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Research Paper

Mirtazapine, in orodispersible form, for patients with preoperative psychological distress: A pilot study

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ABSTRACT

Background: Perioperative psychological distress is associated with preoperative anxiety, depression, and postoperative pain. Mirtazapine is effective as an antidepressant, anxiolytic agent, and sleep enhancer. Moreover, mirtazapine can be made as orodispersible tablets with a fast onset for patients in nil per os status. This study is to determine whether mirtazapine can help psychologically distressed patients reduce perioperative anxiety, depression, and postoperative pain.

Materials and methods: Patients with preoperative psychological distress, undergoing major abdominal surgery, were inquired and assigned to two groups according to their own choice. In the treatment group, patients could choose to take orodispersible mirtazapine 30 mg at each night from Preoperative Day 0 to Postoperative Day 3. There was no other intervention in the nontreatment group. Hospital Anxiety and Depression Scale (HADS), Athens Insomnia Scale (AIS), and pain scores were accessed on the day before operation (Day 0), and on the 1st day (Day 2) and 3rd day (Day 4) after operation. We compared the HADS, AIS, and pain scores, and morphine consumptions between the two groups on a daily basis. Marginal regression models were fitted to our correlated longitudinal data alone with the generalized estimating equations method to estimate the population average effects of time-varying mirtazapine usage on the mean values of HADS, AIS, and pain scores, and daily morphine consumptions.

Results: From September 2007 to December 2008, 86 patients agreed to be enrolled and 79 of them completed the study. Propensity scores and multivariate analysis showed that mirtazapine reduced HADS scores of patients in 2 days. Trial results indicated that mirtazapine lowered the AIS day index and tended to decrease night index as well. Mirtazapine may reduce patients' morphine consumption, but this effect was not statistically significant ($p = 0.2$).

Conclusion: Mirtazapine helps reduce anxiety, depression, and insomnia scores for patients with perioperative psychological distress.

1. Introduction

Patients struggle with anticipation of postoperative pain, separation from family, incapacitation, loss of independence, and fear of surgery and death, which are triggers of anxiety throughout the perioperative period. Psychological distress is a broad array of psychological symptoms including depression, poor coping skills, anxiety, and somatization.[1] According to previous studies, the incidence of preoperative anxiety is between 60% and 92% in unselective surgical types.[2] Anxiety increases in the distress experienced by patients and leads to higher intraoperative anesthetic requirement, which makes management of postoperative pain difficult and also produces a lower level of patient satisfaction.[3] In some susceptible patients, moderate to severe depressive symptoms may occur simultaneously, and identified depressive symptoms are significant predictors of anxiety. Feeling of depression can lead to transient suppression of immune function, increase postoperative complications, and increase acute infections.[3] Adequate

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management of anxiety may facilitate smoother induction and even a better outcome of surgery.[4] Yet, in our clinical practice, perioperative caregivers usually focus on advanced surgical techniques and intensive care rather than on the quality of life of perioperative patients or those with symptoms of preop psychological distress.

In present clinical practice, benzodiazepine is the most widely used premedication for patients with anxiety,[5] but there is no evidence that it can attenuate patients' psychological distress (i.e., anxiety and depression) in the perioperative period. Therefore, we attempt to find a drug that possesses anxiolytic, antidepressant, sleep-promoting, and pain-reducing effects for patients with perioperative psychological distress. This needs to be effective without affecting perioperative vital signs, in order to eliminate their discomfort during perioperative period and hopefully to improve short- and long-term outcomes.

Mirtazapine is a unique antidepressant that can be formulated as orodispersible tablets for patients in nil per os status or those with difficulty swallowing conditions. It is the only member of the noradrenergic and specific serotonergic antidepressant class. Mirtazapine blocks central $\alpha 2$ auto- and heteroreceptors, and it also antagonizes several subtypes of serotonin (5-HT) receptors, such as 5-HT2 and 5-HT3 receptors. The overall effects of the drug are antidepressant, anxiolytic, and sleep-enhancing effects.[6] In clinical use, mirtazapine has potential beneficial effects in the treatment of patients with pain and concomitant depression. Mirtazapine also improves the quality of life of advanced cancer patients with multiple distressing symptoms,[7–9] and has been proved to enhance sleep quality in cancer patients and patients with chronic pain combined with sleep disturbance.[10] Moreover, Chen et al[4] found that a 30 mg tablet of mirtazapine ingested 1 hour before surgery reduced preoperative anxiety as well as the incidence of late postoperative nausea and vomiting. It seems that mirtazapine's unique properties meet the need of patients with perioperative psychological distress and may improve their life quality in the perioperative period.

The aim of our study is to prove that the perioperative use of oral disintegrating mirtazapine (30 mg/tablet) can decrease the degree of anxiety and depression, improve sleep quality, and reduce postoperative pain and morphine consumption in patients with perioperative psychological distress.

2. Methods

2.1. Study design

This study was approved by the Institutional Review Board of National Taiwan University Hospital. It was an open-labeled, quasiexperimental clinical follow-up study conducted in a single medical center. Participants were recruited from those who received major abdominal surgery, including subtotal gastrectomy, hepatectomy, open cholecystectomy, Whipple's operation, hemicolectomy, and anterior resection colectomy. The treatment period is from 1 day before the operation (Day 0) until 2 days after the operation (Day 3). Patients would be discharged on Day 4. Thus, the total treatment period was 4 days and the outcome assessments were performed according to the schedule described in the following subsection.

2.2. Patients

Inclusion criteria:

(1) Being able to sign the consent form
(2) Females of childbearing potential willingly using effective birth control
(3) Receiving upper or lower abdominal operation under general anesthesia in the American Society of Anesthesiologists Physical Status classification system (ASA) I, II, and III confirmed by an anesthesiologist
(4) Brief Symptom Rating Scale (BSRS-5) total score of ≥ 6
(5) Between 18 years and 65 years old

Exclusion criteria:

(1) Physical examination and brief neurological examination showing clinically significant abnormal findings
(2) Significant abnormal laboratory findings during screening
(3) BSRS-5 total score of <5
(4) A history of psychiatric disorder (except depression and anxiety)
(5) A history of epilepsy or seizures
(6) Alcohol or substance abuse categorized by the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV) during the last 6 months prior to baseline
(7) Any unstable chronic physical disease
(8) Actual risk of committing suicide according to the investigator
(9) Participation in other clinical trials in the last 30 days

2.3. Protocol

Eligible patients were approached the day before the surgery (Day 0). Preanesthesia evaluation was completed by the same anesthesiologist. Patients were asked if they agreed to use patient-controlled analgesia (PCA) postoperatively. Those patients were then visited by our study members. Upon their agreement, the patients were asked to complete BSRS-5. If the BSRS-5 total score was ≥ 6, the patient was considered to have "preoperative psychological distress." After a detailed and complete verbal explanation of the study was provided, those patients were free to sign the informed consents. Baseline data on age, gender, weight, height, ASA classification, receiving cancer surgery or not, and postoperative use of PCA were recorded.

Then, these participants could choose to be in the treatment or nontreatment group: patients of the treatment group received mirtazapine (Remeron) 30 mg before sleep from the day before surgery until 2 days after the surgery (from Day 0 to Day 3). On each day of this study period, patients in the treatment group could decide on their own to take mirtazapine or not. Patients in the nontreatment group received no drug therapy. During this the period, all participants were not allowed to receive any other tranquilizers. All participants completed questionnaires of Hospital Anxiety and Depression Scale (HADS) and Athens Insomnia Scale (AIS) in the afternoon of Day 0 and the mornings of Days 2 and 4. Numeric pain score was accessed by a trained nurse 1 hour after the surgery and in the morning of Days 2–4. The amounts of morphine consumption of PCA were recorded daily. The degree of nausea/vomiting, side effects of mirtazapine, and/or the reason why patients did not take mirtazapine were also recorded.

All patients received endotracheal intubation general anesthesia with standard intraoperative care (including electrocardiogram, arterial blood pressure, and pulse oximetry). Patients' vital signs were maintained within 20% of baseline. Intraoperative inhalation gas concentrations were kept around 1.0–1.3 minimum alveolar concentration, and fentanyl was given according to patients' vital signs of pain or surgical stimulation (e.g., increasing heart rate or blood pressure intraoperatively).