Study Protocol and Statistical Analysis Plan

Study Title：Application Research of Hydromorphinone Sustained-release Tablets in the Treatment of Elderly Patients With Cancer Pain Accompanied by Renal Insufficiency

Study ID：YXH2025JS126
Ethics Approval Number：2025022
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NCT Number：[To be assigned]
Sponsor Institution：Tai'an Cancer Hospital

Study Protocol
1.Background and Objectives
1.1 Study Background
With the aging of the population, the proportion of elderly patients with moderate to severe cancer pain complicated with renal insufficiency has increased significantly. First-line opioids (morphine, oxycodone) have problems such as neurotoxic accumulation and high incidence of gastrointestinal adverse reactions, leading to a dilemma between "effective analgesia" and "safe medication" in clinical practice. Domestic hydromorphone sustained-release tablets (Ruining®) have pharmacokinetic advantages (independent of CYP450 enzyme metabolism, few active metabolites, non-renal dominant metabolism), but there is a lack of prospective clinical evidence in elderly cancer pain patients with renal insufficiency. Its efficacy, renal safety and the risk of opioid-induced neurotoxicity (OIN) need to be clarified urgently.
1.2 Study Objectives
To systematically evaluate the analgesic efficacy and clinical safety of domestic hydromorphone sustained-release tablets in elderly patients (≥65 years old) with moderate to severe cancer pain and renal insufficiency;
To focus on observing the dynamic changes of estimated glomerular filtration rate (eGFR) and the occurrence of OIN after medication;
To explore and construct an OIN risk prediction model to provide an individualized medication guide for this special population.
2. Study Design
Study Type：Prospective, single-center, non-randomized cohort study
Sample Size： 62 patients, divided into 2 groups: Hydromorphone - Renal Insufficiency Group and Hydromorphone - Normal Renal Function Group.
Study Site：Department of Medical Oncology, Tai'an Cancer Hospital
Study Period：4 weeks of follow-up after enrollment (7-day titration period + 21-day maintenance period)

3 .Study Population

3.1 Inclusion Criteria

1） Age ≥ 65 years.

2） Pathologically or cytologically confirmed malignant tumor.

3）Opioid-naïve patients with moderate-to-severe cancer pain (Numerical Rating Scale score ≥ 4).

4) Renal function meeting one of the following criteria at baseline:1 ） Mild-to-moderate renal insufficiency group: 30 mL/min/1.73m² ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m².2）Normal renal function group: eGFR ≥ 90 mL/min/1.73m².

5) Expected survival period ≥ 3 months.

6) Ability to take oral medication and cooperate with study assessments.

7) Willing to participate voluntarily and able to provide signed informed consent.

3.2 Exclusion Criteria:

1) Severe renal insufficiency (eGFR < 30 mL/min/1.73m²) or requirement for renal replacement therapy.

2) Severe hepatic insufficiency (alanine aminotransferase / aspartate aminotransferase ≥ 2.5 times the upper limit of normal or Child-Pugh Class C).

3) Paralytic ileus.

4) Pain of unclear origin or pain that is solely acute/incident pain.

5) Symptoms or history of diseases such as intracranial hypertension, head injury, cerebral aneurysm, or other central nervous system disorders.

6) Symptoms of prostatic hypertrophy, thyroid dysfunction, or urethral stricture.Symptoms of asthma, respiratory obstruction, or respiratory failure.

7) Known allergy or hypersensitivity to hydromorphone or oxycodone.

8) Use of monoamine oxidase inhibitors within 14 days prior to enrollment.

9) Participation in any other clinical trial within 1 month prior to enrollment.

10) Any other condition considered by the investigator as unsuitable for participation in this study.

4 .Treatment Regimen

A standardized titration and maintenance regimen was formulated with reference to the NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain (2025 Version), using domestic hydromorphone sustained-release tablets (Ruining®) throughout the study, divided into titration period (D1-D7) and maintenance period (D8 to the 4th weekend).

4.1 Titration Period (D1-D7)

D1: Initially administer hydromorphone injection 0.5mg subcutaneously, and assess pain 30 minutes later:

Ineffective/aggravated pain: increase the next dose by 50%;

Improved but insufficiently controlled pain: keep the titration dose unchanged;

Sufficiently controlled pain: titrate on demand according to the current dose within 24 hours.

Reassess patients with uncontrolled pain after 2-3 rounds of titration; for patients with stable pain, convert the total daily dose of hydromorphone injection in 24 hours to the

equivalent daily dose of oral hydromorphone sustained-release tablets, round down to the whole tablet specification, and administer orally once a day from the next day.
D2-D7: Background medication with sustained-release tablets, rescue treatment for breakthrough pain with hydromorphone injection (dose: 10% of the oral morphine equivalent daily dose (OMEDD) in the previous 24 hours); if the average number of rescue medications for breakthrough pain is ≤3 times/day from D4, maintain the current dose; if >3 times/day, recalculate the dose and round down to the whole tablet.
4.2 Maintenance Period (D8 to the 4th weekend)
Administer hydromorphone sustained-release tablets orally once a day according to the dose determined in the titration period; if the number of breakthrough pain ≥3 times/day, optimize the dose according to the titration period method. Follow up once a week to record the medication dose, number of breakthrough pain, adverse reactions, etc.
4.3 Renal Function and Safety Monitoring
Renal function test: detect serum creatinine at baseline, D7, and the 2nd/3rd/4th weekend, and calculate eGFR;
Special OIN assessment: evaluate OIN manifestations such as delirium, somnolence, myoclonus and hallucination weekly using the Confusion Assessment Method (CAM), Epworth Sleepiness Scale (ESS), Myoclonus Grading Scale, and Brief Psychiatric Rating Scale (BPRS);
General adverse reactions: record nausea, vomiting, constipation, hypertension, respiratory depression, etc. according to CTCAE Version 5.0 grading.
5 . Outcome Measures
5.1 Primary Outcome Measures
Primary safety endpoint: Change in eGFR at the 4th weekend of treatment compared with baseline;
Primary efficacy endpoint: Pain relief rate on the 7th day of treatment (proportion of patients with NRS ≤3 points).
5.2 Secondary Outcome Measures
Efficacy measures: Time to reach stable analgesia, change in NRS score at each follow-up point, number of 24-hour breakthrough pain, consumption of rescue drugs, Sun Yan's Quality of Life (QOL) score, Brief Pain Inventory (BPI) score, Patient Global Impression of Change (PGIC) score;
Safety measures: Dynamic change trend of eGFR, overall incidence of adverse reactions, incidence and grading of OIN, incidence of abnormal liver and renal function.
5.3 Exploratory Outcome Measure
If the number of OIN cases ≥20, a nomogram model for OIN risk prediction based on multivariate Logistic regression will be constructed to analyze risk factors such as age, baseline eGFR, stable dose of hydromorphone, and combined medication.
6. Statistical Analysis Plan
Statistical Software: SPSS 26.0, R 4.5.0
Descriptive Analysis: Normally distributed measurement data are expressed as ($\bar{x} \pm s$), non-normal data as M (Q1-Q3); count data as n (%);

Baseline Balance Comparison: Independent sample t-test/Mann-Whitney U test for continuous variables, χ^2 test/Fisher's exact test for categorical variables;
Primary Outcome Analysis: Analysis of covariance (ANCOVA) for eGFR change (with baseline eGFR as a covariate); χ^2 test for pain relief rate;
Repeated Measurement Data: Generalized Estimating Equations (GEE) for NRS score and number of breakthrough pain; Linear Mixed Model (LMM) for dynamic changes of eGFR;
Survival Analysis: Kaplan-Meier method + Log-rank test for time to reach stable analgesia;
Model Construction: Multivariate Logistic regression for OIN risk prediction, internal validation by Bootstrap method (1000 resamplings), and ROC curve, calibration curve and Decision Curve Analysis (DCA) to evaluate the model;
Missing Data Handling: Complete case analysis as the main method, multiple imputation for missing data <20%, and deletion for missing data ≥20%.
7. Principles of Adverse Reaction Management
Grade 3 or above adverse reactions: Suspend medication, conduct multidisciplinary consultation within 24 hours, and provide symptomatic treatment (e.g., naloxone for respiratory depression);
Moderate to severe OIN: Switch to fentanyl transdermal patch (25μg/h initial dose), and symptomatic treatment with clonazepam 0.5mg bid;
Grade 1-2 adverse reactions: Preventive intervention (e.g., metoclopramide for antiemesis, lactulose for laxation);
Management of acute renal function deterioration: If eGFR decreases by more than 30% from baseline or drops to <30 mL/min/1.73m², immediately suspend the study medication and invite the nephrology department for emergency consultation and disposal.

Informed Consent Form

Cover Page

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Sponsor Institution：Tai'an Cancer Hospital

Dear Patient and Family Members:

We are conducting a clinical study funded by the Shandong Medical Association to evaluate the efficacy and safety of hydromorphone sustained-release tablets in elderly cancer pain patients with or without renal insufficiency, so as to provide evidence for clinical safe medication. This study has been approved by the Ethics Committee of Tai'an Cancer Hospital, and we now invite you to participate in this study. Please read the following content carefully, consult the study physicians if you have any questions, and decide whether to participate voluntarily after full understanding.

1. Study Purpose

To evaluate the analgesic efficacy of domestic hydromorphone sustained-release tablets in elderly patients (≥65 years old) with moderate to severe cancer pain (with or without renal insufficiency), observe the changes of renal function and adverse reactions such as neurotoxicity after medication, and provide evidence for formulating individualized medication plans for this population.

2 .Study Drug and Treatment Plan

The study drug is Hydromorphone Sustained-Release Tablets (Ruining®), an opioid analgesic approved for marketing in China, suitable for moderate to severe cancer pain.The treatment is divided into 2 stages: ① Titration period (7 days): first titrate pain with hydromorphone injection, and convert to oral hydromorphone sustained-release tablets after stability; ② Maintenance period (21 days): take sustained-release tablets orally once a day, and adjust the dose according to pain conditions. The medication plan will be formulated by specialist doctors throughout the study, and pain assessment and liver and kidney function tests related to the study will be provided for you free of charge.

3 .Study Flow

If you meet the enrollment criteria and sign this consent form, you will complete the following study flow:

Baseline assessment: complete pathological examination, pain score (NRS), liver and kidney function, cognitive function assessment, and sign the informed consent form;

Treatment and follow-up: receive drug treatment according to the plan, follow up in the hospital once a week, complete pain assessment, liver and kidney function tests and adverse reaction records, the total follow-up time of the study is 4 weeks;

Final follow-up: after the study, the doctor will formulate a follow-up routine analgesic treatment plan according to your condition.

4. Your Rights

Participation in this study is voluntary, and you can withdraw unconditionally at any stage of the study without affecting your routine diagnosis and treatment and doctor-patient relationship;

The costs of study-related examinations (liver and kidney function, pain assessment, etc.) are borne by the research fund, and you do not need to pay;

Your personal information (name, ID number, medical records, etc.) will be strictly confidential and only used for statistical analysis of this study. Personal information will be concealed when the research results are published;

You have the right to consult the study physicians about the study at any time and get timely and professional answers.

5. Your Obligations

Take medication strictly according to the plan formulated by the doctor, and do not increase/decrease the dose, stop or replace the drug without permission;

Complete all follow-up examinations on time, and contact the study physicians in time if you experience aggravated pain, dizziness, somnolence, nausea, vomiting and other discomfort;

Truthfully inform the study physicians of your medication history, allergy history and physical discomfort, and cooperate to complete various assessments and records.

6 .Potential Benefits and Risks

6.1 Potential Benefits

Obtain an individualized cancer pain analgesic plan formulated by a specialist doctor to control pain more accurately and safely and improve the quality of life;

Complete study-related examinations such as pain assessment and liver and kidney function tests free of charge during the study, saving medical expenses;

The research results will provide evidence for the safe medication of elderly cancer pain patients, benefiting more patients.

6.2 Potential Risks

Common adverse reactions of opioids: nausea, vomiting, constipation, dizziness, somnolence, etc., most of which are mild to moderate. The doctor will take preventive measures in advance (such as antiemetic and laxative drugs), and adjust the medication plan in time if severe discomfort occurs;

Rare severe adverse reactions: opioid-induced neurotoxicity (delirium, myoclonus), respiratory depression, transient renal insufficiency, etc. The research team has formulated a standardized emergency treatment plan, and a multidisciplinary consultation will be initiated immediately once they occur to ensure your safety;

If your pain is not effectively controlled during the titration period, the doctor will replace it with other analgesic drugs in time to ensure the effect of your pain treatment.

7 .Privacy Protection

All your study-related records are kept by a special person in Tai'an Cancer Hospital, with an encrypted database accessible only to the research team. Your personal identity information will not be disclosed during the study and in the publication of research results, in line with the Declaration of Helsinki and domestic medical ethical norms.

8. Consultation Method

If you have any questions, discomfort or suggestions during the study, please go to the Department of Medical Oncology, Tai'an Cancer Hospital to consult the study physicians in time, or call the department consultation hotline: +86 0538-2066855.

9 .Consent Statement

I have carefully read and understood all the contents of this informed consent form. The study physicians have given me a detailed explanation of the study-related issues. I voluntarily participate in this study, am aware of the benefits and risks of the study,

and agree to cooperate to complete all study procedures. This consent form is in two copies, one for the patient/family member and one for the research institution, with the same legal effect.

Patient's Signature： _____
ID Number： _____
Date： ____//__
Family Member's Signature (if the patient cannot sign by himself/herself)：
_____
Relationship with the Patient： _____
Date： ____//__
Study Physician's Signature： _____
Title： _____
Date： ____//__