·Clinical Research·

2

Feasibility to Treat Pediatric Cancer Pain with Analgesics for Adults and Their Efficacy

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[ABSTRACT] BACKGROUND & OBJECTIVE: Lacking enough knowledge of pediatric cancer pain and pediatric dosage form of analgesics, current treatment of pediatric cancer pain in China is unsatisfactory. This study was to probe the efficacy and safety of treating pediatric cancer pain with analgesics for adults through summarizing the experience of diagnosis and treatment in Cancer Center of Sun Yet-sen University. METHODS: Basing on the components and the endurable dosage of each component for children, we formulated the appropriate dosage and usage of a few analgesics (including sustained release tablets of morphine, oxycodone and transdermal fantanyl) available in China, most of which were used in adults. Cancer pain of 139 children with newly diagnosed tumors were treated according to the World Health Organization (WHO) analgesic ladder, including 19 cases of mild pain, 41 cases of moderate pain and 79 cases of severe pain. Efficacy and adverse events were evaluated. RESULTS: Of the 139 patients, 104 (74.8%) were treated with analgesics of 1 WHO ladder step, 35 (25.2%) were treated with increased WHO ladder steps (ladder 1→2 or 2→3) or reduced WHO ladder steps (ladder 3→2 or 2→1). The total response rate for pain relief was 100%: 129 (92.8%) patients had complete relief, 7 (5.0%) had obvious relief, 3(2.2%) had moderate relief. The median time for pain control was 5 days (range, 1–12 days). Sustained release tablets of morphine, transdermal fantanyl, and sustained release tablets of oxycodone were used in 20, 28, and 40 patients, respectively. The median ages of the 3 groups were 10 (5–18), 6 (2.3–16), and 5 (2.5–16) years, respectively. The median of maximum dosages of the 3 single drugs were 20 (10–70) mg, 25 (12.5–50) μg/h, and 10 (5–30) mg, respectively. The median doses used in the 3 groups were 100 (20–360) mg, 5 (1.25–7.5) mg, and 60 (10–200) mg, respectively. The non-steroid anti-inflammatory drug-induced adverse events were nausea and vomiting with very low frequencies. The weak opioid and strong poioid drug-induced adverse events included constipation, nausea, vomiting, and somnolence, all of which were reversible. No severe adverse events, including respiratory depression and drug addiction, happened. CONCLUSIONS: The WHO ladder approach for cancer pain is appropriate for children. Currently in China, most analgesics for adults could be used for pediatric cancer pain treatment.

KEYWORDS: Neoplasm; Cancer pain; Analgesia; Children

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1. Introduction

Cancer pain is the most severe subjective symptom for pediatric cancer patients, and it can bring more physiological and psychological burdens to child patients compared to pyrexia and vomiting [1]. The therapeutic effect of pediatric cancer is superior to that of adult cancer, and approximately 70% children with cancers can obtained long term survivals. Therefore, the treatment against pediatric cancer pain is especially important. Positive and effective treatment can improve life quality of the pediatric patients, make them completely cooperate in treatments, thus doctors can try their best to cure them. Moreover, negative influence on the psychological development of children can also be avoided. However, most analgesics does not have an exclusive dosage type suitable for children. Adult dosages of morphine drugs may produce toxic or adverse events, such as respiratory inhibition or addiction in children. At present, the treatment against pediatric cancer pain in China is not satisfactory. In this study, the experiences of diagnosis and treatment against pediatric cancer pain in Cancer Center of Sun Yat-sen University were summarized, thus to investigate the safety and efficacy of adult analgesics applied to treat pediatric cancer pain.

2. Materials and Methods

2.1 General information

Between Sep. 2003 and Sep. 2006, in total 360 cases of na hve pediatric cancer patients were admitted to Cancer Center of Sun Yat-sen University. Among them, 139 cases had cancer pain at the first visit, and the occurrence rate of cancer pain was 38.6%. In these 139 cases, 99 cases were males and 40 were females. The median age was 8 years old (2 years and 4 months - 18 years), and there were 22 cases of 0-3 years, 39 cases of 4-7 years, 70 cases of 8-14 years, and eight cases of 15-18 years. In these cases with cancer pain, 45 cases had malignant lymphoma, 13 cases had acute leukemia, and 81 cases had other solid cancers. Twenty-two of these patients had received analgesic therapy before admission, but the cancer pain was not effectively controlled. No analgesics were administered to these patients within 12h.

2.2 Evaluation regimen for pediatric cancer pain

Pediatric cancer pain was evaluated according to the Diagnosis and Therapy Guidelines for Pediatric Cancer Pain (2005 version) of National Comprehensive Cancer Network (NCCN). Different evaluation methods were adopted because recognition and compliance of children at different ages are different. The degree of pain was scored as follows: 0, no pain; 1-3, mild pain; 4-6, moderate pain; 7-10, severe pain. Scale evaluation method was applied to children older than 12 years old. The degree of pain was divided into “0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10” points, “0” represented “no pain”, “10” represented “the most severe pain that could be imagined”, and the child would choose a number according to their feelings. Children of 3-12 years adopted Wong-Baker face rating scale, and the degree of pain was evaluated according to the complexions of the children. The painful complexions were represented by 5 faces (face 0, 2, 4, 6, 8 and 10, respectively); face 0 represented “no pain”, and face 10 represented “the most severe pain that could be imagined”. For children younger than 3 years old, or children could not complain for certain reasons, behavior classification was applied. Five behaviors were observed, including complexion, lower limbs, general movement, crying and screaming, consolability: 0-2 points were assigned to each behavior, and the total score of the five behaviors was 0-10 points.

2.3 Manifestations of cancer pain

Fifty-nine cases had abdominal pain, 36 cases had osteoarthrosis, 25 cases had soft tissue pain, and 19 cases had neuralgia. One hundred and eight cases could describe their pains, including 38 cases of dull pain, 26 cases of pricking pain, 20 cases of spasm pain, 15 cases of burning pain, and nine cases of pulse pain. Thirty-one cases could not describe their pains. Nineteen cases had mild pain, 41 cases had moderate pain, and 79 cases had severe pain.

2.4 Therapeutic methods

Tri-Ladder Approach (WHO) was adopted to treat cancer pain. Non-steroid anti-inflammatory drugs (NSAID) were administered to patients with light pain: acetaminophen, 10-15mg/kg every 4 h; the dose for infants was no more than 60mg/kg per day; and the dose to other children was no more than 90mg/kg, per day. Weak opioids

were chosen for patients with moderate pain, combined with or without NSAID: drocode plus acetaminophen (each tablet contained 100mg dihydrocodeine bitartrate and 500mg acetaminophen), and 1mg/kg drocode was administered every 4 h; or oxycodone plus acetaminophen were adopted (each tablet contained 5mg oxycodone and 325mg acetaminophen),, 0.15 mg/kg oxycodone was used every 4 h; or sustained-release oxycodone tablet (the minimal dosage type was 5mg/tablet, in which the sustained-release part accounted for 38%, 1.9mg) was used, the initial dose was 5mg, and the drug was administered every 12h. Because it was recommended by WHO that sustained-release oxycodone should be started at 0.05-0.15mg/kg, only children older than 2 years old (approximately with 12kg body weight) were administered. Strong opiods were chosen for patients with severe pain: sustained morphine tablet (the minimal dosage type was 10mg/tablet), the initial dose was 10mg, and the drug was administered every 12h. Because it was recommended by WHO that sustained release oxycodone should be started at 0.3-0.6 mg/kg, only children old than 4 years old (approximately with 16kg body weight) were administered; or transdermal fantanyl (the minimal dosage type was 5mg/pastet) was administered, the initial dose was 2.5 mg for patients older than 4 years old every 72h (25μg/h), and 1.25mg for patients between 2 and 4 years old every 72h (only a half of fantanyl paste was adhered to the skin). Transdermal fantanyl were stuck to chest, back, or clean and dried areas of the upper arm with no hairs, and it should be pressed with hands for 30s. Oxycodone was considered a weak opioid agalgesic (at a small dose) or strong opioid agalgesic (at a large dose). The analgesic intensity of sustained-release oxycodone was twice of that of sustained-release morphine [2], therefore it was also applied in severe pain relief, and its dose and usage were the same as described above. The doses of sustained-release morphine tablet, transdermal fantanyl and sustained-release oxycodone were adjusted every 24h according to the condition and the analgesic effect of the patient, till satisfactory results were obtained. At the same time, chemotherapy should be administered timely according to the conditions of the patient after diagnosis was confirmed.

2.5 Evaluation on relief of cancer pain

Five grades were divided, including not relieved, light relief (1/4 pain was relieved), moderate relief (1/2 pain was relieved), obvious relief (over 3/4 pain was relieved) and complete relief (cancer pain disappeared). The total effective rate = the rate of (moderate relief + obvious relif + complete relief).

2.6 Observation

The therapeutic effects and adverse events were observed. Because the adverse events of NSAID and opioids were not the same, the occurrence rates of adverse events were divided into adverse events of NSAID, weak opioids plus NSAID, or strong opioids.

3. Results

One WHO analgesic ladder step was applied to 104 cases (74.8%), and 35 (25.2%) of them had to receive upgraded or downgraded therapy of WHO analgesic ladder steps. After treatment, three cases (2.2%) had moderate relief, seven cases (5.0%) had obvious relief, and 129 cases (92.8%) had complete relief. The total response rate to analgesia was 100%. The median time for pain relief was 5 (1-12) days.

Sustained-release morphine tablet was administered to 20 cases, whose median age was 10 (5-18) years old. The median of the maximum dosages was 20mg (10-70mg), and the median of the total doses was 100mg (20-360mg). Transdermal fantanyl was used to 28 cases, whose median age was 6 years (2 years and 4 months - 16 years old). The median of the maximum dosages was 25μg (12.5-50μg), and the median of the total dose was 5mg (1.25-7.5mg). Sustained-release oxycodone tablet was administered to 40 cases, whose median age was 5 years (2 years and 6 months - 16 years old). The median of the maximum dosages was 10mg (5-30mg), and the median of the total doses was 60mg (10-200mg).

The adverse events are shown in Table 1. Only nausea and vomiting were observed in patients treated by NSAIDs, and the occurrence rates were low. Constipation, nausea, vomiting, somnolence, dizziness, dysuresia and sweating, and so on were observed in patients treated by weak and strong opioids. Constipation, nausea, vomiting and somnolence were more common. No severe adverse events, such as respiratory inhibition or addition, were observed.

Table 1 Adverse events in 139 children after cancer pain treatment [cases(%)]

Analgesic	Cases	Constipation	Nausea	Vomiting	Somnolence	Dizziness	Urinary retention	Sweating
NSAIDs	19	0 (0)	3(15.8)	1 (5.3)	0 (0)	0 (0)	0(0)	0(0)
Weak opioid drugs plus NSAIDs	32	12(37.5)	10(31.3)	6(18.8)	6(18.8)	2 (6.3)	2(6.3)	2(6.3)
Strong opioid drugs	88	42(47.7)	24(27.3)	13(14.8)	28(31.8)	14(15.9)	8(9.1)	3(3.4)

NSAIDs, non-steroid anti-inflammatory drugs.

4. Discussion

The specific clinical characters of pediatric cancer pain can be concluded as follows: ① children before school age accounted for a certain proportion, 44.0% in this study. These patients were young, with limited cognitive ability. Their cancer pain should be evaluated based on Wong-Baker face rating scale or behavioral classification. ② Pediatric cancers are mainly sensitive to chemotherapy. Since chemotherapy generally acts quickly, cancer pain can be relieved quickly. The median time of pain relief was only 5 days in this study, which was far shorter than that in adults [3]. ③ Because chemotherapy has a quick action, not many children patients need the adjustment of WHO analgesic ladder. These patients account for 25.2%, while 40.0% adults need the adjustment of the analgesic regimen [4].

Treatment against pediatric cancer pain can also follow the principle of WHO tri-ladder analgesia for adults, which should be administered step by step, timely and non-invasively; the drug administration should be individualized, and attentions should be paid on the therapeutic details. According to the drug ingredients and the recommended doses by WHO, we set the safe dose and the minimal age for drug administration for several adult analgesics. The total response rate was 100%, of which 92.8% were completely relieved. For single-dose morphine drugs, such as sustained-release tablet of morphine, trandermal fantanyl and sustained-release tablet of oxycodone, only the initial dose was set. And dose could be increased gradually according to the conditions of the patients and the analgesic effects, till the cancer pain was completely relieved. If the adverse events were tolerable, there was no "ceiling effect" in principle [5]. In our study, ten cases, who had severe cancer pain, were not completely relieved. The drug dose was not increased for them due to refractory constipation, abdominal distension or dizziness, and no improvement was obtained with the change of analgesic agents. The cancer pain disappeared after chemotherapy started to act.

The categories and incidences of adverse events in this group were similar to those in adults. The adverse events of weak and strong opioids were mainly constipation, nausea, vomiting and somnolence, which could be relieved after active treatments, or after withdrawal of the drug. No severe adverse events, such as respiratory inhibition or addiction, were observed. In recent years, new analgesic agents have showed superiority in administration and/or decrease of adverse events, such as sustained-release tablet of oxycodone and transdermal fantanyl. In a sustained-release tablet of oxycodone, instant and sustained release ingredients are contained simultaneously, so the analgesic effects are quick, and last long. Its analgesic effect is equivalent to two times of that of sustained-release tablet of morphine. Because the dose is relatively small, and adverse events, such as constipation and somnolence, are less. We found that a nine-year old patient with NPC who had multi bone metastasis needed 120mg sustained-release tablet of morphine. But the patient had constipation, and was reluctant to take the drug. Then 60mg sustained-release tablet of oxycodone was administered. The analgesic effect was complete, and constipation was relieved. The advantage of transdermal fantanyl is that, it can permeate skin to release fantanyl at a constant rate, without being affected by pH value in the digestive tract, by food and gastrointestinal functions, so it is especially suitable for pediatric patients with food intake difficulty, severe nausea and vomiting, or patients who were reluctant to take the drug orally, while the analgesic effect is reliable. For the safety reason, the initial dose should be 25μg/h for children older than 4 years, and 12.5μg/h for children younger than 4 years old. The minimal dosage of transdermal fantanyl is 25μg/h, so only half of the protective film of transdermal fantanyl was used for children younger than 4 years old. According to the

theory that serum fantanyl was positively proportional to the size of the agent [6], the release dose of Durogesic is estimated at 12.5 g/h. The whole fantanyl paste should not be halved to destroy the release system.

Before the patients came to Cancer Center, their cancer pain was not formally treated, and the pediatric patients were tortured by the pain for at least one week, or even a few months. At present, there are a few barriers to treat cancer pain of pediatric patients effectively: ① The parents believe that the cancer pain can not be relieved when cancer is not controlled, and they do not pay enough attention. In fact, just like in adults, cancer pain in pediatric patients can also be controlled by drugs. And according to our experiences, non-invasive drugs could basically relieve the pain, and constant intravenous pump or epidural drug administration is not necessary. ② Medical staffs do not have a clear concept of pediatric cancer pain. They may choose improper drugs or administer drugs at an insufficient dose. The principle of WHO tri-ladder analgesia is completely applicable to pediatric cancer pain. ③ In China, the analgesics are mainly produced for adults, and medical staffs dare not use the drug to pediatric patients. ④ People worry about those pediatric patients might get addicted to morphine agents more easily than adults. It is reported that, the occurrence rate of addiction is less than 1% when morphine agents are administered to treat cancer pain in pediatric patients. The risk is actually smaller in children than that in adults when morphine agents are properly applied [7]. ⑤ People have concens that morphine agents may induce respiratory inhibition more easily. However, it has been demonstrated that, application of morphine agents does not increase the occurrence of respiratory inhibition. When the resistance to adverse events is increased in pediatric patients, the resistance to respiratory inhibition is also increased. Therefore, there is no "ceiling effect" when apply morphine in pediatric patients.

In summary, most of the drugs designed for adults can be administered to pediatric patients to treat cancer pain. However, for pediatric patients younger than 2 years old, there is no safe, effective and non-invasive analgesic. Therefore, it is necessary to develop or import exclusive analgesics for children, thus to guarantee the safety, high performance and convenience of drug administration.

References

[1] Ljungman G, Gordh T, Sorensen S, et al. Pain variations during cancer treatment in children: a descriptive survey [J]. Pediatr Hematol Oncol, 2000,17(3):211-221.

[2] Gralow I. Cancer pain:an update of pharmacological approaches in pain therapy [J]. Curr Opin Anaesthesiol, 2002,15(5):555-561.

[3] Flogegard H, Ljungman G. Characteristics and adequacy of intravenous morphine infusions in children in a paediatric oncology setting [J]. Med Pediatr Oncol, 2003,40(4):233-238.

[4] Zech D F, Grond S, Lynch J, et al. Validation of World Health Organization Guidelines for cancer pain relief:a 10-year prospective study [J]. Pain, 1995,63(1):65-76.

[5] Forgeron P A, Finley G A, Arnaout M,et al. Pediatric pain prevalence and parents' attitudes at a cancer hospital in Jordan [J]. J Pain Symptom Manage, 2006,31(5):440-448.

[6] Collins J J,Dunkel I J, Gupta S K, et al. Transdermal fentanyl in children with cancer pain: feasibility, tolerability, and pharmacokinetic correlates [J]. J Pediatr, 1999,134(3):319-323.

[7] Cherny N I, Foley K M. Nonopioid and opioid analgesic pharmacotherapy of cancer pain [J]. Hematol Oncol Clin North Am, 1996,10(1):79-102.

[8] Kart T, Christrup L L, Rasmussen M, et al. Recommended use of morphine in neonates, infants and children based on a literature review:Part 1-Pharmacokinetics [J]. Paediatr Anaesth, 1997,7(1):5-11.