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.

Patients were asked to record their daily average pain intensity, minimum and maximum pain intensity. For drop-out patients, the reasons of drop-out should be recorded.

Pain Relief (PAR)

The investigators evaluated the efficacy according to the degree of pain relief in patients. Grade 0 was assessed as no remission (pain did not ease or even worse); Grade I was assessed as mild remission (at least a 25% decrease in pain intensity); Grade II was assessed as moderate remission (at least a 50% decrease in pain intensity); Grade III was assessed as obvious remission (at least a 75% decrease in pain intensity); and Grade IV was assessed as complete remission (pain completely disappeared). Overall remission rate= complete remission+obvious remission+moderate relief.

QOL

The overall QOL of the patients, including their ability to function physically and socially, was monitored using the questionnaire of assessment of the QOL for cancer patients in China[19]. Each item in the questionnaire related to malignant tumor patients, mainly including appetite, mental status, sleep, daily activities and communicating well with others was scored from 1 to 5, with a score of 1 indicating very bad, and 5 indicating approximately normal. Questionnaires were completed at baseline and at the end of the study.

Patch Adhesion Score

Adhesive properties of the patches were graded at 24, 48 and 72 hours, respectively. Scoring was based on investigators' evaluation of patch appearance: 0=90%–100% patch remained on the skin; 1=75%–89% patch remained on the skin; 2=50%–75% patch remained on the skin; 3=patch was completely detached.

Overall Satisfaction Score

Both investigators and patients completed a global treatment assessment at the end of the treatment. Overall satisfaction with application of TDF using verbal rating scale from 1 to 5, with 1=completely satisfied, 2=satisfied, 3=fairly satisfied, 4=not satisfied, and 5=not at all satisfied.

Adverse Events (AEs)

The safety of treatment was evaluated by measuring vital signs once a day, closely observating the occurrence of side effects. The time of onset and severity of side effects, treatment measurements and prognosis were recorded. The incidence of AEs and serious AEs determined to be related to the study medication were defined by investigators with an assessment of "doubtful", "unlikely", "possible", "probable", or "certain".

Statistical Analysis

Patients' general characteristics were analyzed by descriptive statistical methods. Measurement data (i.e., daily average pain intensity, minimum and maximum pain intensity) were given as $\bar{x}\pm s$; numeration data (i.e., sex, pain type, pain remission rate, the occurrence of AEs were given as frequencies and percentages. Changes of pain score were compared using the paired *t*-test and Chi-square for changes of QOL score. Statistical analysis was performed using the SAS software (Version 9.13). All tests were two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Between December 2007 and June 2008, a total of 474 patients from 18 institutions were enrolled in the study and 459 patients were evaluable for efficacy. Of the evaluable patients, 280 (61.0%) were male and 179 (39.0%) were female. The median age of the patients was 59 years (range 19 to 94 years). Among them, 357 (77.78%) suffered from moderate pain and 102 (22.22%) suffered from severe pain. Specification of pain type included osteodynia (51.2%), visceralgia (42.27%) and neuralgia (13.94%).

Efficacy

In 459 evaluable patients, mean pain intensity score at baseline, as measured by NRS, was 5.63±1.26 and was decreased to 2.03±1.26 at the end of the observation. There was a statistically significant reduction (t=–47.44, $P<0.0001$) of pain intensity at the end of the study compared to baseline. The maximum pain intensity at the beginning was 7.50±1.30 and the minimum pain intensity was 3.81±1.79. A significant reduction was observed in both of them at the last observation, which was decreased to 3.11±1.99 and 1.46±1.29, respectively ($P<0.0001$).

The overall remission rate at the end of study was 91.29% (415/459). Of the evaluable patients, 15 (3.27%) patients were no remission, 25 (5.45%) patients were mild remission, 244 (53.16%) patients were moderate remission, 117 (25.49%) patients were obvious remission and 58 (12.64%) patients were complete relief. In patients with moderate pain or severe pain, overall remission rate was 90.48% and 94.12%, respectively. The proportion of patients' pain relief during the study is shown in Table 1. Of these 245 patients, (53.38%) were opioid-naive patients, and 214 (46.62%), were previously opioid treated patients. Efficacy in opioid-naïve patients and patients with prior opioid use was 97.55% and 95.79%. No statistically significant differences were found in both groups of patients. Pain intensity dropped significantly within 3 days, with an average pain intensity score about 3 at day 3, then, showed a steady decline in the following days (Figure 1).

The dose of TDF applied during the treatment range from 6.3 to 350 μg/h and the dosage range used by most of the patients was from 25 to 50 μg/h with a median dosage on day 15 of 50 μg/h. for moderate pain patients, the median dose was 40 μg/h (range 15.87 to 306.67 μg/h) and for severe pain patients, the median dose was 46.67 μg/h (range 25 to 161.67 μg/h). A total of 230 patients received rescue medications for breakthrough pains, of which 99 (21.75%) patients were given weak opioids and 124 (27.02%) patients were given strong opioids.

AEs

The incidence of AEs was 33.75% (160/474) during the

study. In all 474 enrolled patients, 89 (18.78%) patients experienced moderate side effects and 18 (3.8%) patients experienced severe side effects. Three patients died, which were judged to be no related to study medication. The most common AEs were constipation (14.35%), nausea (11.39), vomiting (6.54%), stomach discomfort (2.53%), dizziness (4.01%) and drowsiness (3.38%). All AEs related to study medication are summarized in Table 2. Most moderate AEs observed were constipation [37 (7.81%) cases], nausea [21 (4.43%) cases], vomiting [15 (3.16%) cases], dizziness [6 (1.27%) cases] and drowsiness [3 (0.63%) cases]. Most severe AEs observed were nausea [5 (1.05%) cases], constipation [4 (0.84%) cases], vomiting [4 (0.848) cases] and dizziness [(0.42%) cases].

Table 1. The proportion of pain relief in patients with moderate and severe pain

Level of pain relief	Moderate pain		Severe pain	
	n	%	n	%
Grade 0: no remission	12	3.36	3	2.94
Grade I: mild remission	22	6.16	3	2.94
Grade II: moderate remission	182	50.98	62	60.78
Grade III: obvious remission	92	25.77	25	24.51
Grade IV: complete remission	49	13.73	9	8.82

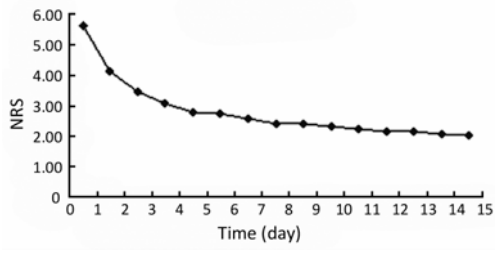

Figure 1. Changes of average pain intensity over time.

In all patients suffering from AEs, 96 (20.25%) patients need no treatments, 96 (20.25%) patients recovered after interventions, 31 (6.54%) patients persisted and 7 (1.48%) patients discontinued the observation. Most persistent AEs were constigation (10 cases), nausea (5 cases), drowsiness (5 cases) and vomiting (3 cases), one case of which discontinued treatment due to severe nausea and vomiting, while others need no specific treatment. Overall 7 patients withdrew prematurely from study because of severe nausea and vomiting (3 cases), severe headache and dizziness (1 case), mild dysuria (1 case), moderate hallucination (1 case) and severe skin allergy (1 case).

Table 2. The incidence of AEs in 474 enrolled patients

AEs	n	%
Constipation	68	14.35
Nausea	54	11.39
Vomiting	31	6.54
Stomach discomfort	12	2.53
Dizziness	19	4.01
Drowsiness	16	3.38
Dysuria	4	0.84
Skin pruritus	4	0.84
Skin allergy	1	0.21
Respiratory depression	2	0.42
Bradycardia	2	0.42

QOL

Total score of QOL in 417 (91.25%) patients increased after treatment, unchanged in 12 (2.63%) patients and decreased in 28 (6.13%) patients. Significant improvement in total score of QOL as well as each item (appetite, mental status, sleep, daily activities and communicating) was found from baseline to the last observation (P<0.0001) as showed in Table 3.

Table 3. Changes of QOL assessment before and after treatment

After to	Total score		Appetite		Mental status		Sleep		Daily activities		Communicating	
before	n	%	n	%	n	%	n	%	n	%	n	%
Increase	417	91.25	253	55.36	327	71.55	351	76.81	181	39.69	86	18.86
Decrease	28	6.13	36	7.88	26	5.69	16	3.50	22	4.82	18	3.95
No change	12	2.63	168	36.76	104	22.76	90	19.69	253	55.48	352	77.19

Patch Adhesion Assessment

Seventy-two hours after first dose of fentanyl, compared with 24 hours, 392 (85.59%) patients' patch adhesion score remained unchanged, 55 (12.01%) increased 1 point, 10 (2.18%) increased 2 points, and 1 (0.22%) completely fell off. These data suggested the patches had good adhesive properties.

Overall Satisfaction Assessment

Both investigators and patients were satisfied with the therapy. In investigators' assessment, 122 (26.70%) were "completely satisfied", 294 (64.33%) were "satisfied", and 31 (6.785%) were "fairly satisfied". In patients' assessment, 124 (27.13%) were "completely satisfied", 274 (59.96%) were "satisfied", and 43 (9.41%) were "fairly satisfied".

DISCUSSION

Pain is probably one of the most frightening cancer symptoms for patients and their families. Patients with moderate to severe cancer-related pain frequently require the use of opioid treatment. Fentanyl, the main component of TDF, is an effective alternative to oral morphine in patient with stable opioid requirements[8,20-23]. In particular, in patients who are unable to take oral medication, it provides constant delivery of fentanyl by less invasive means.

Fentanyl can be delivered in a transdermal controlled release formulation, providing continuous, controlled systemic delivery of fentanyl for up to 72 hours[24]. Fentanyl in the form of transdermal therapeutic system does not undergo the first-pass effect in liver or is not affected by gastrointestinal absorption. The absolute extent of bioavailability is close to 100% considering the dose derived from the claimed absorption. In adults upon initial application, serum fentanyl concentrations increase gradually, generally levelling off between 12 and 24 hours and remaining relatively constant for the rest of the application. In adults, the serum fentanyl concentrations attained are proportional to the size of the patch, and with repeated 72-hour applications, steady state serum concentration is maintained during subsequent applications of a patch of the same size[25].

Two different types of transdermal fentanyl delivery systems are currently available on market: reservoir and the matrix patches. In a reservoir formulation fentanyl is sandwiched between an occlusive backing layer and an adhesive controlled-released membrane and delivery is determined by the special rate-controlling membrane. Recently, novel matrix delivery systems have been introduced. In a matrix formulation, fentanyl is completely dissolved in an adhesive polymer matrix, from which the drug is continuously released into the skin. The dose of drug delivered depends on the amount of drug held in the matrix and the area of the patch applied to the skin. The active ingredient is distributed evenly throughout the patch, so one-half of a patch will have half the original surface area and deliver half the original dose per hour. Good adhesion of the transdermal patch to the skin is essential for maximum efficacy; therefore patients must be instructed on the proper technique for patch application. The novel matrix and reservoir transdermal delivery systems of fentanyl were safe and equally well tolerated. The pharmacokinetic profiles of reservoir and matrix patches are similar, and two delivery systems were considered bioequivalent since they resulted in similar rates and extents of exposure of fentanyl[26-28]. However, the matrix formulation has a number of advantages over the reservoir formulation. Compared to the old system, there is a lower risk of accidental overdose with membrane damage for the matrix type. Furthermore, the new system is expected to be more convenient and more comfortable to wear than the old system due to its smaller size and better adhesive properties. Therefore, the reservoir patch is currently being phased out in nearly all market and replaced with the new design.

The new transdermal fentanyl in matrix formulation has been shown to be comparable in efficacy to standard morphine or fentanyl in reservoir formulation in patients with moderate to severe cancer-related pain[29,30]. This observation is in accordance with the results of previous studies with TDF treatment. Total pain remission rate was 91.29% and there was no significant difference between opioid-naive patients and previously opioid treated patients. For the reason that most patients in this study suffered from chronic visceral pain and/or bone pain but not neuropathic origin[2,31], analgesic effect was remarkable.

Many studies demonstrated that one of the advantages of TDF was significantly lower incidence of AEs especially constipation compared to other oral opioids used for pain control, while some others reported the equal incidence[32]. TDF was found to be safe and well tolerated in this population. The incidence of AEs was 33.75% in our research and the majority of AEs were judged to be mild or moderate in intensity and easy to be managed, similar to most literature reported. No life-threatening or disabling side effects were observed in our study. The most frequent AEs during TDF treatment were constipation, nausea, vomiting, stomach discomfort, dizziness, drowsiness and dysuria, most of which involved the gastrointestinal system and central nervous system.

Respiratory depression is the most serious and potentially life-threatening adverse effect. In the post-marketing experience, deaths from hypoventilation due to inappropriate use of TDF have been reported. Clinically relevant respiratory depression was not observed in patient with chronic pain on opioid analgesics in three randomized trials, but serious or life-threatening hypoventilation has been documented in opioid-naive patient and in the postoperative setting[33-35]. Consequently, patient with hypoventilation should be carefully observed and their respiratory rate must be monitored until respiratory status has stabilized. Two (0.42%) patients developed mild hypoventilation in this study, which was judged to be "probablely" related to study medication, and both of them experienced self-recovery.

QOL scores clearly improved with the use of TDF. After 2 weeks of treatment, total score of QOL in 91.25% patients increased and each item scores improved to different extents. These findings are especially important for these enrolled patients because most of them were in palliative care and nearing end of their lives.

Furthermore, 85.59% (122) of the initial patches administered in the study were still almost completely to completely adhered to the skin at 72 hours, which ensured the efficacy of study medication. In addition, 91.03% investigators and 87.09% patients were satisfied to very satisfied with the new system. The transdermal therapeutic system is needle-free, easy and convenient to use. Therefore, significantly more patients expressed a preference for transdermal fentanyl than for other opioids in future.

The novel TDF, as a useful alternative to other opioid agents, offers a significant improvement of pain treatment in patients with moderate to severe cancer pain. In addition, transdermal fentanyl is safe and well tolerated and the vast majority of patients in this study were satisfied with it.

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