

• Clinical Research •

# Effect of vaginal administration of controlled-release oxycodone on cancer pain

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**[Abstract]** **Background and Objective:** Controlled-release oxycodone is an orally administered strong opioid analgesic for moderate to severe cancer pain. Sometimes, its oral administration has to be stopped because of continuous nausea, vomiting, conscious disturbance, or inability to swallow. This study was to investigate analgesic effect of vaginal administration of controlled-release oxycodone on cancer pain and observe adverse events to provide a new choice for female patients who can not tolerate the adverse events caused by oral administration. **Methods:** Controlled-release oxycodone tablets were vaginally administered to 36 female patients with moderate to severe cancer pain. The initial dose was 10 mg every 12 h to patients who had never taken opioid analgesics; former dose continued to patients switching to vaginal route from oral route. **Results:** Among the 36 patients, six had complete relief of cancer pain, 20 had significant relief, four had moderate relief, and four had slight relief, two had no relief. The relief rate of cancer pain was 83.3%. The mean time for onset of analgesic effect was 49 min; the mean duration of analgesic effect was 13.8 h. Main adverse event was vaginal burning sensation in nine (25.0%) patients. No patient discontinued vaginal administration because of adverse events. **Conclusion:** The vaginal administration of controlled-release oxycodone is a safe, effective and simple means of managing cancer pain in female patients who can not tolerate the adverse events caused by oral administration.

**Key words:** Controlled release oxycodone, cancer pain, analgesic, vaginal administration

Controlled-release oxycodone is an effective orally-administered drug in treating moderate to severe cancer pain, which is now widely used in clinical practice. Continuous nausea, vomiting, consciousness disturbance or dysphagia in some patients often confines its oral administration. Rectal administration of controlled-release oxycodone is safe and effective, but its absorption is subject to the influence of faeces inside the rectus and bowel preparation is often necessary before administration.<sup>1</sup> Based on the physiologic and anatomic characteristics of female patients, the Tumor Treatment Center of the Military General Hospital of Beijing PLA treated 36 female patients with moderate to severe cancer pain who can not accept oral administration, using vaginal administration of controlled-release oxycodone between September

2003 and September 2008. The study was to evaluate its analgesic effect.

## Materials and Methods

**Clinical data.** According to TNM staging, all these patients were females with stage IV tumor. During the observation, no anti-tumor treatment was given. They aged from 32 to 75 years, with a median age of 54 years. Among them, 14 patients were pre-menopausal and 22 were post-menopausal; nine had gastric cancer, seven had breast cancer, five had lung cancer, five had colon cancer, five had ovarian cancer, two had endometrial cancer, two had pancreatic cancer and one had hepatic cancer; 14 had bone metastasis, 12 had intra-abdominal cavity metastasis, six had liver metastasis, five had lung metastasis and four had brain metastasis.

Pain intensity was assessed by Number Rating Scale (NRS): 0 score indicated no pain; 1-3 scores indicated mild pain; 4-6 scores indicated moderate pain, and 7-10 scores indicated severe pain. According to NRS rating, 17 patients had moderate pain and 19 had severe pain.

**Administration route.** The administrator put on gloves, which was lubricated, to place the tablets. When one tablet was required, it was placed into the vagina directly. When two or more tablets were required, they were placed into an empty capsule to reduce administration attempts. For each patient, continuous administration lasted for at least 7 days. Pre-menopausal females were observed during non-menstrual period.

**Dosage.** For opioid-naïve patients, initial dose of controlled-release oxycodone was 10 mg, once per 12 h. Dosage titration was based on that of oral administration. For patients who were unable to continue oral administration of controlled-release oxycodone and switched to vaginal administration, the same dose (as in oral administration) was used for vaginal administration.

**Observed parameters.** Pain relief (PAR) was assessed according to previous report:<sup>2</sup> grade 0 suggested no relief; grade 1 indicated mild relief,

which meant the pain was relieved by 1/4; grade 2 indicated moderate relief, which meant the pain was relieved by 1/2; grade 3 indicated significant relief, which meant the pain was relieved by more than 3/4; grade 4 indicated complete relief, which meant the pain was completely relieved. Total pain relief rate referred to the percentage of patients with relief of grade 2 or above among all patients.

Onset time was defined as the time span from initial administration to when the pain started to relieve; analgesic time indicated the time span from when pain started to relieve to when the next pain episode started.

The onset, severity and duration of adverse events were observed and recorded after vaginal administration.

**Statistical analysis.** Statistical analysis was performed with SAS8.1 software. Measurement data are shown as mean SD, and t test was used for inter-group comparisons between groups; numerical data are shown as patient numbers or percentages, and  $\chi^2$  test was used for inter-group comparisons. All the statistical tests were two-sided.  $P < 0.05$  was considered significant.

## Results

**Dosage titration.** For the 21 patients who switched to vaginal administration from oral administration, initial dose was 30-180 mg/day and no dosage titration was performed. For the 15 opioid-naïve patients, dosage ranged from 10 mg to 90 mg.

**Pain relief.** All patients were evaluated for efficacy on Day 7 of administration: two achieved grade 0 relief, four achieved grade 1 relief, four achieved grade 2 relief, 20 achieved grade 3 relief, and six achieved grade 4 relief, with a total pain relief rate of 83.33%.

Among the 21 patients who switched from oral administration to vaginal administration, one achieved grade 0 relief, three achieved grade 1 relief, two achieved grade 2 relief, 11 achieved grade 3 relief, and four achieved grade 4 relief. Among the 15 opioid-naïve patients, one achieved grade 0 relief, one achieved grade 1 relief, two achieved grade 2 relief, nine achieved

grade 3 relief, and two achieved grade 4 relief. No significant difference in the rate of pain relief of grade 3 or above was observed between the two groups (71.43% vs. 73.33%,  $P>0.05$ ).

Among the 14 pre-menopausal patients, one achieved grade 2 relief, ten achieved grade 3 relief, and three achieved grade 4 relief. Among the 22 post-menopausal patients, two achieved grade 0 relief, four achieved grade 1 relief, three achieved grade 2 relief, ten achieved grade 3 relief, and three achieved grade 4 relief. The rate of pain relief of grade 3 or above was significantly higher in pre-menopausal patients than in post-menopausal patients (92.86% vs. 59.09%,  $P<0.05$ ).

**Onset time and analgesic time.** For all patients in the study, mean continuous administration duration was (9.5 $\pm$ 3.3) days (range, 8-12 days). Median onset time was 49 min (range, 25-72 min); median analgesic time was 13.8 h. Stratified analysis suggested mean onset time and mean analgesic time were 55 min and 12.4 h in the patients who switched from oral administration to vaginal administration, and were 52 min and 13.9 h in opioid-naïve patients, without significant differences between the two groups ( $P>0.05$ ); mean onset time significantly shorter in pre-menopausal patients than in post-menopausal patients (26 min vs. 82 min,  $P<0.05$ ), while no significant difference in mean analgesic time was seen between the two groups (13.5 h vs. 14.0 h,  $P>0.05$ ).

**Adverse events.** Among the patients, nine (25.0%) had vaginal burning sensation, three (8.3%) had nausea, three (8.3%) had abdominal distention, one (2.8%) had vomiting, one (2.8%) had drowsiness, and one (2.8%) had urine retention. No patients had terminated the treatment due to adverse events.

Vaginal burning sensation occurred both in the patients who switched from oral administration to vaginal administration and in opioid-naïve patients. The occurrence rate of vaginal burning sensation was significantly lower in pre-menopausal patients than in post-menopausal patients (14.4% vs. 31.8%,  $P<0.05$ ). Median onset time of vaginal burning sensation was 10 min. The sensation might last

through the entire administration, but tended to weaken with time.

## Discussion

Pain is a common symptom in patients with advanced tumors. Since cancer pain affects patients quality of life severely, freedom from pain for cancer patients has become a goal of medical staff all over the world.<sup>3</sup> Nevertheless, due to the toxicity of drugs and the limitations of established treatments, some patients are still suffering from uncontrolled pain. The mechanisms of pain, new analgesic drugs and administration routes is worthy of further investigation.

Opioid analgesics are a major class of drugs in treating cancer pain. Common oral drugs include controlled-release morphine sulfate and controlled release oxycodone. Oxycodone, a strong opioid agonist, is generated by removing the 0-methyl group of oxymorphone and oxycodone. With high bioavailability, it produces analgesic effect twice as much as that of morphine. Oxycontin is an oxycodone tablet manufactured by Beijing Mundipharma Pharmaceutical using Acrocotin technology, with 32% instant-release ingredient and 68% controlled-release ingredient. The instant-release ingredient is released rapidly, which can help achieve analgesic effect within one hour in most patients, while the controlled-release ingredient is released stably and continuously, which maintains stable serum drug concentration for 12 h. Oral administration of Oxycontin produces considerably high bioavailability and achieves a relief rate of over 90% in the patients with moderate to severe cancer pain.<sup>4</sup>

As an effective and safe drug, controlled-release oxycodone is widely used on a global scale. However, some patients are incapable of oral administration due to various reasons. Scientists have tried rectal administration when giving orally administered analgesics and suggested that rectal administration was effective in controlling pain but was limited because bowel preparation was often needed before administration.<sup>1,5</sup> No reports have yet described

the vaginal administration of controlled-release oxycodone.

Among the 36 patients who were given vaginal administration of controlled-release oxycodone in our study, the total relief rate was 83.33%. The onset time and analgesic time of controlled-release oxycodone via vaginal administration were similar to those via oral administration; adverse events were tolerable, and no patients terminated the treatment due to adverse events. Common adverse events included constipation, nausea, vomiting, abdominal distention, and drowsiness, with a low occurrence rate in our study. This might be related to a high percentage of the patients who switched from oral administration to vaginal administration in the study. Generally, these adverse events gradually disappeared with administration time. In addition, vaginal administration helped avoid direct irritation of oxycodone on the gastrointestinal mucosa, which might help to reduce digestive tract reactions, such as nausea and vomiting. Vaginal burning sensation was a relatively frequent adverse event in vaginal administration route. When switching to vaginal administration from oral administration, most patients could achieve smooth transition with no need of dosage modification.

No significant differences were seen in pain relief rate, onset time, analgesic time and adverse events between the patients who switched from oral administration to vaginal administration and opioid-naïve patients. Notably, multiple observed parameters were different between pre- and post-menopausal patients, for example, the occurrence rate vaginal burning sensation was significantly higher in post-menopausal patients than in pre-menopausal patients. The reason might be that post-menopausal patients produce less vaginal secretion and a few patients even have

vaginal dryness, which interfere with the dissolution and absorption of the drug and thereby affect the onset time and efficacy.

Vaginal administration of controlled-release oxycodone is safe and effective, and avoids irritation on gastrointestinal mucosa and thus reduces the occurrence of digestive tract reactions such as nausea and vomiting, which make it an option of administration route in female patients who is incapable of oral administration. Its shortcomings are that modification on administration approach is necessary in pre-menopausal females during menstruation, and that it leads to frequent vaginal burning sensation in post-menopausal females. Special suppository may reduce local irritation by vaginal administration of the drug and further favor drug absorption. Currently, no suppository has been put into clinical application in our country. Our study was a self-control open trial, with a small sample size. The efficacy and safety of vaginal administration of controlled-release oxycodone need to be further confirmed by prospective large-scale controlled study.

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