Int J Clin Exp Med 2016;9(9):18579-18582
www.ijcem.com /ISSN:1940-5901/IJCEM0031875

Original Article

The effect of hydromorphone for postoperative analgesia in children

Fang Chen*, Huacheng Liu*, Gaojiao Zhang, Zhilian Huang, Xutong Zhang, Yi Lu, Jun Li, Qingquan Lian, Wangning Shangguan

*Department of Anesthesiology, Critical Care and Pain Medicine, The 2nd Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China. *Equal contributors.*

Received May 8, 2016; Accepted July 26, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Despite commonly used in postoperative analgesia, there are limited and inconclusive data for the comparison between morphine and hydromorphone in pediatric population. In this study, we evaluated the efficacy of morphine and hydromorphone intravenously for postoperative analgesia in children. Sixty patients were enrolled and randomly received bolus morphine (group M, 50 μg/kg), or hydromorphone (group H, 7 μg/kg) for postoperative analgesia (30 cases per group). VAS at rest and with cough was assessed at the post-operative 1, 2, 3, 6 and 24 h. The frequency use of morphine or hydromorphone and cumulative dose of other opioid, e.g. fentanyl use and their related side effects were recorded for 48 h postoperatively. The satisfaction of analgesia given by young patients or their parents was analyzed. Compared with the group M, the onset time of VAS < 4 cm was shorter ($P < 0.05$), and the frequency of study drug use in PACU was less ($P < 0.05$) in the group H; the resting VAS scores at 1, 2, 3, 6, 24 h after bolus injection were no significant differences between two groups, while the coughing VAS scores at 2, 3, 6 h after bolus injection were lower in the group H. Eight patients in group M and two patients in group H need extra fentanyl to relieve pain ($P < 0.05$) during PACU stay. There were no significant differences in adverse events and satisfaction score of analgesia between two groups. Our results demonstrate that hydromorphone can be effectively used for postoperative pain relief in young patients.

Keywords: Morphine, hydromorphone, postoperative analgesia, children

Introduction

Hydromorphone is a semisynthetic derivative of morphine. Both drugs exert their analgesic effect at μ-opioid receptors and have typical opioid-associated side effects including respiratory depression, nausea, vomiting and pruritus [1-3]. Despite commonly used in postoperative analgesia, there are limited and inconclusive data for the comparison between morphine and hydromorphone and, furthermore, rare informative data are available in pediatric population [2, 4]. It has been suggested switching morphine to hydromorphone for postoperative analgesia in pediatrics for reasons of pruritus and inadequate pain control [2]. However, more prospective studies are needed to determine their comparative efficacy and safety profile. In this prospective study, we aimed to compare the postoperative pain relief efficacy and systemic side effects between morphine and hydromorphine in young patient population.

Materials and methods

Patients' selection

This clinical trial was registered at http://www.chictr.org.cn; the registration number is ChiCTR-IPR-14005345. After obtained informed written consent from all parents, sixty ASA I or II school-age children, aged 7-14 yr of normal intelligence, scheduled for elective ENT, and orthopedic surgery for lasting from 30 min to 2 hrs, who required intravenous administration of opioid for postoperative analgesia, were randomly enrolled into the morphine group (group M) or hydromorphone group (group H).

The exclusion criteria included: body mass index (BMI) < 13.5 kg/m^2 or > 31 kg/m^2; severe respiratory or cardiovascular system disease and hepatic or renal insufficiency; a history of neuromuscular disorder; airway abnormalities; asthma; cachexia; received sedatives, anti-

Table 1. Demographic and surgical characteristics of patients

Variable	Morphine (n = 22)	Hydromorphone (n = 28)
Age (yrs)	8.7 ± 0.4	8.1 ± 0.3
Male/Female	13/9	17/11
Weight (kg)	29.6 ± 1.7	28.7 ± 1.3
Surgery types		
ENT operation	14 (63.6%)	16 (57.1%)
Orthopedic surgery	8 (36.4%)	12 (42.9%)
Duration of surgery (min)	52.6 ± 4.1	56.8 ± 3.7
Fentanyl (μg)	88.8 ± 5.2	86.0 ± 3.8
Remifentanil (μg)	613.6 ± 61.3	644.9 ± 48.9

Values are means ± SEM. There were no statistically significant differences (P > 0.05) between groups.

emetic or antipruritics 24 hrs before the operation; a history of an allergy to any opioids; diabetes; serious acid-base imbalance or electrolyte disorder; and have participated in any clinical studies within 30 days before the study.

Medication

All patients were monitored with heart rate (HR), electrocardiogram (ECG), pulse oximetry (SpO_2), non-invasive blood pressure (BP), capnometry and capnography ($P_{ET}CO_2$). A standard total intravenous anesthesia was used for all patients. Anesthesia was induced with midazolam 0.1-0.2 mg/kg, propofol 2-3 mg/kg, fentanyl 3.0 μg/kg and cisatracurium 0.15-0.2 mg/kg, maintained with propofol (3-15 $mg \cdot kg^{-1} \cdot min^{-1}$) and remifentanil (0.1-0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) continus infusion, any other drugs were excluded during the intraoperative period. After the operation finished, all patients were transferred to post anesthesia care unit (PACU). In the PACU, the patients whose visual analogue scale (VAS, 0-10 cm, 0 represents no pain and 10 represents the worst pain possible) ≥ 7 cm, were enrolled and assigned by computer-generated randomization to receive either morphine or hydromorphone postoperative administration. Morphine (LOT: H20080520, Jiangsu Nhwa Pharmaceutical Co., LTD) 50 μg/kg or hydromorphone (LOT: H20080520, Jiangsu Nhwa Pharmaceutical Co., LTD) 7 μg/kg was administered intravenously. Medications were prepared by an anesthesia nurse, all caregivers and observers were blinded to the drug administered. Opioid administration could be repeated 10 min later if necessary until VAS was < 4 cm. Patients who received three times of study drug administration and the VAS was still ≥ 4 cm were terminated from the clinical trial, and the analgesia was rescued with fentanyl 1-3 μg/kg. Patients with the Alderete score ≥ 9 then were sent back to ward.

Data collection

Patients, who received either intravenous morphine or hydromorphone for postoperative pain relief, were followed up for 48 hrs. The pain assessment started in the PACU using the VAS scale and was repeated every 5 min within 30 min after the first bolus injection of morphine or hydromorphone until the VAS < 4 cm. The onset time of VAS < 4 cm (from the first bolus injection of morphine or hydromorphone to VAS < 4 cm) was recorded. The resting and coughing VAS scores at 1, 2, 3, 6 and 24 h following the first administration were recorded as well. The frequency of opioid rotation and any side-effects such as respiratory/cardiovascular depression were recorded. Any supplementary pain relief drugs were also recorded for 48 h postoperatively. Finally, the satisfaction scores of patients or their parents for pain control were recorded (0 = extremely dissatisfied, 50 = neutral, and 100 = most satisfied).

Statistical analysis

All data are presented as mean ± SD, median plus range or number (%), as appropriate. The normal distribution of data was examined with one-factor ANOVA and Fisher's-LSD test. Fisher exact Chi-square test was used to compare gender, surgery types, and supplementary analgesics in PACU. VAS and satisfaction scores were examined with Mann-Whitney U test. Data were analyzed using SPSS software (SPSS 16.0, SPSS, Inc., Chicago, IL, USA). A p value less than 0.05 was considered as to be a significant difference.

Results

There were ten cases terminated from the clinical trial (8 cases were from group M, 2 cases from group H, $P < 0.05$), due to the inadequate analgesia in PACU. Finally, fifty patients were enrolled and their data were collected for the further analysis. There were no significant

Table 2. Comparison of resting and coughing VAS scores

Time points	Resting VAS scores		Coughing VAS scores	
	Morphine (n=22)	Hydromorphone (n=28)	Morphine (n=22)	Hydromorphone (n=28)
1 h	2 (1-2)	1 (1-2)	2 (2-3)	2 (2-3)
2 h	2 (0-2)	1 (0-2)	2 (2-3)	1 (1-2)*
3 h	1 (0-2)	1 (0-0)	1 (1-2)	1 (0-1)*
6 h	0 (0-1)	0 (0-1)	1 (1-2)	0 (0-1)*
24 h	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-0)

Values are [median (first quartile-third quartile)], *, $P < 0.05$ vs. M group.

demographic and surgical characteristics differences between the two groups (**Table 1**).

Compared with the group M, the onset time of VAS < 4 cm was shorter (20.0 ± 6.9 vs. 9.6 ± 4.5 min, $P < 0.05$), and the frequency of study drug use in PACU was less (2.3 ± 0.7 vs. 1.3 ± 0.4 times, $P < 0.05$) in the group H; the resting VAS scores at 1, 2, 3, 6, 24 h after bolus injection were no significant differences between two groups, while the coughing VAS scores at 2, 3, 6 h after bolus injection were lower in the group H (**Table 2**); the satisfaction score of analgesia were no significant differences between two groups [88 (75-100) vs. 93 (80-100)].

There was one patient had nausea and vomiting respectively in each group. There was one patient who needed aminopyrine phenacetin (tablets 1#) 24 hrs postoperatively in the ward in each group, and there was one patient had postoperatively urinary retention in the group M.

Discussion

Hydromorphone is a semisynthetic derivative of morphine and was introduced as an analgesic with less side-effect [3-7]. A potency ratio of 5-10:1 of hydromorphone relative to morphine was indicated in a previous study [4, 8]. Most of the previous reports were about hydromorphone compared with morphine for postoperative analgesia in the literatures in adult, but rare in children.

In our study, we assumed a potency ratio of 7:1 for hydromorphone to Morphine, derived from adult studies, which is also applicable to children [1]. We discovered that hydromorphone achieved a better and more rapidly pain control, with less frequency of bolus injection. It has been reported that the time to peak effect of a bolus of hydromorphone is shorter than morphine [2, 8]. This delay in attaining maximum analgesia for morphine is consistent with the hypothesis that one of the metabolites of morphine, morphine-6-glucuronide (M6G), plays a role in analgesia [2, 7]. A more rapid onset of maximum analgesia could give the patient better pain control. Some researches had reported that patients experienced relief from inadequate analgesia when switched from morphine to equivalent hydromorphone [2, 9]. In addition, other studies indicated that hydromorphone may be better suited than morphine for titration of acute analgesia [4, 10-12].

Our study demonstrated no significant difference between two drugs in side effects. Although, there is pharmacological evidence that there may be a higher incidence of side effects with morphine as compared to hydromorphone. Morphine has been shown to induce histamine release while hydromorphone has not [1, 2, 6, 13]. Histamine release may increase the incidence of one of the undesirable effects of opioids: pruritus. Additionally, Morphine has two major metabolites: morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). M6G can accumulate in patients with renal dysfunction, leading to respiratory depression and failure [14]. Hydromorphone does not form an active 6-glucuronide metabolite; however, it does have the 3-glucoronide metabolite (H3G). Both M3G and H3G could be accumulated and potentially cause opioid-induced neuroexcitation [3, 4, 8, 14-16]. One potential advantage of hydromorphone is H3G is not associated with respiratory depression mediated by the mu-2 receptor, whereas M6G is. A similar incidence of side effects between the two medications was found before [1, 4, 6-9]. A meta-analysis also showed an advantage for hydromorphone for analgesia but not for side effects [4] .

Although hydromorphone has a faster onset of maximum analgesic effect (10-20 min) than morphine [1, 10], and also it has been reported that hydromorphone could improve mood which might influence patient satisfaction [6, 8, 9], there was no difference in satisfaction score

between morphine and hydromorphone groups in our study. The reasons could be that there was no significant difference in the incidence or severity of side effects and the resting VAS scores between two groups. It might be possible that patients would have had higher satisfaction scores in hydromorphone group if our measurements occurred at the PACU owing to better and more accurate pain control assessment.

In conclusion, hydromorphone can be effectively used for postoperative pain relief in children but warrants a large sample study.

Acknowledgements

The research was funded by Wenzhou science and technology foundation of China (Y20150064), and Zhejiang provincial public welfare technology application research foundation of China (2015C33100). The authors of this article would like to thank Dr. Daqing Ma, associate professor from Faculty of Medicine, Imperial College London, and Chelsea and Westminster Hospital, for his valued assistance.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wangning Shangguan, Department of Anesthesiology, The 2nd Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China. Tel: 86-13587637891; Fax: 86-577-88002925; E-mail: sgwning@163.com

References

[1] Hong D, Flood P and Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 2008; 107: 1384-1389.

[2] DiGiusto M, Bhalla T, Martin D, Foerschler D, Jones MJ and Tobias JD. Patient-controlled analgesia in the pediatric population: morphine versus hydromorphone. J Pain Res 2014; 7: 471-475.

[3] Sarhill N, Walsh D and Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. Support Care Cancer 2014; 9: 84-96.

[4] Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D, Geisslinger G and Lotsch J. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth 2011; 107: 319-328.

[5] Miller MG, McCarthy N, O'Boyle CA and Kearney M. Continuous Subcutaneous Infusion of Morphine vs. Hydromorphone: A Controlled Trial. J Pain Symptom Manage 1999; 18: 9-16.

[6] Rapp SE, Egan KJ, Ross BK, Wild LM, Terman GW and Ching JM. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 1996; 82: 1043-1048.

[7] Collins JJ, Geake J, Grier HE, Houck CS, Thaler HT, Weinstein HJ, Twum-Danso NY and Berde CB. Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone. J Pediatr 1996; 129: 722-728.

[8] Gulur P, Koury K, Arnstein P, Lee H, McCarthy P, Coley C and Mort E. Morphine versus Hydromorphone: Does Choice of Opioid Influence Outcomes? Pain Res Treat 2015; 2015: 482081.

[9] Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. J Pain Symptom Manage 2003; 25: 169-178.

[10] Coda B, Tanaka A, Jacobson RC, Donaldson G and Chapman CR. Hydromorphone analgesia after intravenous bolus administration. Pain Res Treat 1997; 71: 41-48.

[11] Chang AK, Bijur PE, Baccelieri A and Gallagher EJ. Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: a prospective, randomized, double-blind clinical trial. Am J Geriatr Pharmacother 2009; 7: 1-10.

[12] Chang AK, Bijur PE, Meyer RH, Kenny MK, Solorzano C and Gallagher EJ. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. Ann Emerg Med 2006; 48: 164-172.

[13] Pick CG, Cheng J, Paul D and Pasternak GW. Genetic influences in opioid analgesic sensitivity in mice. Brain Res 1991; 566: 295-298.

[14] Sutter ME, Wintemute GJ, Clarke SO, Roche BM, Chenoweth JA, Gutierrez R and Albertson TE. The Changing Use of Intravenous Opioids in an Emergency Department. West J Emerg Med 2015; 16: 1079-1083.

[15] Sartori D, Lewis T, Breaud A and Clarke W. The development of a high-performance liquid chromatography-tandem mass spectrometric method for simultaneous quantification of morphine, morphine-3-beta-glucuronide, morphine-6-beta-glucuronide, hydromorphone, and normorphine in serum. Clin Biochem 2015; 48: 1283-1290.

[16] Kullgren J, Le V and Wheeler W. Incidence of hydromorphone-induced neuroexcitation in hospice patients. J Palliat Med 2013; 16: 1205-1209.