

An Audit of Perioperative Use of Tramadol in Children in a Specialized Children Hospital

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Abstract: Background: Tramadol is widely used worldwide to treat moderate to severe pain in children. There are growing concerns regarding the safety of tramadol use in children in recent years when the US FDA (Food and Drug Administration) issued a safety announcement that restricts tramadol use in children less than 18 years old to treat pain after tonsillectomy and adenoidectomy. After this FDA announcement, our hospital stopped using tramadol in children less than 18 years old. Objective: we planned to audit our experience in the use of intravenous tramadol in children for postoperative pain management in recovery area. Methods: Institutional Review Board (IRB) waived written informed consent. After getting the IRB approval, we reviewed the anesthesia records of 16130 patients between the years 2015 and 2017. We looked for patients who received tramadol postoperatively in PACU (post-anesthesia care unit). We looked for postoperative complications or adverse events in the form of apnea, hypopnea, bradycardia, postoperative nausea and vomiting, prolonged stay in recovery, unplanned admission, or admission after discharge within 48 hours. Statistical analysis was done using Wilcoxon scores for variables, Wilcoxon 2 sample test, calculated odd's Ratio and 95% confidence interval and P-values where P values less than 0.05 were considered significant. Results: Seven patients desaturated out of 430 patients. They needed oxygen support in the form of simple facemask or nasal cannula but no one needed positive pressure ventilation. No one developed apnea or bradycardia or needed naloxone administration. There was no readmission after discharge from the hospital. There was only one unplanned admission due to a surgical cause. The average duration of stay in the PACU was 86 minutes. Almost all (418) patients stayed more than 45 min (97.2%). Ninety-two patients had PONV (postoperative nausea and vomiting) (21.39%). There was positive correlation between PONV and total tramadol dose, while a comparison of the Pearson correlations showed that duration of the procedure was the best predictor of PACU duration with an R-value of 0.188 which was highly significant at the $P < 0.0001$. Conclusion: Tramadol does not cause respiratory depression in children, especially when given in a controlled

and monitored setup in the operating room and recovery area however Still, Tramadol needs to be studied more in pediatric anesthesia and analgesia and more comparative data is required to determine the safety of available opioids in this setting.

Keywords: Intravenous Tramadol, Peri-operative Pain, Pediatric Anesthesia, Postoperative Analgesia

1. Introduction

Although many countries are using tramadol off-label in children below 17 years old, the US FDA does not yet approve it. That recent announcement by FDA in April 2017 about restriction of use of tramadol and codeine in children was related to nine cases who had problems in breathing, and three cases of mortality, that were related to use of tramadol in children less than 18 years in between 1969 and 2016. [1] After FDA announcement, our hospital stopped using tramadol in children. The labeling for codeine and tramadol containing drugs was changed, and these drugs are contraindicated for analgesia in children younger than the age of 12. The labeling for codeine-containing medication says that it is contraindicated as antitussive children below 12 years. Two new warnings were added: these drugs should not be prescribed to adolescents ages 12 to 18 who have comorbidities that may increase the risk of serious respiratory problems, or to breastfeeding women due to the risk of excessive sedation in their infants. [1] A 2013 warning from the FDA had previously cautioned against the use of codeine for postoperative analgesia in children younger than 18 years after adenotonsillectomy; [2] however, the updated warnings are more restrictive, the label of contraindication is the strongest warning the FDA issues. Besides these contraindications, warning labels have been given for the use of codeine, tramadol for children ages 12 to 18 years who are obese, or have any conditions associated with respiratory disorders, such as obstructive sleep apnea or severe lung disease. [3] An important metabolic pathway for tramadol is that provided by CYP2D6 to form O-desmethyltramadol; the active M1 metabolite, this active M1 metabolite has a μ -receptor affinity approximately 200 times greater than tramadol. It is worrisome that this active metabolite may depress respiration in certain children those who are ultra-rapid metabolizers. Metabolism of Tramadol is mainly in the liver by O - and N-demethylation and conjugation ending in formation of glucuronides and sulfates. Elimination of tramadol and its metabolites is predominantly through the kidneys. [4] Being synthetic and acting on Central Nervous System both by weak opioid agonist and by monoamine neurotransmitter re-uptake inhibitor makes Tramadol the most prescribed opioid worldwide. [5] The pharmacokinetics of tramadol inside the body differ in some humans according to the genetic variation of how rapid and complete the liver convert tramadol to its active form that so-called O-desmethyltramadol. The ultra-rapid metabolizers who have large amounts of O-desmethyltramadol after tramadol administration are prone to even cardiac arrest due to the resulting breathing difficulties, they would experience. [6] Most of the drugs used in anesthesia and intensive care are off-label in children, even if

they present solid clinical evidence in adults because studies in children are rarely conducted by the pharmaceutical companies or by the academic investigators. This lack of authorization is caused by many factors, including the great difficulty of researching in this area. [7] There is little evidence concerning the use of the drug in the pediatric population. We planned to audit the use of intravenous tramadol in children in PACU over two years.

2. Aim

Our primary objective was to detect patients who developed respiratory complications in form of apnea, desaturation related to the use of intravenous tramadol in children in our PACU. Our secondary objectives were to look for the length of stay in PACU, Readmission after discharge in the next 48 hours and PONV and if any of them is related to tramadol administration.

3. Methods

Written informed consent was waived by IRB. After getting the IRB approval, we reviewed the records of all patients who were given anesthesia between the years 2015 and 2017 looking for patients who received intravenous tramadol postoperatively in PACU. We looked for postoperative complication or adverse events in the form of apnea, decreased oxygen saturation below 94%, postoperative nausea and vomiting, duration of stay in recovery longer than 45 minutes. Patients are considered ready for discharge from PACU when PACU score "Table 1" is equal to 12 if no regional anesthesia and 15 according to sensory level, if with regional anesthesia according to our local guidelines. We looked for patients who had unplanned admissions; either from short stay to the ward, or from regular ward to HDU (High dependency unit) or PICU (Pediatric intensive care unit) and admissions after discharge home within 48 hours following surgery. We looked for the reasons behind the prolonged stay and unplanned admissions if any is related to tramadol. We found that 530 patients had received intravenous tramadol postoperatively in PACU during this period. We excluded 100 patients who had incomplete data; either lacking documentation or anesthesia sheets were missing. Tramadol in our hospital is available in 2 ml ampoules with a concentration of 50 mg/ml. We dilute tramadol in 10 ml syringes as 10mg/ml. When using tramadol intraoperative, 1mg/kg is given intravenously as an adjunct to fentanyl. In PACU, the anesthetist prescribes tramadol as 1-2 mg/kg divided into 5 doses 5 minutes apart. PACU nurse gives tramadol when pain score is more than four on a Wong baker scale for those above 3 years old

“Figure 1” and on a FLACC (Face Legs Activity Cry Consolability) scale for those less than 3 years old “Figure 2”. Tramadol administration or opioid either in OR (Operating room) and PACU, is based on the anesthetist’s

judgment. Statistical analysis was done using Wilcoxon scores for variables, Wilcoxon 2 sample test, calculated odd's Ratio and 95% confidence interval and P-values where P values less than 0.05 were considered significant.



Figure 1. Wong Baker Scale.

	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaints	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or "talking to". Distractable	Difficult to console or comfort

Figure 2. FLACC scale.

FLACC SCALE ©University of Michigan Health System.

Table 1. PACU score.

Variable	Highest	Lowest
Oxygen Saturation	2	0
Mental Status	2	0
Respiration	2	0
Pain	2	0
Blood pressure	2	0
Colour	2	0
Spinal level/sensory	3	0
Total	12 no regional 15 if regional block	

4. Results

430 patients had received intravenous tramadol for breakthrough pain in PACU, 98 patients out of those also received intravenous tramadol intraoperative. Demographic data is shown in table 2.

Table 2. Demographic data.

Demographics	Number	Percentage
ASA		
I	266	61.86%
II	139	32.32%
III	25	5.82

Demographics		Number	Percentage
Gender	M	250	58.2%
	F	180	41.8%
Age	>12y	51	11.86%
	2-12y	265	61.63%
	<2y	114	26.51%

Procedures done according to specialty are in “table 3”.

Table 3. Types and Number of Procedures.

	Number	Percentage
Otorhinological	138	32.09%
General surgery	95	22.09%
Orthopedic	84	19.53%
Plastic	38	8.84
Dental	27	6.3%
Urology	20	4.65%
Ophthalmology	13	3.02%
Neurosurgery	10	2.32%
Oncology	5	1.16%

Only six patients had abnormal renal and liver function tests (0.014%). Age, weight of patients, Tramadol doses, duration of Procedures and PACU are represented as median and interquartile range in table 4.

Table 4. Age and weight of patients, Tramadol doses postoperative and total, duration of Procedures and PACU.

Variables	Median	IQR (Range)
Age of patients in months	88.17	74.75 (4-192)
Weight of patients in kg	27.33	20.125 (2-87)
Tramadol in PACU in mg/kg	0.871	0.779 (0.037-5)
Total tramadol dose in mg/kg	1.117	0.996 (0.037-5)
Procedure duration in min	72.156	57 (33-322)
PACU duration in min	86	30 (4-560)

Only one unplanned admission, from PACU to the ward, the admission was for observation due to a surgical complication but not related to tramadol. 92 patients had PONV (21.39%) and needed intervention inspite of PONV prophylaxis intraoperative, 41.3% of these patients were post ENT procedures (“Table 5”).

Table 8. Predictors of PONV.

	p-value	Odd's Ratio	95% Confidence Interval	
Age (months)	0.9391	1.000	0.993	1.007
Weight (kg)	0.0602	1.018	0.999	1.036
Total tramadol (mg/kg)	0.0378	1.378	1.018	1.864
Duration of procedure (Minutes)	0.4162	0.998	0.993	1.003

In table 9, a comparison of the Pearson correlations shows positive correlation between the duration of the procedure and PACU duration.

Table 9. Pearson Correlation Coefficients (r-values) and Predictors of PACU duration.

	PACU duration (minutes)
Age (months)	Pearson Correlation (r)
	0.10262
Weight (kg)	Probability
	0.0338
Total tramadol (mg/kg)	Pearson Correlation (r)
	0.07804
Duration of procedure (min)	Probability
	0.1069
	Pearson Correlation (r)
	0.01356
	Probability
	0.7797
	Pearson Correlation (r)
	0.18806
	Probability
	0.0001

Table 5. Procedures with PONV.

ENT	38	41.3%
GS	20	21.7%
ORTHOPEDIC	15	16.3%
PLASTIC	4	0.04%
DENTAL	4	0.04%
UROLOGY	4	0.04%
OPHTHALMOLOGY	3	0.03%
NEUROLOGY	3	0.03%
ONCOLOGY	1	0.01%

418 patients stayed in PACU more than 45 min (97.2%) and reasons for prolonged stay are shown in Table 6.

Table 6. Causes of prolonged PACU duration.

Reasons for prolonged stay in PACU	Number	Percent
Pain	134	32%
PONV	92	22%
Age less than 2 years	51	12.2%
Waiting for ward Beds	48	11.4%
Waiting for HDU/PICU	14	3.3%
Desaturation less than 94%	7	1.67%
Allergic reaction	1	0.23%

Correlation between PONV and increased PACU duration from one side and on the other side; age, weight, total tramadol dose, and duration of procedures are shown in table 7.

Table 7. PONV correlation.

	PONV	NO PONV
Number of patients (%)	92 (21.39%)	338 (78.61%)
Age (months) Mean (SD)	96.09 (42.75)	86.01 (47.15)
Weight (kg) Mean (SD)	31.94 (18.31)	26.50 (16.24)
Total tramadol (mg/kg) Mean (SD)	1.23 (0.76)	1.08 (0.74)
Procedure duration (min) Mean (SD)	68.04 (46.54)	73.26 (60.27)

In table 8 the estimated odds ratio shows positive correlation between tramadol dose and PONV.

5. Discussion

Looking through the results, seven patients were desaturated out of 430 patients. They needed oxygen support in the form of simple facemask or nasal cannula but no one needed positive pressure ventilation. There were no serious respiratory events; no apnea no bradycardia nor naloxone administration, no readmission after discharge. Even those who needed oxygen supplementation, it was temporary and only delayed the discharge from PACU. Almost all patients stayed in PACU more than 45 min (97.2%). Statistical analysis showed positive correlation between PACU duration and the duration of procedures, however this does not necessarily mean that long procedures is the reason for long PACU duration, there were other associations that may have contributed; 32% of these patients had pain score more than 5/10, some of them received extradoses of tramadol and total tramadol exceeded 2mg/kg. Also 22% of these patients had PONV, that needed intervention, and there was a positive correlation with total tramadol dose. 12.2% of those patients were less than 2 years old. Also 11.4% of patients were planned for ward admission and ward beds were not ready, 3.3% of patients were preplanned for HDU/PICU beds but were not ready, and one patient had an allergic reaction to tramadol in form of redness in the face, which resolved spontaneously without medication. There was no readmission after discharge from the hospital within 48 hours. Surprisingly there were 40 patients received tramadol doses that exceeded 2mg/kg and whether they were extradoses to control pain intentionally given or unintentionally due to mistakes, in calculation, this was not mentioned in the files and there was no complications or side effects. Most of the patients 32% of patients who stayed longer duration in PACU were having pain, which goes with the fact that tramadol is a weak opioid, used for breakthrough pain, and as a secondary analgesic when NSAIDs, or paracetamol fail.

Many pediatric anesthesiologists in our institution, used tramadol as a postoperative analgesic over the past years. Tramadol may represent an equivalent or even superior alternative to morphine for those patients at risk of complications postoperatively [4]; this could be due to a reduction in airway interventions or ICU admissions. It may however, potentially improve safety margins for those patients not requiring PICU admission and deemed appropriate to be managed postoperatively on the ward. [8] There are few data on respiratory depression from tramadol in children. Respiratory depression is minimal in children undergoing hernia repair after tramadol 1 mg/kg. [9] And was less than respiratory depression after pethidine 1 mg/kg. Data comparing tramadol 0.6 mg/kg IV revealed no respiratory depression when compared to pethidine 0.6 mg/kg IV or oxycodone 0.04 mg/kg IV in adults. [9, 10] Tramadol caused less respiratory depression at a dose of 1 mg/kg than 2 mg/kg in adults and children. [11] The main

use of Tramadol is acute pain management in the context of trauma or in the postoperative setting. [7, 9-13] It is also used for treatment of the acute vaso-occlusive crisis in sickle cell disease [14, 15]. Nine cases of respiratory depression were behind the new warning of FDA; this included three deaths in children below 18 years of age between 1969 and 2016 reported to the FDA Adverse Event Reporting System. [16] These events happened within the first 24 hours of tramadol administration. All deaths involved children younger than six years old. They reported supratherapeutic concentrations of tramadol. [3, 17] In acute pain when CYP2D6 activity is not known and this is not readily available test in many hospitals. Inpatients can be monitored for any adverse events 24 h before discharge. However, it is better to start small doses (0.5 mg/kg/dose; three to four times daily maximum of 2mg/kg/day) and adjust the doses according to tolerance and efficacy. [18] At discharge, tramadol can be continued at the minimal effective dose depending on tolerance and efficacy. [19] In this aspect SPANZA (Society for Paediatric Anaesthesia in New Zealand and Australia) has responded to FDA warning in May 2017, emphasizing that these warnings are issued to protect patients and is a part of drug education, however they are not drug coffins, since the use of general anesthesia in children under age of two years is currently being reviewed. [20] They issued two recommendations; Tramadol can be used as part of multimodal analgesia for acute pain in children, it will be very useful, its use can be limited to acute pain after tonsillectomy and for those with obstructive sleep apnea they should be monitored overnight in hospital. [18] Again, in June 2017, in response the strengthened warning about Tramadol use in breast-feeding mothers and neonates, SPANZA added that Tramadol is safer than other opioids that are also excreted in breast milk, and alternatives to Tramadol as oxycodone and morphine are more likely to cause sedation and respiratory depression. [21] We did not find serious respiratory events in our data. However, being a retrospective study, having no control group and the relatively small number of the sample are limitations of our study. Besides, we did not have sub analysis of high-risk patients as tonsillectomies, and obese children. In addition, heterogeneity of patients; (wide age range, diversity of surgical procedures) adds to the limitations and hence we recommend having another prospective study testing the safety and respiratory complications of tramadol.

6. Conclusion

Tramadol does not cause respiratory depression in children, when given in a controlled and monitored setup in the Post anesthesia recovery area. Tramadol is not an ideal analgesic for children but it is one of the options. It can be of use in fragile patients who do not tolerate strong opioids. however still, Tramadol needs to be studied more in pediatric anesthesia and analgesia and more comparative data is required to

determine the safety of available opioids in this setting.

Declarations

Consent for Publication

Not Applicable.

Ethical Approval and Consent to Participate

It is a retrospective study and only chart review, patient's privacy and confidentiality was assured, no identifiers was collected and all data is kept in a secure place within NGHHA premises both hard and soft copies. Institutional Review Board (IRB) waived written informed consent.

Availability of Data and Materials

The data was collected in paper-form and then entered in a digital form (Excel Sheet). Data is kept in a secure place within NGHHA premises both hard and soft copies. All records are kept safely in locked cabinet with access only to investigators. The digital form is password protected.

Competing Interests

There is no conflict of interests to disclose.

Funding

There are no financial disclosures.

List of Abbreviations

FDA: Food and Drug Administration
 KASCH: King Abdullah Specialist Children's Hospital
 IRB: Institutional Review Board
 PACU: Post anesthesia care unit
 PONV: Postoperative nausea and vomiting
 HDU: High dependency unit
 PICU: Pediatric intensive care unit
 FLACC: Face Legs Activity Cry Consolability
 OR: Operating room
 NSAIDs: Non-steroidal anti-inflammatory drugs
 SPANZA: Society for Paediatric Anaesthesia in New Zealand and Australia

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