

## Ketamine dosing for sedation during repeated radiotherapy sessions in children

Oya YALÇIN ÇOK\* , Hatice EVREN EKER , Aniş ARIBOĞAN

Department of Anesthesiology and Reanimation, School of Medicine, Adana Research and Education Center, Başkent University, Adana, Turkey

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**Background/aim:** We report the analysis of ketamine doses needed and the recovery times in pediatric oncology patients undergoing repeated radiotherapy sessions.

**Materials and methods:** In a single-blind prospective study design, thirty-three pediatric patients undergoing radiotherapy due to oncologic disorders received 2 mg/kg ketamine and 10 µg/kg atropine intravenously and the rescue drug to be administered was ketamine at 0.5 mg/kg when the sedation level was inadequate. Total ketamine consumption, additional doses, and recovery time were recorded.

**Results:** Data of 635 consecutive radiotherapy sessions were evaluated. There was no significant alteration in total ketamine consumption required to complete the radiotherapy periods during consecutive procedures ( $P > 0.05$ ). However, the recovery times started to decrease by the fourth session ( $P = 0.02$ ) and continued to decrease onwards during the whole study period ( $P = 0.001$ ). The mean of the first recovery time was  $13.68 \pm 3.99$  min, whereas the mean of the last recovery time was  $7.66 \pm 6.35$  min.

**Conclusion:** A requirement for an incremental increase in ketamine dose after subsequent administrations was not detected, despite a significant decrease in recovery times being anticipated when ketamine is used repeatedly for sedative purposes in consecutive radiotherapy sessions.

**Key words:** Ketamine, sedation, radiotherapy, pediatrics, tolerance

### 1. Introduction

Ketamine has been a subject of debate in recent years due to its illicit use in some parts of the world. However, in regions with limited resources, it is still a very valuable option. Ketamine was first publicized as a “battle field anesthetic” and it still preserves its unique place in pediatric anesthesia with features such as maintaining a state of dissociated consciousness along with spontaneous breathing, intact laryngeal reflexes, and hemodynamic stability (1). For anesthesiologists who are in the “battle field” of anesthetic management every day, ketamine provides a safety zone for sedated but spontaneously ventilated children, especially in remote conditions such as radiotherapy units where sedation is an essential practice to keep children calm and motionless (2). However, there has been disagreement about the ketamine doses needed for a continuous and steady level of sedation during repeated radiotherapy sessions in children. A tendency to tolerance occurrence to ketamine has been claimed when it is used in a repetitive manner and the opposite has also been reported (3–5). The current literature also suggests

that N-methyl-D-aspartate (NMDA) receptor antagonists themselves have tolerance-preventive effects and may inhibit tolerance during long-term sedative and opioid administration (6,7).

Any alteration in drug requirement to maintain therapeutic or targeted effects has always been an issue of interest for clinicians when repeat doses of any agent are used. In this paper, we report the analysis of ketamine doses needed and the recovery times in pediatric oncology patients undergoing repeated radiotherapy sessions. This paper may also add some more recent information for the use of ketamine where circumstances limit the anesthetic options.

### 2. Materials and methods

After approval from the Başkent University School of Medicine’s Ethics and Research Committee (KA09/247) and informed consent of the patients’ parents, 33 pediatric patients undergoing radiotherapy due to oncologic disorders were enrolled in this single-blind prospective study. Patients younger than 1 year and older than 14 years;

\* Correspondence: oyacok01@yahoo.com

patients with cardiac, renal, or liver function abnormalities; those who were already under sedative drug treatment or allergic to the drugs to be used; and patients for whom the study drugs were contraindicated were excluded from the study.

Pediatric patients who were fasted for 6 h were admitted to the preparation room, where they received 2 mg/kg ketamine and 10 µg/kg atropine intravenously. All patients were monitored by electrocardiography, noninvasive blood pressure, and pulse oximeter and a closed-circuit camera system in the room. Sedation level was assessed by the Children’s Hospital of Wisconsin Sedation Scale and scores of 3 and 4 were accepted as adequate for the procedure to start radiotherapy (8). If the score exceeded 4, the rescue drug to be administered was ketamine at 0.5 mg/kg. After the procedure, the patients were observed until they achieved a score of 20 according to the Vancouver Sedative Recovery Scale and this stage was defined as “full recovery” to record the duration of “recovery time”.

Patients’ demographic data (age, sex, weight), cancer type, ASA physical status, and duration and total number of radiotherapy sessions were noted. We included details about patients’ pain according to the nurses’ notes (as none, mild, moderate, or severe) in the files, since the age group of the patients was not even suitable for Wong-

Baker Faces Pain Scale. Total ketamine consumption to maintain the targeted sedation level during each session, additional dose administration, and recovery time were recorded. Adverse events such as apnea, laryngospasm, bronchospasm, desaturation (SpO<sub>2</sub> < 93%), respiratory depression, bradycardia, sedation levels deeper or more superficial than intended, excessive salivation, allergy, nausea and vomiting, and need for emergency medication were also noted after each session. The study drugs were prepared, labeled, and administered by an anesthetist according to the study protocol and data were recorded by an anesthetist blind to the amount of the study drug used.

**2.1. Statistical analysis**

Data analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). Data of the continuous variables were presented as mean with standard deviation (SD) and minimum and maximum values. Categorical data were described in numbers or percentages as appropriate. The Friedman ANOVA test was used for analysis of repeated measures such as total ketamine consumption and recovery times. P < 0.05 was considered as statistically significant.

**3. Results**

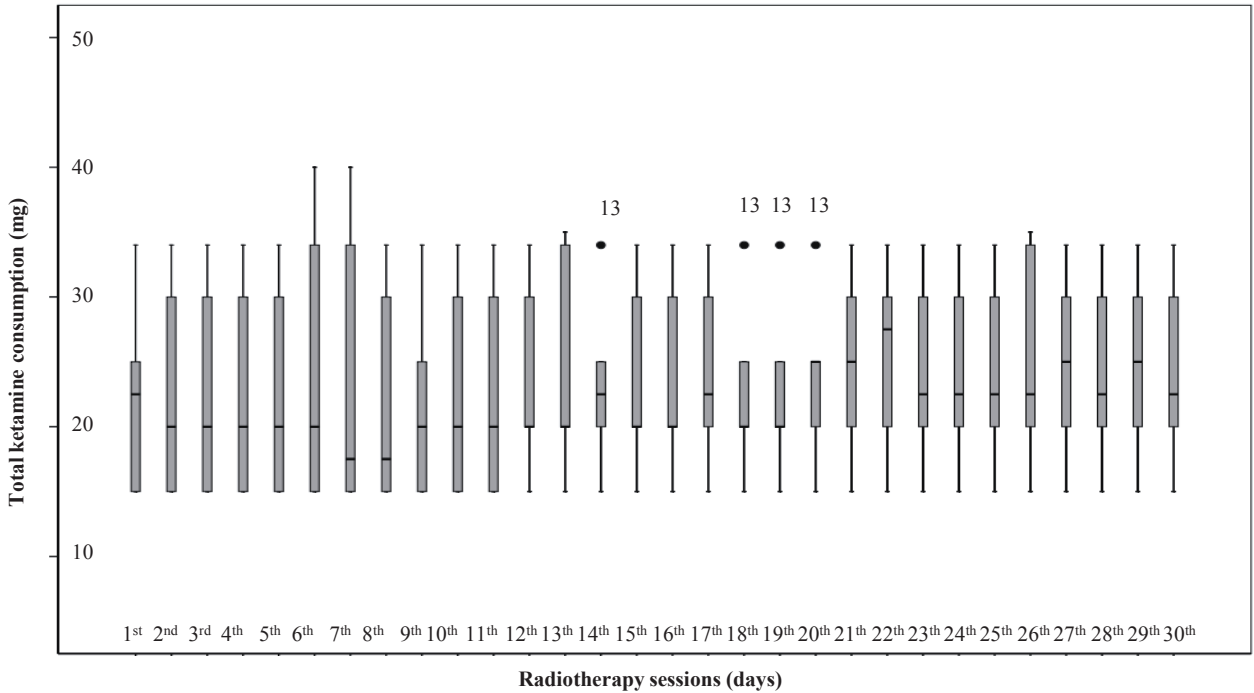
Data of 33 patients during 635 consecutive radiotherapy sessions were evaluated. For one patient, radiotherapy was stopped at the 5th session due to the critical condition of the

**Table.** Demographic data of the patients and duration and total number of radiotherapy sessions (mean ± SD or n).

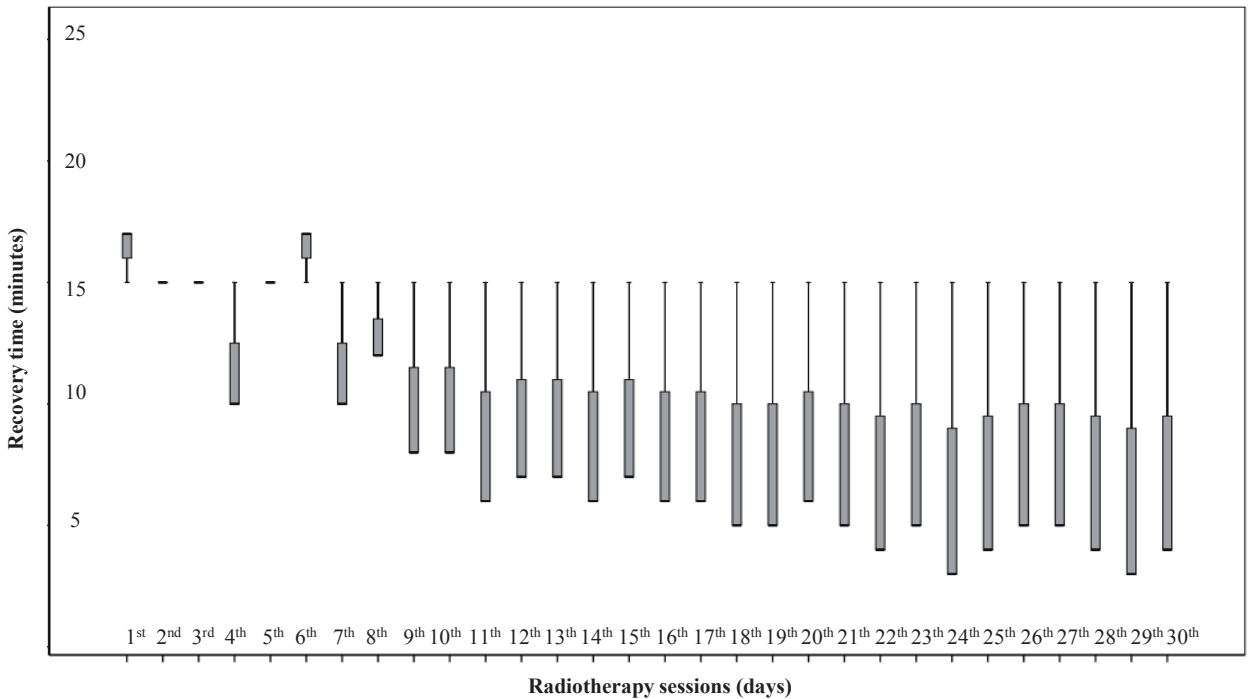
	(n = 32)
Age (years)	2.70 ± 0.84
Weight (kg)	13.02 ± 2.51
Sex (M/F)	19/13
ASA physical status (II/III)	31/1
Duration of radiotherapy sessions (min)	3.79 ± 1.77
Total number of sessions	19.68 ± 8.37
Cancer types of the patients (n)	
Primary spinal glioma	1
Neuroblastoma	1
Atypical teratoid tumor	12
Leukemia	4
Rhabdomyosarcoma	1
Sacral bone tumor	2
Medulloblastoma	8
Neuroectodermal tumor	3
Pain levels according to nurse notes in the files (n)	
None	0
Mild	4
Moderate	16
Severe	12

patient. This case was excluded from the data analysis due to paucity of the number of repeat sessions. The patients who required benzodiazepines due to hallucinations and restlessness were also excluded from the study so as not

to intervene with the sole assessment of ketamine use. Demographic data of the patients included and duration, total number of radiotherapy sessions, cancer type, and pain assessment are presented in the Table.



**Figure 1.** Total ketamine consumption required to complete the consecutive radiotherapy sessions.



**Figure 2.** The recovery times after each consecutive radiotherapy session.

Mean ketamine consumption at the first session and the last session was  $25.8 \pm 14.5$  mg and  $25.4 \pm 10.3$  mg, respectively. There was no significant alteration in total ketamine consumption required to complete the radiotherapy periods during consecutive procedures ( $P > 0.05$ ) (Figure 1). However, the recovery times started to decrease by the fourth session ( $P = 0.02$ ) and continued to decrease onwards during the whole study period ( $P = 0.001$ ) (Figure 2). The mean of the first recovery time was  $13.68 \pm 3.99$  min, whereas the mean of the last recovery time was  $7.66 \pm 6.35$  min. The patients required additional ketamine administration 54 times in 47 of 635 sessions (7.4%).

One patient in one session experienced transient desaturation ( $SpO_2$ : 90%), which was resolved with a jaw-thrust maneuver in less than 2 min (the approximate duration we approached the patient). He also had coughing and needed repositioning and aspiration of secretions. Another patient developed a mild allergic reaction with cutaneous manifestations to atropine.

#### 4. Discussion

In this study, we evaluated ketamine doses needed and the recovery times during repeated radiotherapy sessions in pediatric oncology patients. There was no significant alteration in total ketamine consumption required to complete the radiotherapy periods during consecutive procedures; however, the recovery times started to decrease by the fourth session and continued to decrease onwards during the whole study period.

Efficient sedation with an absolute motionless state and intact airway is essential during radiotherapy sessions where the treated child and the anesthesia team have been isolated from each other. These requirements lead anesthetists to convey a sedation plan providing a similar sedated state and a recovery profile even after many numbers of repeated procedures such as radiotherapy sessions (9). However, repeat sessions may cause tolerance to the sedative agent used (10,11). Tolerance is a challenging situation that physicians often encounter during opioid use in clinical practice. The severity and duration of the stimulus as well as pharmacokinetic and pharmacodynamic alterations have been suspected for development of tolerance to the therapeutic action of drugs.

Ketamine has been a preferable anesthetic/analgesic drug with its predictable sedation and recovery features for diagnostic and therapeutic procedures in children outside the operating room, such as in radiotherapy units (12). Due to many receptor interactions, ketamine's unique properties are not limited to sedation and analgesia; it is also efficient in maintaining the airway and stable hemodynamics along with antihyperalgesic and antiinflammatory effects (1). Ketamine anesthesia has

been reported to be related to increased radiosensitivity of tumors (13). This may also prove that ketamine would be more beneficial during radiotherapy. However, ketamine may also raise a concern for increased dose requirements or insufficient sedation levels and/or durations after repeat administrations, although ketamine itself has been suggested to play a tolerance-preventive role for opioids during sedation in pediatric intensive care units (1,11).

Since there is no real pain experience or invasive stimulus during radiotherapy sessions, the main aim of ketamine-induced sedation is to preserve a steady "dissociated" state in children. In this study, sufficient sedation level and duration were achieved without a need for an increase in initial ketamine dose or additional drug administrations. The expected recovery time after 2 mg/kg ketamine was more than 15 min (12), but in our study the recovery time decreased by approximately 50% after repeat sessions at a rate higher than in previous reports (14). This may be interpreted as a decrease in the dissociation period of the thalamus and the limbic system, which basically enables the sedative effect of ketamine via NMDA receptors. Upregulated or desensitized NMDA receptors may hypothetically be responsible for the limited duration of desynchronization of the thalamus and limbic system after recurrent exposure to the drug. If there has been a strong stimulus, such as pain in burn patients who also undergo repeat ketamine-induced sedation sessions for dressing changes, tolerance occurrence may become more explicit by stimulation of miscellaneous receptors, which may cause a noticeable tolerance-like response in subjects (5,14). However, lack of an ongoing strong procedural stimulation during radiotherapy sessions lessens the anticipation for the upregulation of receptors. Thus, we may speculate that this tolerance-like effect depends more on a pharmacokinetic mechanism than a pharmacodynamic one. Besides, after repeated administrations, hepatic metabolism-based alterations in the pharmacokinetics of ketamine were shown to decrease circulating and brain levels of the drug and its active metabolites and increase inactive oxidation metabolites, thus resulting in a more rapid recovery (15).

The first limitation of our study may be the ketamine dose regimen, which may be considered as a flaw in the methodology. Although this dose was not very small, our initial intention was to cover all procedures, even with planning sessions, which require more time. However, eventless procedural periods and acceptable recovery durations allowed us to continue with this dosing. Another reason to choose ketamine at a higher dose was that most of the patients already had painful tumors, which required some pain relief for positioning. Another limitation was the brief duration of the sessions to detect a need for dose increase to cover the therapy duration in

each consecutive session. Any need for increased doses could have been observed if the duration of the procedure was long enough for ketamine's sedative effect to disappear during the intervention. However, we tried to prevent an unintentional and subjective tendency to change the amount of drug used for the procedure by using a sedation scale that clarifies the end-point for the level of sedation. Thus, this allowed us to optimize and standardize the amount of ketamine. In addition we tried to identify the recovery time according to a recovery scale to assess the time required for a similar recovery level in each child.

In conclusion, a requirement for an incremental increase in ketamine dose after subsequent administrations was not detected, despite a significant decrease in recovery times being anticipated when ketamine is used repeatedly for sedative purposes in consecutive radiotherapy sessions. The cross-section of this procedural overview might be reproduced with further larger studies.

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