

## ORIGINAL RESEARCH

## PEDIATRIC ANESTHESIA

# Tolerance development in children undergoing repeated exposure to anesthesia drugs for radiation therapy

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## Abstract

**Background & Objectives:** Radiation therapy is one of the modalities used in cancer treatment to destroy rapidly growing tumor mass. The fractionated radiation session targets up to four fields of 90 sec each, over 10-15 min. Young children require deep sedation or general anesthesia to make them immobile, for the safe delivery of radiation fractions. Common drugs used for sedation are propofol, ketamine and midazolam. Repeated exposure to anesthetic drugs over a short period of time may lead to development of tolerance and increased dose requirements.

We aimed to determine if drug tolerance phenomenon develops in children receiving frequent doses of anesthetic drugs over a short time period.

**Methodology:** This is a retrospective observational study of the pediatric population who underwent frequent radiotherapy sessions with deep sedation from January to May 2019. The data of the first and last day of drugs administered was analyzed to determine if the dose requirement for any of the three drugs increased over time.

**Results:** We collected data of twenty-one patients and applied two tailed student's t-test on the mean dose of drugs on the first day and the last day of the treatment. It remained unchanged with insignificant p value (propofol  $p = 0.15$ ; midazolam  $p = 0.5$ ; ketamine  $p = 0.32$ ). To minimize the drug augmenting each other's effect, multilinear regression analysis of the drugs over the time period showed that there was neither an increase nor a decrease in the doses used ( $\alpha$ - propofol coefficient  $0.019 \pm 0.053$ ;  $\beta$ - midazolam coefficient  $-0.002 \pm 0.007$ ;  $\gamma$ - ketamine coefficient  $0.049 \pm 0.218$ ). The overall duration of the recovery time was not different from the first to the last day of radiotherapy.

**Conclusion:** Frequent and repeated doses of sedative drugs over a short period of time in children undergoing repeated deep sedation for radiation therapy, do not result in the development of tolerance.

**Key words:** Sedation; Tolerance; Radiotherapy

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## 1. Introduction

Radiation therapy is one of the modalities used for destroying cancer mass. It has to be delivered at an exact location with completely immobilized patient.

Radiation is planned to mark the target location and an immobilization cast may also be made before the session. Fractionated radiation is then given daily over several weeks.<sup>1</sup> Each session may last up to 10-15 min.<sup>2</sup>

**Table 1: Mean dose of drugs over time in weeks (Mean  $\pm$  SD)**

Therapy	Week 1	Week 2	Week 3	Week 4	Week 5
Propofol	2.85 $\pm$ 0.69	2.8 $\pm$ 0.9	3.09 $\pm$ 1.2	3.3 $\pm$ 1.9	3.3 $\pm$ 2.2
Midazolam	0.07 $\pm$ 0.02	0.07 $\pm$ 0.02	0.06 $\pm$ 0.03	0.05 $\pm$ 0.03	0.05 $\pm$ 0.04
Ketamine	0.3 $\pm$ 0.2	0.26 $\pm$ 0.2	0.24 $\pm$ 0.22	0.19 $\pm$ 0.29	1.07 $\pm$ 1.8

This painless procedure needs absolute patient immobility. Immobility is ensured by deep sedation or general anesthesia.<sup>3,4</sup> The use of anesthetics makes the radiation delivery safe. The aim is to keep the child immobile and spontaneously breathing with short recovery time, and it is performed as an out-patient procedure.<sup>5</sup> Commonly used anesthetics drugs are: propofol, midazolam and ketamine.<sup>6</sup> Propofol (2,6-diisopropylphenol) is a short-acting sedative drug, known to cause apnea. Therefore, either the doses are very cautiously titrated or with a combination of drugs for augmented effect.<sup>7</sup>

Repeated exposure to anesthetic drugs daily or over a short period of time may lead to the development of tolerance,<sup>8,9,10,11</sup> and increased dose requirements. Tolerance is decreased effect over time or the need to increase the dose to produce the same effect.

We conducted this study with an aim to determine if drug tolerance developed in children exposed to repeated anesthetic drugs over a short time period.

## 2. Methodology

This was a retrospective, observational study that included all children aged 16 y or younger who underwent deep sedation for radiotherapy sessions from January 2019 to May 2019. The Institutional Review Board (IRB) approval was sought and obtained. Data was collected from anesthesia records available as archived charts and clinical notes from electronic hospital information system (HIS) as per proforma (Appendix 1).

Exclusion criteria were;

1. Children who had only planned simulation.
2. Less than five radiation therapy sessions.
3. Used facial cast for radiation.
4. On regular opioid/ sedative drugs.

Each session lasted for 10 to 15 min. For radiotherapy commonly used anesthesia drugs are propofol, midazolam and ketamine. Anesthetists vary in their practice of using one drug or combination of drugs. However, endpoint is good parental separation and sedation level at which child is asleep and does not respond to mild prodding (Appendix 2).

### Statistical analysis:

1. Multilinear regression analysis of the drug doses for each patient was carried out to fit a linear hyperplane to this data. The hyperplane coefficients for each patient were then pooled to drive mean coefficients. The sign of the coefficients determine, keeping the other two drug doses constant, whether the drug dose corresponding to that coefficient will increase with time or decrease.
2. Mean recovery time (and standard deviation) of the first and last radiation therapy day along with recovery stay time was calculated and plotted as a box plot.

## 3. Results

Twenty one patients (six female and fifteen male) underwent radiation therapy, with a median age of 3 y (1.75 – 8 y). A total of eleven to thirty fractions of radiations were given within a period of maximum forty-four days (average of twenty fractions). No adverse event was observed and there was no unplanned admission for day cases.

The mean amount of propofol, midazolam and ketamine over the time periods is given in Table 1.

The variation between the individual cases is higher with increasing numbers of fractions. However, the amount of medicine for a particular case remains more or less the same. The data of the first and last day of drugs administered was analyzed to determine if the

dose requirement of anyone of the three drugs increased between the first and last therapy session (Table 2). The p-values were calculated with the null hypothesis that the population means of the drug doses administered on the first and the last day were the same. The two tailed student T-test under the assumption of heteroscedasticity on the data supported the null hypothesis with p-values given in Table 2. Given that in the overall population there is no change in the mean dose on the first and the last day of therapy, we further divided patients into two categories, resistant and non-resistant, based on the apparent increase of drug dose for any of the drugs.

**Table 2: Comparison of mean dose of drugs for first and last therapy session (Mean  $\pm$  SD).**

Therapy	Mean dose (mg/kg)		p-value
	1st session	Last session	
Propofol	2.6 $\pm$ 1.2	3.26 $\pm$ 1.7	0.15
Midazolam	0.06 $\pm$ 0.04	0.05 $\pm$ 0.04	0.51
Ketamine	0.3 $\pm$ 0.5	0.4 $\pm$ 0.5	0.32

**Table 3: Comparison of resistant and non-resistant groups for mean dose of first and last therapy session**

Therapy	Non-resistant group (n = 8)			Resistant group (n = 13)		
	First day	Last day	p-value	First day	Last day	p-value
Propofol	3.1 (1.5)	2.36 (0.6)	0.2	2.31 (1)	3.75 (1.9)	0.03
Midazolam	0.03 (0.04)	0.06 (0.03)	0.12	0.08 (0.04)	0.05 (0.04)	0.98
Ketamine	0.11 (0.3)	0.45 (0.5)	0.22	0.39 (0.6)	0.39 (0.5)	0.074

We performed subgroup analysis to figure out if this particular group has markedly different dose requirements but was not obvious in overall analysis. There is no increase in dose rather there is a decrease in midazolam and ketamine dose in the resistant group, however it could be explained by the increase in propofol dose (Table 3). Therefore the apparent increase or decrease compensated by the other drug requires another way of analyzing this data.

We performed a multilinear regression analysis, for each patient obtaining a linear hyperplane which gives the dependence of the drugs on each other and on the number of days. The equation of the linear hyperplane is given below:

$$\text{(Equation 1) } \frac{P}{\alpha_i} + \frac{M}{\beta_i} + \frac{K}{\gamma_i} - D = \kappa_i, \quad i = 1, \dots, N$$

where  $P$ ,  $M$ ,  $K$  are the doses, normalized by patient weight, of the three drugs (propofol, midazolam, ketamine),  $D$  is the number of days and  $N$  is the number of patients in the study. For each patient, labelled by the index  $i$ , one obtains such a hyperplane which is uniquely determined by the coefficients ( $\alpha_i$ ,  $\beta_i$ ,  $\gamma_i$ ,  $\kappa_i$ ). Whether these coefficients are positive or

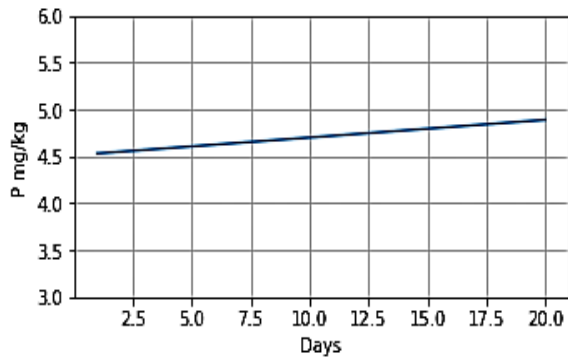
negative determines, for any given patient, if the corresponding drug increases with time or decreases with time keeping the other two drugs fixed. The mean and the standard deviation of these coefficients are given in Table 4.

**Table 4: Mean and standard deviation of coefficients**

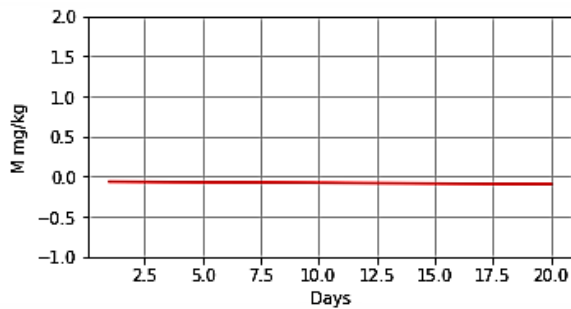
	$\alpha_i$ -propofol coefficient	$\beta_i$ -midazolam coefficient	$\gamma_i$ -ketamine coefficient	$\kappa_i$ -Intercept
Mean	0.019	-0.002	0.049	200.91
SD	0.053	0.007	0.218	1142.42

The regression analysis of the drugs over the time period shows that there is neither an increase nor a decrease in dose of drugs used over the time period. This can be seen by projecting the hyperplane (Equation 1) to the three ( $P$ ,  $D$ ), ( $M$ ,  $D$ ) and ( $K$ ,  $D$ ) planes by fixing the value of the other two drugs to its mean value. The resulting three graphs are shown in the figure below. The graph in Figure 1(a) shows the variation of  $P$  with the number of days when  $M$  and  $K$

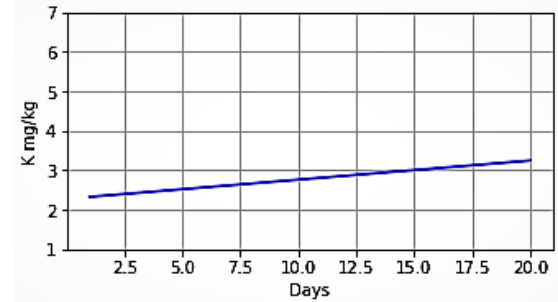
has been taken to be equal to their mean value. The other two graphs shown in Figures (b & c) can be interpreted similarly.



**Figure 1(a): The graph of propofol doses keeping the other two fixed to their mean value.**



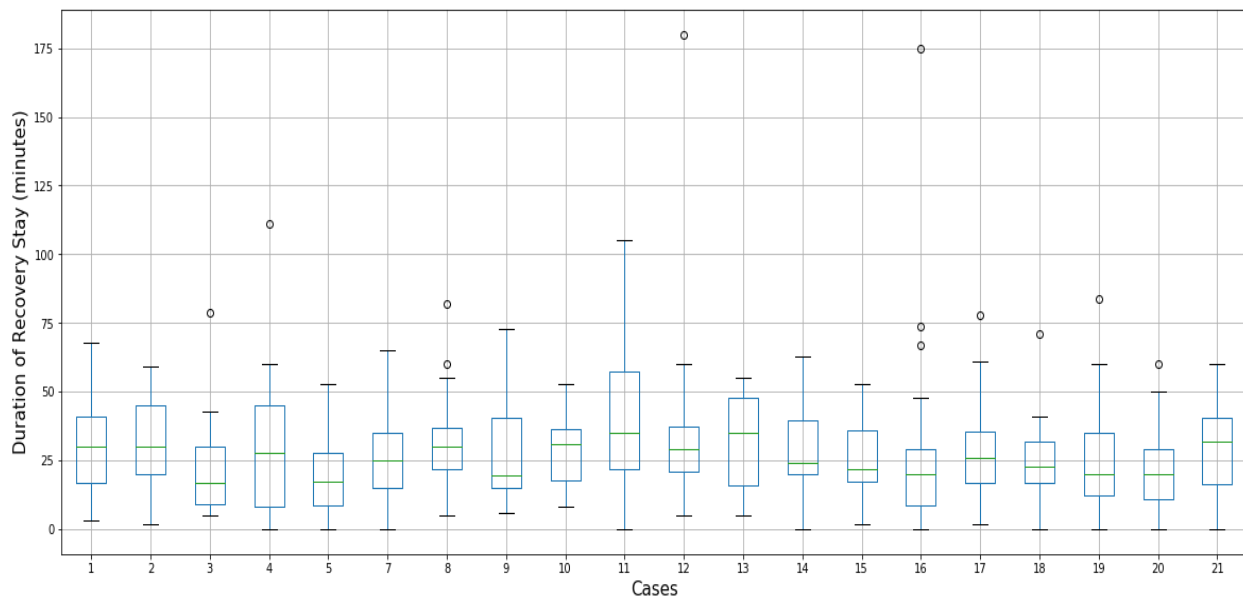
**Figure 1(b): The graph of midazolam doses keeping the other two fixed to their mean value.**



**Figure 1(c): The graph of ketamine doses keeping the other two fixed to their mean value.**

The second parameter measured was the patient's length of stay in recovery which is calculated from receiving patient in recovery to discharge time.

The mean length of stay in recovery time is 29.3 min, with standard deviation of 4.7 min which is in line with the data of 1033 pediatric cancer patients presented by Seiler et al.<sup>12</sup> The recovery length of stay for the resistant group 29.6 min (SD 5.6 min) versus non-resistant group 30.1 min (SD 20.1 min) is not significantly different. Overall, the length of recovery stay on the last day is 28.6 min (SD 20.3 min) which is not clinically significant, shorter than on the first day length of recovery stay of 35 min (SD 20.8 min). The box plot of length of stay in recovery (in min) is given in Figure 2.



**Figure 2: Length of stay in recovery (in min)**

## 4. Discussion

Tolerance to a drug is defined as the decrease in the effect of drug overtime requiring an increase in drug dosage to achieve the same effect as previous.<sup>13</sup>

Propofol is a short acting, highly lipophilic drug, with very quick distribution in the body, followed by a quick redistribution. It causes positive modulation of the inhibitory function of the neurotransmitter gamma-aminobutyric acid (GABA) through GABA-A receptors.<sup>14</sup>

Drug abuse by medical personnel is common. There are multiple studies and case reports highlighting propofol as a drug of abuse especially among the anesthesiologists. Many experiments have been done to find the addictive potentials of the drugs.<sup>15,16</sup> The drugs mainly studied and mentioned in literature are propofol, midazolam and Ketamine.<sup>17,18</sup> Propofol seems to act on the dopaminergic reward system in ventral tegmentum and nucleus accumbens.<sup>19,20</sup> Animal studies has revealed the same effect by Li et al. on rat brain.<sup>20</sup>

After waking up from anesthesia patients have described the experience as relaxing pleasant, feeling high, drunk and having good dreams with illusions and fantasies.<sup>21</sup>

Many deaths have been reported after self-administration of propofol.<sup>22,23</sup> Cause of death included respiratory and cardiac depression. With availability data on propofol as abusive drug, the chances are development of tolerance are marked, but there is lack of clarifying evidence.<sup>24,25</sup> However, withdrawal symptoms have been observed after long term propofol sedation in ICU.<sup>26</sup> A study by Yitzhak Cohen et al.<sup>9</sup> concluded that repeated propofol doses for ECT (electroconvulsive therapy) can cause tolerance like reaction. But none other studies have yet supported this, especially in the pediatric population.<sup>13</sup>

In our study, we found that the tolerance to anesthetic drugs did not develop in the pediatric population undergoing repeated use of anesthetic drugs for radiotherapy sessions.

It is reported by Setlock and Soyka M et al., that there was no development of tolerance to the repeated doses of propofol, as a sole agent or in combination with adjuvants for short procedures.<sup>15,27</sup>

## Tolerance in children in repeated anesthesia

The limitation of this study was the small cohort of patients. The tolerance was assessed by clinical judgement rather than any objective methods e.g., BIS values.

In our study, there is no increase in dose requirements of the anesthetic drugs. The decrease in dose of one drug could have been counterbalanced by an increase of the other drug. To minimize this effect, multilinear regression analysis revealed no change in the drug dosage over time.<sup>27</sup>

## 5. Limitations

Our study is a retrospective study in which plasma levels of the drugs could not be measured. Plasma levels would have helped to predict tolerance to anesthetic drugs and on recovery based on pharmacokinetics and pharmacodynamics<sup>28</sup>.

## 6. Conclusion

Children undergoing frequent repeated exposure to anesthetic drugs for chemotherapy over a short time period do not develop drug tolerance.

## 7. Conflict of interest

None declared by the authors

## 8. Authors' contribution

AI, HS: Conduction of study

AI: Concept

RSD, AI: Manuscript editing

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### Appendix 1: Child behavior and inference for sedation

Behavior on parental separation	Sedation
1 = Crying, cannot be reassured	Alert, awake
2 = Awake, anxious, can be easily reassured	Alert, awake
3 = Good separation, awake, calm	Drowsy, sleepy, lethargic
4 = Asleep	Asleep but responds only to mild prodding or shaking
	Asleep and does not respond to mild prodding or shaking