Original Article

Multicenter Clinical Study for Evaluation of Efficacy and Safety of Transdermal Fentanyl Matrix Patch in Treatment of Moderate to Severe Cancer Pain in 474 Chinese Cancer Patients

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ABSTRACT

Objective: Although a new matrix formulation fentanyl has been used throughout the world for cancer pain management, few data about its efficacy and clinical outcomes associated with its use in Chinese patients have been obtained. This study aimed to assess the efficacy and safety of the new system in Chinese patients with moderate to severe cancer pain.

Methods: A total of 474 patients with moderate to severe cancer pain were enrolled in this study and were treated with the new transdermal fentanyl matrix patch (TDF) up to 2 weeks. All the patients were asked to record pain intensity, side effects, quality of life (QOL), adherence and global satisfaction. The initial dose of fentanyl was 25 μg/h titrated with opioid or according to National Comprehensive Cancer Network (NCCN) guidelines. Transdermal fentanyl was changed every three days.

Results: After 2 weeks. The mean pain intensity of the 459 evaluated patients decreased significantly from 5.63±1.26 to 2.03±1.46 (P<0.0001). The total remission rate was 91.29%, of which moderate remission rate 53.16%, obvious remission rate 25.49% and complete remission rate 12.64%. The rate of adverse events was 33.75%, 18.78% of which were moderate and 3.80% were severe. The most frequent adverse events were constipation and nausea. No fatal events were observed. The quality of life was remarkably improved after the treatment (P<0.0001).

Conclusion: The new TDF is effective and safe in treating patients with moderate to severe cancer pain, and can significantly improve the quality of life.

Key words: Transdermal fentanyl matrix patch (TDF); Cancer pain; Efficacy; Safety; Quality of life

INTRODUCTION

Cancer in general remains one of the most life-threatening diseases nowadays[1]. There are about 2 million cancer patients in china, and 80 to 90 percent of advanced cancer patients suffer from pain. Pain is one of the most common symptoms associated with cancer and an important factor affecting the quality of life (QOL) of cancer patients. Prompt and effective pain management can prevent needless suffering, may significantly improve the quality of their lives, and may potentially spare families the feeling of helplessness and despair.

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According to 3-step "analgesic ladder" of cancer pain relief guideline by World Health Organization (WHO), opioids are the mainstay of management of cancer pain; the therapeutic goal for cancer pain treatment with opioids is to achieve maximal analgesia and minimize occurrence of adverse events. They work by binding to μ-opioid receptors within central nervous system, which are responsible for opioid-mediated analgesia, respiratory depression, sedation, physiological dependence, and tolerance. Opioids such as morphine, hydromorphone, oxycodone, fentanyl and buprenorphine, have been shown to be highly effective in alleviating moderate to severe malignant and nonmalignant chronic pain[2-5]. Little difference would be expected between opioids in efficacy or improvements in QOL which is confirmed by studies in cancer pain[6].

Fentanyl, a synthetic, highly selective opioid agonist, is 75 to 100 times more potent than morphine[7]. The low molecular weight, high potency, great transdermal permeation rte and lipid solubility of fentanyl make it very suitable for transdermal administration[8-10]. The development of transdermal therapeutic systems for opioid administration has resulted in several advantages compared to oral, sublingual or parenteral administration. These systems represent a non-invasive method, effective and well accepted by cancer patients who often have gastrointestinal problems and difficulties with oral medication either due to the cancer itself or due to the side-effects on oral or parenteral concomitant medication.

Fentanyl in the form of a transdermal patch (DURAGESIC®) was approved in the USA in 1990, and now is used in more than 50 countries including Europe[11-14]. In China, the reservoir patch of fentanyl was released in July 1999, which is most widely used in palliative medicine. The efficacy and tolerability of transdermal fentanyl for long-term treatment of cancer pain have been extensively studied and very well documented[15-18]. The novel matrix patch replaced the original reservoir formulation on China market in 2007. Although the new system has been used throughout the world and been the focus of a number of clinical studies, few data about its efficacy and clinical outcomes associated with its use in Chinese patients have been obtained. Therefore we designed the current study to investigate the efficacy and safety of the new transdermal fentanyl matrix patch (TDF) in Chinese patients with moderate to severe cancer pain. Pain intensity, patients' QOL, investigators and patients' overall satisfaction will be evaluated as clinical utility.

MATERIALS AND METHODS

Setting and Participants

Eighteen hospital locations in nation participated in this multicenter, open-label and single-arm prospective study. Between December 2007 and June 2008, all hospitalized patients with cancer pain seen at participating centers during the study period were screened. Patients of either sex and aged over 18 years were eligible to participate in the study if they had histological or cytological evidence of cancer with a pain score of ≥4 [by numerical rating scale (NRS)], were in need of continuous strong opioids administration assessed by the investigators, demonstrated high compliance with therapeutic regimens and had sufficient communication abilities to ensure follow-up. Specialized oncology staffs informed patients about the study and written informed consents were obtained in all participants. The study was approved by the institutional review boards of the respective institutions.

Exclusion criteria included: (1) known allergy to opioids; (2) a history of abuse of opioids or alcohol; (3) previous extensive dermal damage in the patch area; (4) pregnant or lactating women; (5) impaired level of consciousness; (6) severe renal or hepatic insufficiency, as defined by serum creatinine greater than 2.5 times upper limits of normal (ULN), and aspartate amino transferase greater than 2.5 times ULN; (7) cardiac, respiratory or neurologic dysfunction that would, in the investigators' judgment, increase risk from the opioids; and (8) treatment with monoamine oxidase inhibitors.

Methods

TDF (DURAGESIC®) was prescribed for patients enrolled in the study. For opioid-naive patients, titrated with low dose of opioid as the initial dose until up to 25 μg/h TDF equivalent, then converted to the 25 μg/h TDF patch. Patients with opioid tolerance should switch from other opioids to an equivalent dosage of fentanyl. In order to determine the starting dose, it is necessary to calculate the previous 24-hour analgesic requirement, then convert this amount to the corresponding DURAGESIC® dose by standard conversion formula: oral morphine dose (mg/d) × 1/2=DURAGESIC® (μg/h), i.v. morphine dose (mg/d) × 3/2=DURAGESIC® (μg/h). It is crucial to continue the previous regular opioid for 12 to 18 h after commencing treatment with a fentanyl patch. Immediate release morphine (5–10 mg orally or 5 mg s.c./i.v. every four hours) was supplied as rescue medication when sufficient relief from pain was not adequate, because of either inadequate TDF dose or breakthrough pain. The recommended starting dose should be titrated over as much as possible in three days until effective pain relief (score ≥3) was achieved. The duration of the study was 2 weeks.

The patches were applied to flat areas of skin, such as the chest, abdomen, upper arm, and thigh for 72 h. When the patches were replaced, they were applied to different sites to minimize irritation to the skin.

Measures

At the beginning of the study, all patients had a physical examination and routine laboratory tests. Baseline assessments included recording the patients' characteristics, pain score using a NRS and QOL evaluation. During treatment period, further data including the change in pain score and QOL score, patch adhesion score, overall satisfaction score and the adverse effects of TDF were collected.

Pain Intensity (PI)

PI was evaluated according to a NRS (from 0 = no pain to 10 = worst pain imaginable). A score of 1–3 was assessed as mild pain, 4–6 as moderate pain, and 7–10 as severe pain.