Int J Clin Exp Med 2020;13(8):6115-6121
www.ijcem.com /ISSN:1940-5901/IJCEM0109750

Original Article

The effect of oxycodone titration on analgesia after spinal surgery

Xiyue Zhao[1], Qingquan He[2], Enyi Qiu[3], Lei Chen[1], Xuzhong Xu[1], Xiuling Jin[1]

[1]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China; [2]Department of Anesthesiology, Taizhou Cancer Hospital, Wenling, Zhejiang, China; [3]Department of Radiation Oncology, Wenzhou Central Hospital, Wenzhou, Zhejiang, China

Received February 24, 2020; Accepted March 19, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: *Objective*: This study sought to determine the efficacy and safety of intravenous oxycodone titration in the recovery room after anesthesia for spinal surgery in comparison to morphine. *Methods:* 138 patients with elective spinal anesthesia underwent elective general anesthesia, either ASAI or II and were divided into two groups: the oxycodone group (group Q, n=69) and the morphine group (group M, n=69). All the patients received a pain assessment after they were revived using the visual analogue scale (VAS). Their mean arterial pressure, heart rates, respiratory rates, and pulse oximetry were recorded along with the total doses, number of times, and frequency of the intervention from the first titration to the last. In addition, the VAS scores, sedation RSS scores, and the occurrence of adverse reactions such as nausea, vomiting, itching, lethargy, urinary retention, and severe respiratory depression within 4 hours after the patient started titration were observed and recorded. *Results:* The doses and frequencies of titration in group Q were significantly lower than those in group M ($P<0.01$). The incidence of nausea in the group Q was significantly reduced compared to the incidence in group M ($P<0.05$), but there was no difference in vomiting between the two groups ($P>0.05$). No serious adverse reactions occurred during the titration. *Conclusion:* Intravenous oxycodone titration analgesia presents a markedly rapid effect of pain relief in patients undergoing spinal surgery, compared to morphine, with a reduced dosage and incidence of nausea.

Keywords: Morphine, oxycodone, titration, recovery room after anesthesia, postoperative analgesia, spinal surgery

Introduction

The fifth vital sign, pain has always been the focus of anesthesiologists. In particular, pain relief post operation has been an important task. Although the clinical application of non-opioid analgesics is gradually increasing, opioids are still the main drug for relieving pain in the early postoperative period [1]. Among the numerous postoperative analgesia regimens, morphine titration analgesia has been widely used as the gold standard for postoperative analgesia in all types of surgery. In the post-anesthesia Care Unit (PACU), the intravenous infusion of small dose of morphine can rapidly lead to pain relief through an accumulating effect [2]. However, due to the limitations of the pharmacological properties of morphine, there are several shortcomings: first, the onset time of morphine is usually slower than that of fat-soluble opioids such as fentanyl and sufentanil.

Second, it takes a long time to completely relieve pain. Although the two intervals before and after the titration are very short (5 min), the time of complete pain relief is 15 min (range: 5-60 min) [3]. Third, in the process of pain relief, the relationship between the overall VAS score and time do not seem to be linear but rather nonlinear actually [4]. Therefore, during the titration, the VAS score usually does not change significantly until the cumulative dose of morphine titration reaches the effect of pain relief. Finally, this technology requires a lot of time for PACU nurses [4].

Oxycodone is an opioid analgesic. It is characterized as a pure opioid μ, a κ receptor agonist. The κ receptor is distributed in the brain, brain stem, and spinal cord. The agonistic κ receptor

can produce analgesia and a sedative effect, and the incidence of respiratory depression is frequently lower than it is with the simple μ receptor. Its structure and pharmacological action are similar to morphine, and the equivalent dose of morphine is easy to convert. However, oxycodone is more prone to pass the blood-brain barrier compared to morphine [5, 6], so it is ubiquitously recognized as having a faster onset and a lasting effect. In addition, it is especially suitable for the titration of analgesics in patients with acute pain who require rapid relief [7]. In recent years, it has been shown that oxycodone may have an advantage over morphine in postoperative analgesic effects with few side effects [8].

In PACU, morphine titration is generally used for postoperative analgesia [9]. The application of oxycodone titration in PACU for postoperative analgesia has not been reported. This study was thus undertaken to determine the efficacy and safety of intravenous oxycodone titration on analgesia after spinal surgery, using the evaluation of VAS scores, sedation RSS scores, and the adverse reactions, seeking to open new avenues for future anesthesia regimens in addition to morphine.

Materials and methods

Research cohort

The study was approved by the hospital ethics committee and all the patients enrolled were required to sign an informed consent form. 138 patients who received spinal surgery were enrolled at the First Affiliated Hospital of Wenzhou Medical University.

Inclusion and exclusion criteria

The inclusion criteria included adult patients, aged 18 to 75, with American Society of Anesthesiologists scores I tolI, body weight 45-80 kg, body mass index (BMI) <30 kg/m^2, and scheduled for spinal surgery. All the patients had to have normal coagulation, liver and kidney function, and were contacted one day prior to their surgery to make sure they understand the rules of analgesia and the criteria for understanding the VAS scores. The exclusion criteria were: history of previous lumbar spinal surgery (whatever the level), an expected duration of the surgery >3 hours, emergency surgery, pregnancy, breastfeeding, coagulopathy, bronchial asthma, chronic obstructive pulmonary disease, pulmonary heart disease, intracranial hypertension, or craniocerebral trauma, World Health Organization level III opioid current medication, drug addiction, the intake of either glucocorticoid or gabapentinoid treatment within the 48 hours before surgery, allergy or other contraindication to the molecules used in the protocol, any cognitive impairment that might interfere with informed consent, or the collection of endpoints, intraoperative major bleeding or changes in surgical procedures, based on a previous study [10].

Grouping

138 patients undergoing spinal surgery were equally and randomly assigned into the morphine group (the M group) or the oxycodone group (the Q group), the doses of morphine and oxycodone were 3 mg per dose, with an interval of 5 min.

Anesthesia method

Prior to the surgery, the analgesia program was interpreted and the use of the visual analogue scale (VAS) (0-100 mm, hand-held slider type) [11] were explained to the patients. The patients did not take any premedication. An IV was started in each patient, and their blood pressure, heart rate (HR), pulse oximetry (SPO_2), end-tidal carbon dioxide partial pressure, and electrocardiogram (ECG) were monitored. The anesthesia induction was performed using propofol 1.5-2 mg/kg, sufentanil 0.3 μg/kg, and rocuronium 0.9 mg/kg. The patients were administered muscle relaxation after the oral intubation, to ensure the tracheal intubation. $PETCO_2$ 35-45 mmHg, the intraoperative intravenous infusion of propofol 2-4 mg/kg/h, remifentanil 8-12 μg/kg/h, inhaled sevoflurane (content maintained at 0.4~0.6 MAC) were performed to maintain mechanical ventilation and anesthesia. An appropriate amount of sufentanil and rocuronium was added to sustain moderate analgesia and muscle relaxation one hour before the end of the surgery. 50 mg of intravenous kay was administered half an hour before the end of the operation as well. After the extubation indication was shown, the tube was pulled into the PACU.

Titration of drugs and personnel preparation

An anesthesiologist who did not participate in the test had marked on the syringe according to a previously-determined, randomly assigned number, and the test drug was diluted to 10 ml (1 mg/ml) with 0.9% saline. The diluted drug was given to another patient. The anesthesia nurse responsible for the titration (the anesthesia nurse was blinded to the actual name and grouping of the titrated drug), the VAS scores and records were completed by the nurse responsible for the titration; the follow-up was performed by a senior anesthesiologist, and the anesthesiologist and patients who received the titration analgesia were blinded to the experimental design, including the test drugs and grouping.

Titration method

The patient was sent to the PACU after extubation, and the pain assessment was performed after the patient woke up. The VAS (0-100 mm) pain score was evaluated. When the VAS was greater than 30 mm, intravenous oxycodone 3 ml (1 mg/ml) or morphine 3 ml (1 mg/ml) were administered. After a 5 min interval, the VAS score was determined again, and if it was still greater than 30 mm, 3 ml of the test drug was further provided until the VAS score was lower than or equal to 30 mm. If serious adverse reactions occurred, the titration was terminated. The mean arterial pressure (MAP), heart rates (HR), respiratory rates (RR), and pulse oximetry (SpO_2) of the patients were monitored during the titration.

Titration termination standard and treatment plan

(1) The patient's VAS score was less than or equal to 30 mm; (2) The patient had excessive sedation during the titration (the Ramsay score was greater than 4 points), SpO_2 was less than 92% (in the case of nasal catheter oxygen inhalation, 3 L/min). If the respiratory rate was less than 10 secondary/minute, or if severe nausea and vomiting, dizziness, headache, itching and other adverse reactions appeared, the administration was immediately stopped. If the patient experienced severe respiratory depression, intravenous naloxone was administered immediately until the respiratory rate was greater than 12 beats/min and the SpO_2 level was greater than 95% [12]; (3) The patient was administered the drug 7 times (morphine 21 mg or oxycodone 21 mg), and if the patient's VAS score was still greater than 30 mm, then other drugs were used to relieve pain [13].

Out of the PACU standard

Before leaving the PACU, the patient was scored by an anesthesiologist according to the Aldrete criteria [14] and at least 10 points were required, without vomiting, severe pain, or surgical bleeding, and then the patient was able to return to the ward with the approval of the PACU supervisor.

Observation indicators and data collection

Each patient's clinical data were recorded, including age, gender, body mass index, ASA grade, and duration of surgery.

Each patient's hemodynamics, including mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and pulse at five time points immediately before the first titration (T0) and after 30 min, 1 h, 2 h, 3 h, and 4 h were recorded. The oxygen saturation (SpO_2) index, which consisted of the total dose, number, and the length of time from the first titration to the end, as well as the VAS scores immediately before the start of titration (T0) and the following five time points (represented by T1, T2, T3, T4, T5, respectively), along with the sedation RSS score within 4 hours after the patient started titration (2-4 was classified as sedation-satisfactory and greater than 4 was classified as sedation-over) were observed.

The Ramsay sedation score (RSS) criteria [15] are: 1 point, not quiet, irritability; 2 points, quiet cooperation; 3 points, lethargy, can listen to instructions; 4 points, sleep state, but can wake up; 5 points, the call was slow; 6 points, deep sleep, calling was unable to wake up the patient.

The visual analogue scale (VAS) criteria [16] are: 0 indicates no pain, 100 mm indicates unbearable severe pain, 10-30 mm indicates mild pain, >30-60 mm indicates moderate pain, >60-100 mm indicates severe pain.

The occurrences of adverse reactions such as nausea, vomiting, itching, lethargy, urinary retention, and severe respiratory depression within

Table 1. Comparison of the general patient data (n=69)

Group	Age	Gender (M/F)	BMI (kg/m^2)	ASA (I/II)	Time of surgery (min)
M	59±14	42/27	23.1±4.8	24/45	131±45
Q	58±12	39/30	23.5±4.3	29/40	134±39
P value	0.65	0.60	0.61	0.38	0.68

Table 2. Comparison of the doses, frequencies, and titration times in the two groups (n=69) (mean ± standard deviation)

Group	Dose (mg)	Times (range)	Time (min)
M	12.1±2.7	2.7±0.6	21.5±2.6
Q	10.8±2.5	2.5±0.7	20.6±2.4
P value	0.0039*	0.074	0.036*

Compared with group M, *P<0.05.

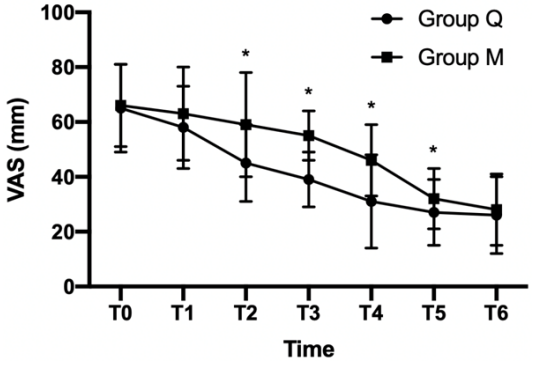

Figure 1. The relationship between the analgesic time points of titration and the VAS scores. Compared with the M group, *P<0.05.

4 hours after the patient started titration were recorded.

Statistical analysis

The data analysis was performed using SPSS 15.0 software. The data in this study were presented as the mean ± standard deviation. T tests were used for the intergroup comparisons, and chi-square tests were used for the enumeration data. The continuous data from multiple groups were analyzed using one-way ANOVA, using Tukey's post hoc test. *P*-values <0.05 were considered statistically significant.

Results

General information

There were no significant differences in terms of gender, age, BMI, ASA grade, or length of surgery between group M and group Q (P>0.05) (**Table 1**).

Dosing, frequency, and time of the two groups

Compared with group M, the dose and time required for the pain relief in the group Q were significantly reduced (P<0.01) (**Table 2**).

The relationship between titration analgesia and the VAS score

Before the titration, the VAS score of group M was 66±15 mm, and the VAS score of group Q was 65±16 mm. There was no significant difference between the two groups (P>0.05). After the drug administration, the VAS scores at the following time points of titration analgesia of group Q was significantly lower than it was in group M at the same time point (P<0.05) (**Figure 1**).

Changes in MAP, HR, SpO_2, and RR

There were no significant differences in the MAP, HR, SpO_2 and RR levels in the two groups at each time point (P>0.05) (**Table 3**). Compared with the baseline values, the respiratory rate (RR) of the patients in group M decreased significantly at 30 min, 1 h, and 2 h (P<0.05) (**Table 3**). The respiratory rate of the patients in group Q decreased significantly at 30 min, 1 h, and 2 h (P<0.05) (**Table 3**).

Adverse reactions

Compared with group M, the incidence of nausea in group Q was significantly reduced (P<0.05). There was no significant difference in the incidence of vomiting between the two groups (P>0.05) (**Table 4**).

During the PACU observation period after the end of the intravenous titration, SpO_2 decreased to 94% or less in 5 minutes after the end of the titration in group M. The patient responded such that the SpO_2 recovered to 97% after 3 minutes of oxygen inhalation.

In group M, 16 patients had RSS scores of 3-4 after the titration, and 10 patients in the Q group had RSS scores of 3-4, and the difference was not statistically significant (P>0.05) (**Table 4**). There were no patients with exces-

Table 3. Comparison of the MAP, HR, SpO_2 and RR in the two groups (n=69)

	Group	Baseline	30 min	1 h	2 h	3 h	4 h
MAP (mmhg)	M	107±15	93±13	95±19	95±18	96±15	98±19
	Q	105±16	92±19	93±18	92±17	94±14	95±13
HR (times/min)	M	78±17	71±14	70±19	72±15	74±15	73±16
	Q	79±15	70±18	72±14	71±18	73±15	72±12
SpO_2 (%)	M	99.0±1.4	99.1±1.6	99.3±1.3	99.2±1.2	99.1±1.5	99.2±1.3
	Q	99.2±1.6	99.1±1.9	99.2±1.6	99.3±1.8	99.5±1.5	99.4±1.8
RR (times/min)	M	17.8±1.7	16.2±1.8*	16.6±2.8*	16.5±2.3*	17.1±2.5	17.3±2.6
	Q	17.9±1.8	16.3±2.1*	16.6±2.2*	16.9±2.8*	17.4±2.4	17.5±2.0

Compared with the baseline value, *P<0.05.

Table 4. The number of adverse reactions in both groups (the incidence rate)

Adverse events	M (n=69)	Q (n=69)	*P* value
Nausea	29 (42%)	10 (15%)	0.0003
Vomiting	11 (16%)	8 (12%)	0.46
Itching	5 (7%)	4 (6%)	0.73
Urinary retention	3 (4%)	4 (6%)	0.70
Allergy	3 (4%)	1 (1%)	0.31
Calm	16 (23%)	10 (15%)	0.19
Excessive sedation	0 (0%)	0 (0%)	1
Respiratory depression	4 (6%)	2 (3%)	0.40

sive sedation (an RSS score greater than 4 points). Also, there were no significant differences in itching, urine retention, or allergic reactions in the two groups (P>0.05) (**Table 4**).

Discussion

Our results showed that intravenous oxycodone titration significantly shortens a patient's pain time and markedly reduces the dose required for titration in pain relief compared with intravenous morphine titration in PACU. The incidence of nausea reactions caused by oxycodone was evidently decreased compared to that of morphine.

Traditional spinal surgery often comprises subcutaneous tissue and an extensive dissection of bones and ligaments, resulting in considerable postoperative pain. Severe pain usually lasts for 3 days, or even weeks [17], so it is necessary to provide complete analgesia in the early stages of surgery to avoid the possible switch to chronic pain. Spinal surgery mostly causes physical pain and even severe pain equivalent to a VAS score of 7 or more. For ethical reasons, we gave intravenous injections of 50 mg of flurbiprofen axetil 30 minutes before the end of the operation to prevent the patient from waking up due to severe pain, which may influence the prognosis of the patient.

Oxycodone has been used in clinic since 1997 and is often used to treat acute pain in Northern Europe. Currently, intravenous oxycodone has been considered a very effective way to treat severe pain in the early stages of orthopedics. Its analgesic effects have been reported in a multitude of studies, such as in the operations of shoulder angioplasty [18], spinal surgery [19, 20], hip joints [21], and knee joints [22] after analgesia. Xu Xing et al. [23] showed that the use of oxycodone hydrochloride in patients with orthopedic surgery after PCIA had an analgesic effect that was similar to morphine. Moreover, it can safely and effectively relieve pain, and reduce the incidence of nausea and vomiting during analgesia compared to morphine. Consistently, we found that in the analgesia after spinal surgery, oxycodone presents a considerably fast onset time, along with a low dose and few side effects compared with morphine. In another study of lumbar disc surgery, the oral administration of 20 mg of oxycodone sustained-release tablets twice daily significantly reduced morphine requirements during the first 24 hours after surgery. The effect of the same amount was also shown to last 25-48 hours after surgery (intravenous PCA morphine after oxycodone was 13 mg vs. morphine in the placebo group was 33 mg). In both groups, the patients received intravenous acetaminophen as a basic analgesia every 6 hours. The additional administration of oxycodone can reduce the incidence of postoperative nausea and vomiting and facilitate the recovery of intestinal function, which is in line with our data [24].

However, the limitation in this study still exists, namely that the analgesic efficacy of different doses of oxycodone should be further validated, and the possibility of a combination strategy with distinct types of analgesic drugs ought to be explored in the future.

Conclusion

In summary, oxycodone, a titration analgesic used in the PACU, quickly and effectively relieves postoperative pain and has relatively few side effects, providing new leads for the analgesic regime.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiuling Jin, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, South of Shangcai Village, Nanbaixiang Street, Ouhai District, Wenzhou 325000, Zhejiang, China. Tel: +86-0577-55579095; Fax: +86-0577-55579095; E-mail: xiulingjin224@163.com

References

[1] White PF and Kehlet H. Improving postoperative pain management: what are the unresolved issues? Anesthesiology 2010; 112: 220-225.

[2] Pöyhiä R. Opioids in anaesthesia: a questionnaire survey in Finland. Eur J Anaesthesiol 1994; 11: 221-230.

[3] Aubrun F, Monsel S, Langeron O, Coriat P and Riou B. Postoperative titration of intravenous morphine. Eur J Anaesthesiol 2001; 18: 159-165.

[4] Evans G, Stavrinos P, Dawe S, Harvie M, Wilson M, Maxwell A, Brentnall A, Cuzick J, Astley S and Howell A. Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. Anesthesiology 2003; 98: 1415-1421.

[5] Boström E, Hammarlund-Udenaes M and Simonsson US. Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine. Anesthesiology 2008; 108: 495-505.

[6] Boström E, Simonsson US and Hammarlund-Udenaes M. In vivo blood-brain barrier transport of oxycodone in the rat: indications for active influx and implications for pharmacokinetics/pharmacodynamics. Drug Metab Dispos 2006; 34: 1624-1631.

[7] King SJ, Reid C, Forbes K and Hanks G. A systematic review of oxycodone in the management of cancer pain. Palliat Med 2011; 25: 454-470.

[8] Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. Anesthesiology 2006; 104: 835-846.

[9] Joppich R, Richards P, Kelen R, Stern W, Zarghooni K, Otto C, Böhmer A, Petzke F, Treptau T and Lefering R. Analgesic efficacy and tolerability of intravenous morphine versus combined intravenous morphine and oxycodone in a 2-center, randomized, double-blind, pilot trial of patients with moderate to severe pain after total hip replacement. Clin Ther 2012; 34: 1751-1760.

[10] Momon A, Verdier B, Dolomie JO, Gardette M, Pereira B, Curt I and Duale C. A single preoperative administration of dexamethasone, low-dose pregabalin, or a combination of the 2, in spinal surgery, does not provide a better analgesia than a multimodal analgesic protocol alone. Clin J Pain 2019; 35: 594-601.

[11] Huskisson EC. Measurement of pain. Lancet 1974; 2: 1127-1131.

[12] Aubrun F, Mazoit JX and Riou B. Postoperative intravenous morphine titration. Br J Anaesth 2012; 108: 193-201.

[13] Aubrun F, Valade N, Coriat P and Riou B. Predictive factors of severe postoperative pain in the postanesthesia care unit. Anesth Analg 2008; 106: 1535-41, table of contents.

[14] Aldrete JA and Kroulik D. A postanesthetic recovery score. Anesth Analg 1970; 49: 924-34.

[15] Ramsay MA, Savege TM, Simpson BR and Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974; 2: 656-659.

[16] Myles PS, Troedel S, Boquest M and Reeves M. The pain visual analog scale: is it linear or nonlinear? Anesth Analg 1999; 89: 1517-1520.

[17] Bianconi M, Ferraro L, Ricci R, Zanoli G, Antonelli T, Giulia B, Guberti A and Massari L. The pharmacokinetics and efficacy of ropivacaine continuous wound instillation after spine fusion surgery. Anesth Analg 2004; 98: 166-172.

[18] Laurila PA, Löppönen A, Kangas-Saarela T, Flinkkilä T and Salomäki TE. Interscalene brachial plexus block is superior to subacromial bursa block after arthroscopic shoulder surgery. Acta Anaesthesiol Scand 2002; 46: 1031-1036.

[19] Blumenthal S, Min K, Marquardt M and Borgeat A. Postoperative intravenous morphine consumption, pain scores, and side effects with perioperative oral controlled-release oxycodone after lumbar discectomy. Anesth Analg 2007; 105: 233-237.

[20] Rajpal S, Gordon DB, Pellino TA, Strayer AL, Brost D, Trost GR, Zdeblick TA and Resnick DK. Comparison of perioperative oral multimodal analgesia versus IV PCA for spine surgery. J Spinal Disord Tech 2010; 23: 139-145.
[21] Rothwell MP, Pearson D, Hunter JD, Mitchell PA, Graham-Woollard T, Goodwin L and Dunn G. Constipation after total hip replacement may be lower with oral opioid analgesia than with intravenous opioid analgesia. Br J Anaesth 2012; 108: 528-529.
[22] Silvanto M, Lappi M and Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. Acta Anaesthesiol Scand 2002; 46: 322-328.
[23] Xu X, Wu X, Xue Z, Wang X, Xiong L, Tian M and Yao C. Efficacy and safety of oxycodone hydrochloride injection for postoperative analgesia in patients with general anesthesia: prospective, randomized, blinded, multicenter, positive control clinical study. Chinese Journal of Anesthesiology 2013; 33: 269-274.
[24] Singla N, Barrett T, Sisk L, Kostenbader K and Young J. Assessment of the safety and efficacy of extended-release oxycodone/acetaminophen, for 14 days postsurgery. Curr Med Res Opin 2014; 30: 2571-2578.