat the same dose during each procedure for each child instead of randomising the dose. Another strength of the present study is the evaluation and inclusion of a less-than-optimal dose level to ascertain the inclusion of the optimal level in the evaluated dose range. A weakness with repeated fixed doses is the difficulty in detecting dose-dependent intraindividual variability. Other limitations are the lack of evaluating inter-rater reliability for FLACC assessment between the involved nurse anaesthetists and the fact that clinical experience instead of a fixed FLACC and UMSS value, respectively, guided the decision to deepen analogsedation. Even though this is a single-centre study, we argue that the dose finding results are generalisable.

The guidelines and recommendations regarding the optimal dose of ketamine for analgosedation can easily be found, but the rectal route is often not mentioned. We have shown that a dose of 6mg/kg for burn wound dressing with a length of approximately 30min could be considered the optimal dose. A higher dose did not positively affect patient pain relief or procedural feasibility but rather increased the depth of sedation and presence of known dose-related side effects. In line with earlier results [20], 4mg/kg of ketamine gave adequate analgesia. It is possible that in other types of procedural analgosedation this is a sufficient dose, although procedure feasibility in the specific setting under study was affected.

Table 1 – Patient and procedure characteristics.

	K-4 (n=30)	K-6 (n=30)	K-8 (n=30)	p-Value
Age (months)	22±8	17±6	19±8	0.019
Weight (kg)	12.4±1.9	11.4±1.7	12.3±2.5	0.102
Length (cm)	86±8	79±6	83±7	0.034
Sex (boys/girls)	20/10	11/19	19/11	0.037
ASA classification				
I	29 (97)	28 (93)	28 (93)	
II	1 (3)	2 (7)	2 (7)	0.809
III	0 (0)	0 (0)	0 (0)	
Type of trauma				
Scalding	17 (57)	19 (63)	23 (77)	
Flame burns	0 (0)	3 (10)	0 (0)	0.057
Contact burns	13 (43)	8 (27)	7 (23)	
Total body surface area burned (%)	1.4 (0.5–6.1)	2.4 (0.7–3.9)	2.6 (1–6.3)	0.515
1st procedure in study				
days since burn injury	4 (2–7)	5 (4–7)	4 (4–8)	0.302
in order of all procedures	2 (1–2)	2 (2–3)	2 (2–3)	0.265
Procedures completed (n)				
One study procedure	7 (23)	6 (20)	6 (20)	0.421
Two consecutive study procedures	7 (23)	14 (47)	10 (33)	
Three consecutive study procedures	16 (53)	10 (33)	14 (47)	

Data are presented as mean±SD, median (IQR) or number of patients (%).
Abbreviations: ASA=American Society of Anesthesiologists; K-4=ketamine 4 mg/kg; K-6=ketamine 6 mg/kg; K-8=ketamine 8 mg/kg.

Various routes for ketamine administration can be used. No significant differences in the effectiveness of sedation and route of administration have been observed, but oral and rectal administration have shown shortened time for recovery compared with i.v. administration [10]. Drugs administered intravenously or rectally have similar half-life elimination, but rectal administration has a lower bioavailability (51%) [21]. Rectal administration has the advantage of partly bypassing the first metabolism when compared with the oral or the nasal route [22] or the oral route. The rectal uptake of a liquid solution may be interrupted because of absorption by defaecation, and application using syringe injection also needs to be correct to minimise the risk of rectal loss. Our study shows that wound dressing procedures could start after nystagmus, approximately 15 min after rectal administration. With a plasma maximal concentration for ketamine being reached within 42 min [23], children were given appropriate analgesia and sedation during the whole 30-min procedure. Rectal administration is a feasible route of medication for infants and most toddlers, but with increasing age, there may be a lack of patient acceptability [24].

I.v. and intramuscular administration has high bioavailability and fast onset. The use of topical anaesthetics can be helpful to reduce pain and distress during needle procedures, but repeated procedures causes repeated venous punctures that can have negative psychological effects on children, making it more difficult for them to undergo further procedures. Intranasal administration of ketamine is an alternative to rectal administration. Except the irritation and discomfort that may occur during intranasal administration bioavailability is low, 35.8% [25]. This is explained by the difficulty in having full nasal absorption of the administrated dose because of accidental swallowing by children [23]. The standard deviation for the distribution of the plasma concentrations and absorption time are high [26], with plasma maximum concentration for intranasal ketamine occurring within 20 min [23]. Because of the risk of swallowing and the variation of absorption, the intranasal route is not useful for larger volumes of drugs. Another route for the administration of ketamine is orally. Because concentrated ketamine has a bitter and astringent taste [27], it should be mixed with a tastier fluid to be accepted [28]. From our experience, oral intake in this age group is sometimes difficult and presents with severe objections. The bioavailability for oral administration is 0.45 (CI 0.33–0.58), with a high interindividual $t^1/_2$ and the need to be administrated 45–60 min before the start of the procedure [29]. Regardless of which route of administration is used, there are benefits and difficulties with application, acceptability and pharmacokinetics. Depending on the situation, the state of the child and age, rectal administration could be an alternative to other routes of administration.

The FLACC scale was used to measure pain which was the primary outcome. This behavioural observation pain scale has frequently been used for different age groups and settings, although it was originally developed and validated for postoperative pain assessment in children aged 2 months to 7 years [30]. However, a recent study in the field has shown that FLACC is reliable and sensitive also for procedural pain assessment [31].

Ketamine with the addition of benzodiazepine has been shown to have the least adverse events when compared with the most commonly used drugs and combinations, including anticholinergics during procedural sedation [3]. The few events of hypersalivation in our study occurred in children who received the highest dose of ketamine, where one event resulted in laryngospasm and airway obstruction. To avoid airway events, anticholinergic drugs have been used as a prophylactic, with the intention to reduce ketamine-induced hypersalivation [9], but it remains unclear if this reduces

Table 2 – Per- and postprocedural data.

	K-4 (n=69)	K-6 (n=64)	K-8 (n=68)	p-Value
Maximum FLACC (0-10)				
All procedures	0 (0-2)	0 (0-1)	0 (0-1)	0.079
1st procedure	0 (0-2)	0 (0-1)	0 (0-2)	0.512
2nd procedure	0 (0-2)	0 (0-1)	0 (0-0)	0.084
3rd procedure	0 (0-2)	0 (0-0)	0 (0-0)	0.355
Procedures with FLACC >3 (n)	6	1	6	0.255
Maximum UMSS (0-4)				
All procedures	2 (1-2)†††	2 (1-2)	2 (2-2)$^{\#}$	<0.0001
1st procedure	2 (1-2)†	2 (1-2)	2 (2-3)	0.030
2nd procedure	1 (1-2)†	2 (1-2)	2 (2-2)	0.011
3rd procedure	1 (1-2)	2 (1-2)	2 (2-2)	0.081
Procedures with affected vital signs (n)				
Bradycardia	2	0	0	–
Desaturation	0	0	0	–
Respiratory depression	3	3	5	0.693
Tachycardia	22*	10	22$^{\#}$	0.066
Procedures with side effects (n)				
Hypersalivation	0	0	3$^{\#,\dagger}$	–
Postprocedural vomiting	0	1	1	1.000
Procedures with need of rescue medication (n)				
N_2O/O_2	1	0	1	–
N_2O/O_2 and sevoflurane	0	0	2	–
Propofol	1	0	0	–
Dressing time (min)	31±7	30±6	31±8	0.886
1st procedure	33±7	31±5	33±9	0.491
2nd procedure	31±7	31±8	30±6	0.730
3rd procedure	29±6	28±5	29±5	0.898
Procedure feasibility (1-4)	1 (1-2)*,†	1 (1-1)	1 (1-1)	0.010
Recovery time				
All procedures (min)	25±15††	27±20	36±22$^{\#}$	0.010
1st procedure	27±15†	35±24	45±27	0.018
2nd procedure	23±13	22±14	31±15	0.059
3rd procedure	22±17	23±9	26±9	0.764

Data are presented as mean±SD or median (IQR).

Abbreviations: FLACC=Face, Legs, Activity, Cry, Consolability behavioural pain scale; K-4=ketamine 4mg/kg; K-6=ketamine 6mg/kg; K-8=ketamine 8mg/kg; N_2O=nitrous oxide (50%); O_2=oxygen (50%); UMSS=University of Michigan Sedation Scale.

K-4 versus K-6: $^{*}p<0.05$; K-6 versus K-8: $^{\#}p<0.05$; K-4 versus K-8: $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$, $^{\dagger\dagger\dagger}p<0.0001$.

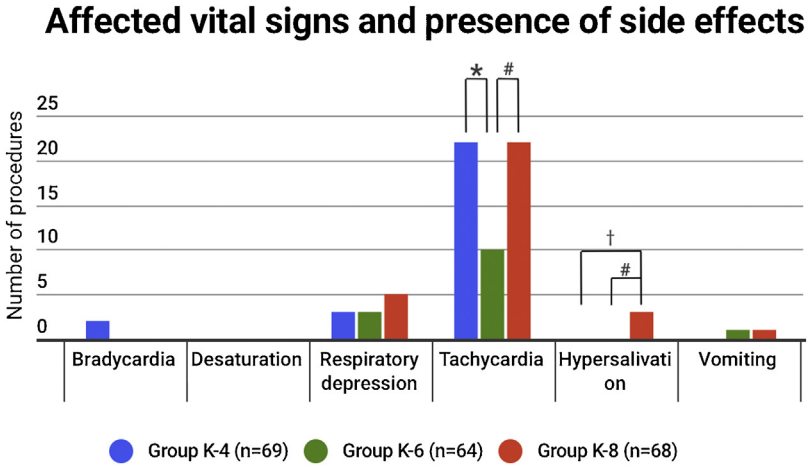

Fig. 2 – Affected vital signs and presence of side effects. K-4 versus K-6: $^{*}p<0.05$; K-6 versus K-8: $^{\#}p<0.05$; K-4 versus K-8: $^{\dagger}p<0.05$. *Abbreviations*: K-4=ketamine 4mg/kg; K-6=ketamine 6mg/kg; K-8=ketamine 8mg/kg.

airway and respiratory adverse events [32,33]. The low incidence of significant side effects also strengthens the argument that ketamine can be used for sedation at different locations within hospitals and with limited bedside support of anaesthetic personnel [9].

5. Conclusions

We find this dose-finding study important because it provides clear information on an alternative way to perform analgo-sedation on children (0.5–4 years) for painful burn wound dressing procedures with a duration of 30 min, without the need of an i.v. line. The pain level and the need for patient manipulation during the procedure make the findings generalisable to other demanding paediatric procedures.

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Conflict of interest

None.

Clinical trial number

2013-002012-27, https://www.clinicaltrialsregister.eu/.

Author's contribution

Benjamin Grossmann: This author helped creating the study design, statistical analysis, and writing of the manuscript.

Andreas Nilsson: This author helped creating the study design and writing of the manuscript.

Lena Nilsson: This author helped creating the study design and writing of the manuscript.

Folke Sjöberg: This author helped creating the study design and writing of the manuscript.

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