Original Article

Efficacy and safety of intravenous oxycodone for general anesthesia in children

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Background: Oxycodone had been widely used for cancer pain control and postoperative pain control. However, its efficacy and safety for general anesthesia in pediatric patients have not been reported. The study aimed to investigate the analgesic effect and safety of oxycodone as compared to sulfentanil.

Methods: This was a retrospective study conducted in a tertiary care medical center. In the oxycodone group, anesthesia was induced by propofol (3 mg/kg), cisatracurium (0.1–0.15 mg/kg) and oxycodone (0.2–0.4 mg/kg). In the control group, the oxycodone was replaced by sulfentanil (0.3–0.6 ug/kg). Both groups had remifentanil (11–13 ug/kg/hr) administered continuously via intravenous pump during operation. Anesthesia was maintained by propofol (6–9 mg/kg/hr) and cisatracurium (0.05–0.1 mg/kg/hr) in all patients.

Results: A total of 94 children fulfilled our inclusion criteria and were used for analysis. There was no significant difference in demographics and baseline characteristics between oxycodone and control groups. Propofol and ramifentanil doses for anesthesia maintenance were similar between both groups. Postoperative analgesic uses were slightly higher in the control group than oxycodone group (27.6% *vs.* 20.0%; P=0.636). The incidence of adverse events including nausea, vomiting tended to be higher in the control group (26.1% *vs.* 12%; P=0.147).

Conclusions: The results showed that oxycodone had comparable analgesic effect to sulfentanil, and tended to have lower postoperative analgesic requirement and less adverse events.

Keywords: Oxycodone; anesthesia; postoperative analgesic; pediatric anesthesia

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Introduction

Oxycodone is a kind of semisynthetic opioid that has analgesic effect for moderate to severe pain. Unlike morphine, which is an agonist of μ-opioid receptors, oxycodone acts on k-opioid receptor (1). Furthermore, oxycodone is metabolized in the liver to oxymorphone. The later metabolite is a more potent opioid agonist with higher binding affinity to μ-opioid receptors compared to oxycodone. However, subsequent researches revealed that the action of oxycodone is far more complex that its effect is mediated by different receptors in different situations (2,3). Oxycodone can be administered orally and intravenously. The bioavailability of oral administration of oxycodone averages 60–87% (4). Oxycodone is eliminated from sweat and urine and thus it accumulates in patients with renal dysfunction.

Since its first synthesis 100 years ago, oxycodone has been widely used in clinical practice (4). For example, oral formulas of oxycodone has been widely used for cancer pain (5-9). Some other studies have reported the efficacy and safety of oxycodone for the management of postoperative pain [e.g., in the form of patient controlled analgesia (PCA)] (10-12). These studies consistently show

that oxycodone is a safe and effective analgesic. There is also evidence supporting that IV oxycodone may be associated with greater pain control, fewer severe adverse events, and faster onset of action, although the results are not consistent across all studies (13-16). Oxycodone used for intraoperative analgesia has also been reported in adult but the evidence is scarce (17,18). In pediatric patients and infants, oxycodone administered postoperatively has been reported (19-21). However, to the best of our knowledge, there is no study reporting on intravenous use of oxycodone for analgesia (administered before surgery) in children. In the present study, we aimed to explore the efficacy and safety of analgesia with intravenous oxycodone for children.

Methods

Study population

The study was a retrospective study enrolling children (<15 years old) underwent general anesthesia from May 2015 to November 2015. Medical chart of eligible patients were reviewed. Patients were eligible if they fulfill the following criteria: (I) age younger than 15 years old; (II) patients underwent general anesthesia. Patients would be excluded if they (I) had on analgesics for chronic pain before operation; (II) underwent local anesthesia and/or spinal anesthesia; (III) used fentanyl for anesthesia; and (IV) were neonates (<28 days) or infants (<12 months). This was a comparative study by using historical controls. The study was approved by the institutional review board of Jinhua Municipal Central Hospital. Informed consent was waived due to retrospective nature of the study.

Anesthesia procedure

Our institution started to use intravenous oxycodone for anesthesia for pediatric patients from October 2015. In the study group, anesthesia was induced by propofol (3 mg/kg), cisatracurium (0.1–0.15 mg/kg) and oxycodone (0.2–0.4 mg/kg). In the control group, the oxycodone was replaced by sulfentanil (0.3–0.6 ug/kg). Both groups had remifentanil (11–13 ug/kg/hr) administered continuously via intravenous pump during operation. Anesthesia was maintained by propofol (6–9 mg/kg/hr) and cisatracurium (0.05–0.1 mg/kg/hr) in all patients. After operation, remifentanil was discontinued and patients were sent to the post-anesthesia care unit (PACU) for recovery. Volume controlled mechanical ventilation was instituted to reach a tidal volume of 10–12 mL/kg, and respiratory rate was set to maintain an end-tidal carbon dioxide level of 36–44 mmHg. During anesthesia period, oxygen saturation, heart rate, respiratory rate, blood pressure and end-tidal carbon dioxide were monitored continuously and recorded every 5 minutes. According to our local anesthesia protocol, patients were weaned from mechanical ventilation and extubated once they were awaken, hemodynamically stable and recovered stable respiration (tidal volume >6 mL/kg persistently).

Postoperative follow up

Postoperative pain was measured by using visual analogue scale (VAS) score if possible (22). VAS score ranged from 0 to 10 points, with 0 represented no pain and 10 points represented the worst the patient had ever experienced. Postoperative analgesics required were also recorded, which included diclofenac, tramadol, parecoxib, tetrandrine, flurbiprofen and somedon. Patients were followed for 72 hours postoperatively. The postoperative adverse events such as nausea, vomiting and itching and dizziness were also recorded within 72 hours. These adverse events were coded as dichotomous variables with "yes" or "no" status.

Statistical analysis

Continuous variable such as age and body weight were expressed as mean (standard deviation) if they were normally distributed. Otherwise, they were expressed as median (interquartile range). Univariate analysis was performed to compare the difference of baseline characteristics between oxycodone group and conventional group. Student *t*-test was employed for data with normal distribution, and Mann-Whitney U test was used for skewed data. Categorical variables such as sex, type of surgery and adverse events were expressed as the number and percentage. Their difference between oxycodone group and conventional group were tested by using Chi-square test.

If there are statistically significant differences in baseline characteristics between oxycodone and control group, analysis would be performed by using propensity score matching. Because missing data were present in the retrospective study and propensity score matching cannot be performed with missing values, we employed multiple imputation (MI) technique to estimate the missing values (23). This method had advantage that it takes account of the uncertainty in missing value estimation.

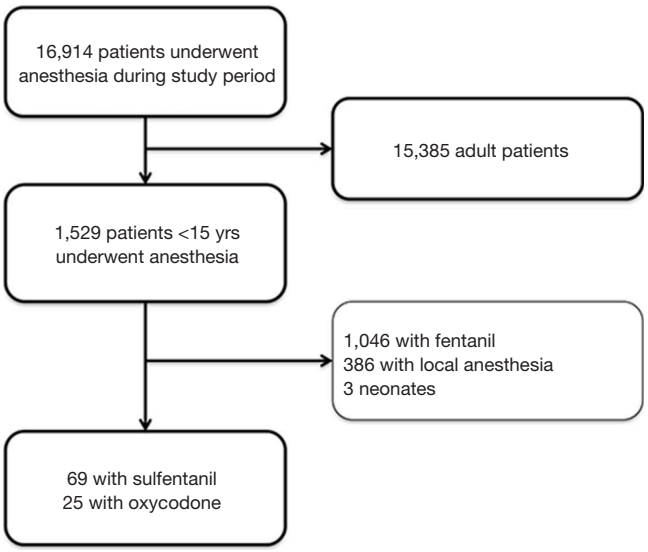

Figure 1 Flow chart of patient section.

Specifically, we created five complete datasets from original dataset containing missing values. Predictive mean matching was used to predict continuous missing values and logistic regression was used for dichotomous missing values (24). Thereafter, multivariable regression model was performed to examine the association between oxycodone use and postoperative analgesics use, by adjusting for other confounding factors. From clinical perspective, these confounding factors included age, type of surgery, length of operation, and sex. Five models were fitted, from which five coefficients were obtained from each imputed datasets. Finally, these datasets were combined to obtain final results. In this way, the variance would not be underestimated as compared to single imputation (25).

All statistical analyses were performed by using R software (R version 3.2.2), statistical significance was considered at P<0.05.

Results

During the study period, a total of 16,914 patients underwent anesthesia in our department (*Figure 1*). Of them, there were 1,529 children. After exclusion of 1,046 children with fentanyl for anesthesia, 386 children with local anesthesia, and 3 neonates, the remaining 94 children fulfilled our inclusion criteria and were used for analysis. There were 69 children in the control group and 25 children in the oxycodone group (*Table 1*). There were no significant differences in percentage of male (69.6% *vs.* 56.0%; P=0.327) and body weight (median: 25.5 *vs.* 21 kg; P=0.405) between the two groups. Patients in control group appeared to be older than oxycodone group (median: 8 *vs.* 7 years old; P=0.094). Most children had ASA score of I or II and there was no significant difference between the two groups. However, there was one child with IV ASA score in the control group. There were seven cases of abdominal surgery in the control group, but there is no one in the

Table 1 Comparison of baseline characteristics between patients with and without oxycodone

Variables	Non-oxycodone (n=69)	Oxycodone (n=25)	P
Gender (male, %)	48 (69.6%)	14 (56.0%)	0.327
Age (years, median, IQR)	8 (6.0–12.0)	7 (5.0–10.0)	0.094
Weight (kg, median, IQR)	25.5 (20.0–39.6)	21.0 (18.0–35.0)	0.405
ASA (No., %)			0.519
I	20 (29.0%)	10 (40.0%)	
II	48 (69.6%)	15 (60.0%)	
IV	1 (1.4%)	0	
Diagnostic/surgical type			0.132
Abdominal	7 (10.1%)	0	
Cranial	3 (4.3%)	1 (4%)	
Ear	1 (1.4%)	0	
Facial	13 (18.9%)	3 (12%)	
Bone fracture	19 (27.5%)	5 (20%)	
Hernia	3 (4.3%)	5 (20%)	
Ophthalmology	3 (4.3%)	4 (16%)	
OSAS	11 (15.9%)	4 (16%)	
Urinary	9 (13.0%)	3 (12%)	
Vital signs on admission			
Temperature	36.7 (36.5–36.9)	36.5 (36.3–36.8)	0.060
SBP	106 (96.0–114.0)	106 (99.0–116.0)	0.552
DBP	64 (58.0–70.0)	63.5 (55.5–72)	0.988
Respiratory rate	20 (20.0–21.0)	20 (18.0–20.0)	0.096
Heart rate	89 (78.0–101.0)	90 (80.0–98.0)	0.948

IQR, interquartile range; ASA, American Society of anesthesiologists; OSAS, obstructive sleep apnea syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2 Raw comparisons of intraoperative vital signs between oxycodone and non-oxycodone group

Variables	Non-oxycodone (n=69)	Oxycodone (n=25)	P
Minimum SPO_2 (%)	100 [99–100]	100 [98–100]	0.746
$EtCO_{2min}$	35 [32–37]	35 [33–38]	0.338
$EtCO_{2max}$	38 [35–39]	37.5 (35–42.5)	0.564
Minutes after starting operation (min)			
HR 5	81.5 (72–99.3)	85 [79–100]	0.218
HR 10	82 (67.8–96.3)	85 [77–90]	0.400
HR 20	82 (64–99.5)	90 (80.5–98)	0.159
HR 30	79 [60–95]	87 (82–99.5)	0.108
HR 60	74.5 (57–92.3)	89.5 (75.3–98.5)	0.532
SBP 5	107 [98–119]	106 [98–112]	0.683
DBP 5	60 (47.5–63.5)	58 [53–64]	0.737
SBP 10	106 [98–116]	102 [95–111]	0.265
DBP 10	57 [48–63]	58 [43–62]	0.710
SBP 20	107 [98–118]	102 (93.5–111)	0.453
DBP 20	59 [49–74]	55 (43.5–63.5)	0.379
SBP 30	111 (95.5–118)	110 (103–117.5)	0.830
DBP 30	60 (49–70.5)	60 (51.5–71)	0.775
SBP 60	110 (100.8–119.5)	121 (117.8–128.8)	0.228
DBP 60	65 (54–73.3)	76 [67–82]	0.201

HR, hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

oxycodone group. However, the statistical significance of the difference in diagnosis/surgical type was not reached. Vital signs on admission were not significantly different between the two groups. However, the control group appeared to have higher temperature [36.7 (36.5–36.9) *vs.* 36.5 (36.3–36.8); P=0.06] and respiratory rate {20 [20–21] *vs.* 20 [18–20]; P=0.096} than the oxycodone group.

Because we failed to identify covariates that were significantly associated with oxycodone use, propensity score matching was not adopted. During operation we monitored blood pressure and heart rate consecutively and found there was no difference between oxycodone and control group at 5, 10, 20, 30, 60 minutes after starting operation (*Table 2*). The SPO2 and EtCO2 were both maintained at a safe range. *Figure 2* shows the trends of heart rate after starting operation, stratified by oxycodone and control groups. The mean heart rate was slightly higher in the oxycodone group over the entire operation course. However, the standard deviation (dashed line, colors indicate different groups) overlapped with each other. *Figure 3* shows the trends of SBP and DBP over the course of operation. There was no significant difference between oxycodone and control groups.

The efficacy of oxycodone could be assessed by the intraoperative use of analgesics and propofol, as well as the postoperative analgesic requirement (*Table 3*). The propofol {20 [15–20] *vs.* 16 [15–25] mL/hr; P=0.582} and ramifentanil {15 [12–20] *vs.* 15 [12–20] mL/hr; P=0.985} requirements were similar between both groups. Postoperative analgesic uses were slightly higher in the control group than oxycodone group (27.6% *vs.* 20.0%; P=0.636). The incidence of adverse events including nausea, vomiting tended to be higher in the control group (26.1% *vs.* 12%; P=0.147).

Discussion

The pilot study showed that oxycodone was able to provide

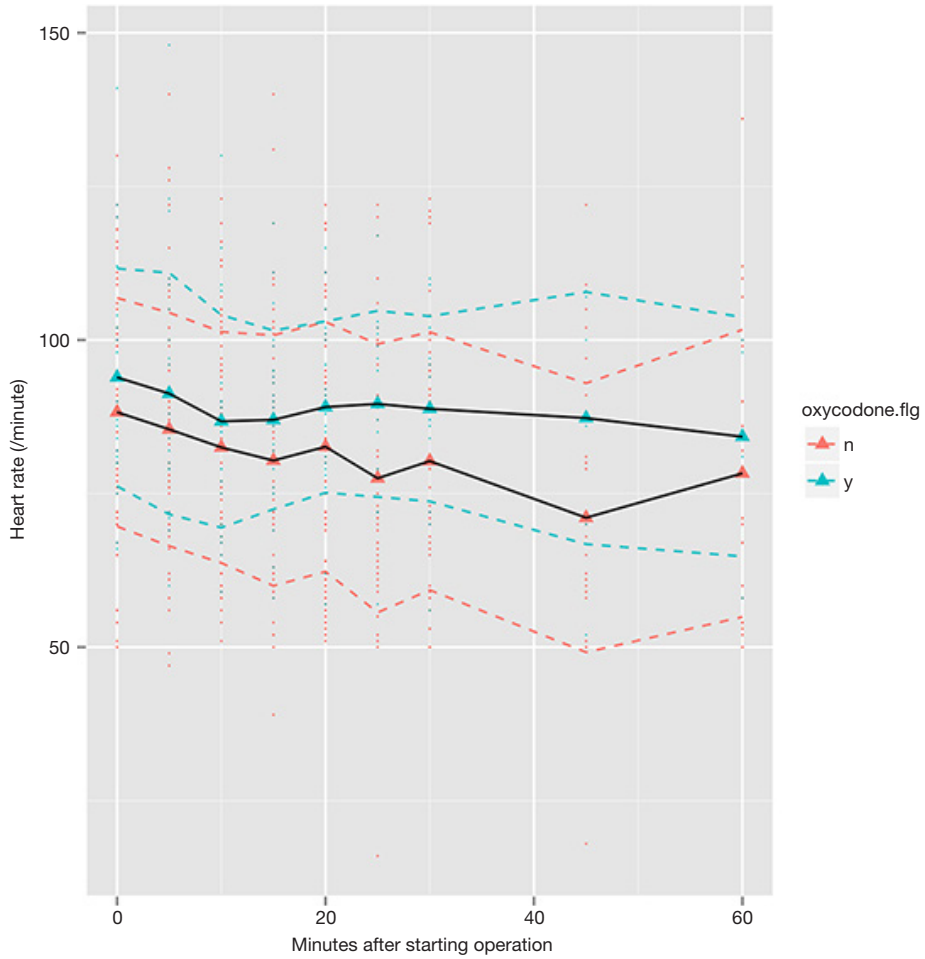

Figure 2 Trends of heart rate after starting operation, stratified by oxycodone and control groups. The mean heart rate was slightly higher in the oxycodone group over the entire operation course. However, the standard deviation (dashed line, colors indicate different groups) overlapped with each other.

potent analgesic effects during and after operation, and the effect was comparable to the sulfentanil. This is the first study reporting the use of oxycodone for general anesthesia, which provided an alternative analgesic for pediatric anesthesia. However, the study is limited by its retrospective design and small sample size. The promising results of the study provided rationale for designing a randomized controlled trial to explore whether oxycodone can provide additional benefits in pediatric patients undergoing general anesthesia.

In a recent small study, Wang and coworkers compared preemptive analgesic effect of oxycodone and control (normal saline) and found that oxycodone significantly reduced intraoperative hazard ratio (HR) and mean arterial pressure (MAP), and postoperative VAS scores (17). Postoperative tramadol requirement was also lower in the oxycodone group. The message from this study is that oxycodone can provide analgesic effect, but it was not compared to other more commonly used drugs such as sulfentanil. Our study compared oxycodone with sulfentanil as the major analgesics and found that the analgesic effects were similar. When oxycodone was given immediately before the end of surgery or as PCA, it could provide more potent analgesic effect than morphine for visceral pain (10,13,16). Other study showed similar analgesic effect between oxycodone and morphine (15). However, there is evidence that postoperative use of oxycodone is associated with more adverse events (14). This is in contrast to the present results, which suggested lower rate of adverse events in children receiving oxycodone.

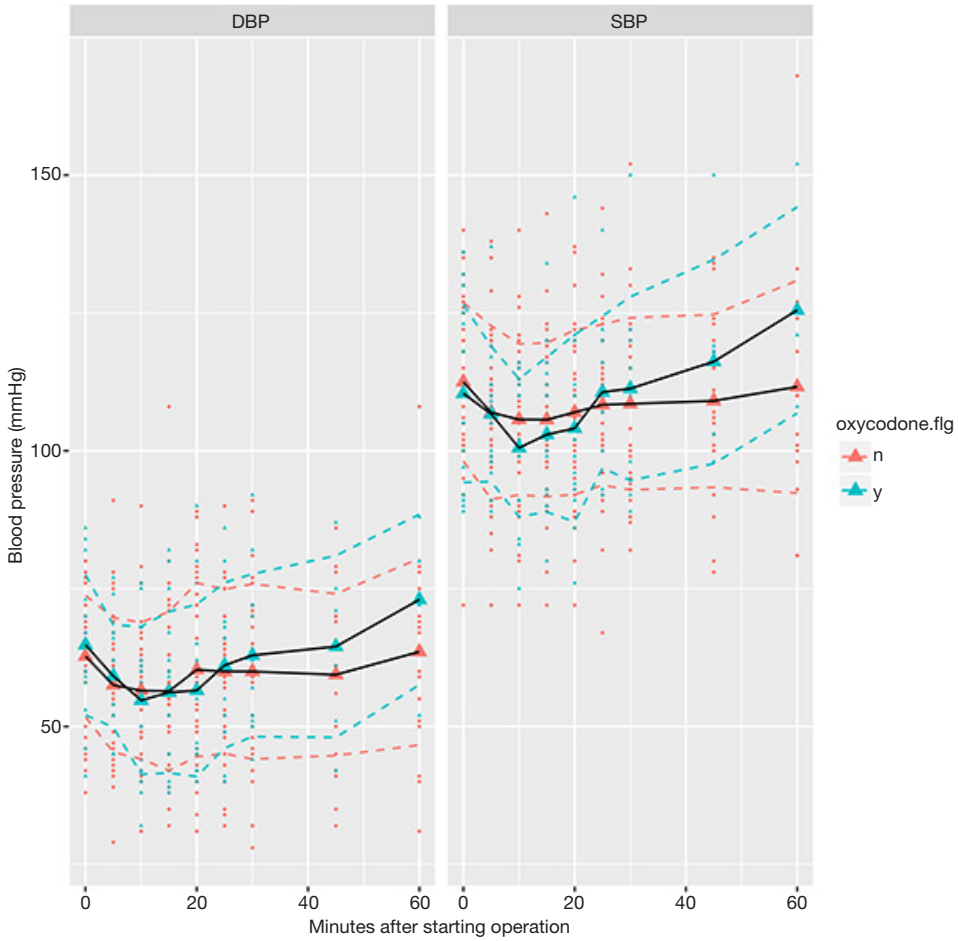

Figure 3 Trends of systolic blood pressure and diastolic blood pressure over the course of operation. There was no significant difference between oxycodone and control groups. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Comparisons of analgesic use between oxycodone and non-oxycodone group

Variables	Non-oxycodone (n=69)	Oxycodone (n=25)	P
Maintain propofol (mL/hr)	20 [15–20]	16 [15–25]	0.582
Maintain ramifentanil (1 mg/50 mL; mL/hr)	15 [12–20]	15 [12–20]	0.985
Postoperative analgesic use (No. %)	19 (27.6%)	5 (20.0%)	0.636
Adverse events	18 (26.1%)	3 (12%)	0.147

The above-mentioned studies reporting analgesic effect of oxycodone were all performed in adult population, and oxycodone was given primarily after surgery for postoperative pain control. There is no report on the intravenous use of oxycodone for general anesthesia in children, partly because pharmacokinetics of oxycodone varied substantially in young children (21). Therefore, there is no data on the efficacy and safety of oxycodone for pediatric anesthesia. There are studies reported on postoperative oxycodone use for pediatric patients. One study involving 18 children showed that oxycodone appeared to cause greater ventilator depression (19). The greatest concentration of oxycodone appeared at 8 minutes after bolus injection. The administration way of oxycodone was similar to our study. The greatest respiratory depression occurred at 8 minutes after injection, during which our children were under general anesthesia and the respiration was controlled by mechanical ventilation. That was why respiratory side effect of oxycodone was not observed in our

study. Other study showed that IV oxycodone administered postoperatively could provide supplementary analgesic effect for children (20).

Several limitations of the study need to be mentioned. First, the study was retrospective in nature and there could be selection bias. However, all available baseline demographic and clinical variables were comparable between oxycodone and control groups. At the design stage, we intended to use propensity score matching to exclude confounders. Second, the study is small in sample size and is prone to random errors. Similarly, the statistical power is also limited. Postoperative analgesic use and adverse events tended to be lower in the oxycodone group, but statistical significance was not reached. If statistical power is responsible for this insignificance, further studies with large sample size are mandatory. Third, patients included in our study are heterogeneous. There is evidence that oxycodone may have better analgesic effect for visceral pain. Therefore, further studies restricted to certain types of surgery can have greater statistical power to detect biological efficacy of oxycodone.

In conclusion, the study reported for the first time intravenous use of oxycodone for general anesthesia in pediatric patients. The results showed that oxycodone had comparable analgesic effect to sulfentanil, and tended to have lower postoperative analgesic requirement and less adverse events. Randomized controlled trials are mandatory to confirm the efficacy and safety of oxycodone in pediatric patients.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Review Board of Jinhua Municipal Central Hospital on October 10th, 2015 (approval code: 2015-041). Informed consent was waived due to retrospective nature of the study.

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