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# Long-Term Stability of Tramadol and Ketamine Solutions for Patient-Controlled Analgesia Delivery

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** Subanesthetic doses of ketamine as an adjuvant to tramadol in patient-controlled analgesia (PCA) for postoperative pain have been shown to improve the quality of analgesia. However, there are no such commercially available drug mixtures, and the stability of the combination has rarely been assessed.

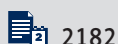
**Material/Methods:** Admixtures were assessed for periods of up to 14 days at 4°C and 25°C. Three different mixtures of tramadol and ketamine (tramadol 5.0 mg/mL + ketamine 0.5 mg/mL, tramadol 5.0 mg/mL + ketamine 1.0 mg/mL, and tramadol 5.0 mg/mL + ketamine 2.0 mg/mL) were prepared in polyolefin bags by combining these 2 drugs with 0.9% sodium chloride (normal saline [NS]). The chemical stability of the admixtures was evaluated by a validated high-performance liquid chromatography (HPLC) method and by measurement of pH values. Solution appearance and color were assessed by observing the samples against black and white backgrounds. Solutions were considered stable if they maintained 90% of the initial concentration of each drug.

**Results:** The percentages of initial concentration of tramadol and ketamine in the various solutions remained above 98% when stored at 4°C or 25°C over the testing period. No changes in color or turbidity were observed in any of the prepared solutions. Throughout this period, pH values remained stable.

**Conclusions:** The results indicate that the drug mixtures of tramadol with ketamine in NS for PCA delivery systems were stable for 14 days when stored in polyolefin bags at 4°C or 25°C.

**MeSH Keywords:** Analgesia • Analgesia, Patient-Controlled • Drug Stability • Ketamine • Tramadol

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## Background

PCA drugs with different analgesics have been widely used in the treatment of postoperative pain, although little or no information is available about the stability of these analgesic mixtures. Mixing of 2 or more analgesia drugs together in PCA delivery can create potential problems relating to instability and drug incompatibilities, which may reduce efficacy and precipitation/crystallization [1].

Tramadol hydrochloride (Figure 1A) trans-(+/-)-2-[(Dimethylamino) methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride, a synthetic, centrally-acting analgesic with opioid and nonopioid actions, is commonly used for cancer, postoperative, gynecologic, and obstetric pain [2,3]. PCA tramadol as a convenient regimen for postoperative control has worldwide popularity in clinical practice, but is associated with troublesome adverse effects such as, pruritus, nausea, vomiting, urinary retention, and respiratory depression. Ketamine hydrochloride (Figure 1B) (2-(2-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride) is an analgesic/sedative that is a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptor. Ketamine used in higher doses is less desirable due to adverse effects such as hallucinations, nightmares, nausea, dizziness, and blurred vision. However, subanesthetic doses of ketamine as an adjuvant to an opioid can help to reduce requirements for and potential adverse effects of the opioid [4–6]. Randomized controlled trials have evaluated the efficacy of ketamine in conjunction with tramadol-based intravenous PCA for postoperative pain and demonstrated superior pain control and significantly reduced incidence of postoperative nausea or vomiting [7–9].

Known incompatibilities arising from the combination of therapies in i.v. PCA pumps can affect the physical and chemical stability of the analgesia drugs. These incompatibilities may include drug-drug interactions, pH shifts, precipitation, particle formation, and crystallization during delivery by PCA pumps. Typically, factors examined in the stability studies include the effects of concentration, temperature, storage time, potential leaching from the i.v. administration components, and adsorption to the container material. However, to the best of our

knowledge, no published information is available on the stability of tramadol in combination with ketamine in solution for PCA administration. Thus, the aim of the current study was to develop an HPLC assay to determine the stability of tramadol/ketamine solutions at 3 different concentration combinations, prepared in NS and stored for a period of up to 14 days at 4°C and 25°C.

## Material and Methods

### Preparation of tramadol-ketamine solutions

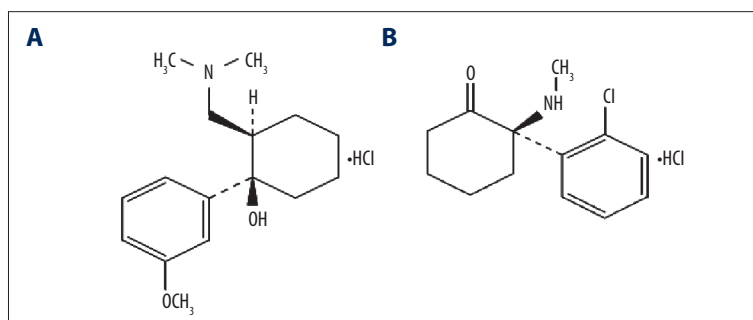
The drug solutions were made up in volumes reflecting those used in 2-day intravenous microcomputer-controlled drug-infusion devices (BoChuang Med. Co., Shanghai, China) under aseptic conditions. Commercial tramadol hydrochloride injection (100 mg/2 mL, lot number 879B01, Grunenthal Pharmaceutical Co., Ltd) and ketamine hydrochloride injection (100 mg/2 mL, lot number 130705, Qilu pharmaceutical Co., Ltd, Shangdong, China) were transferred into commercial polyolefin bags (100-mL, Jierui, Weigao Med., Shangdong, China) and adjusted to volume with NS (0.9 g/100mL, lot number A141025, Kelun Pharmaceutical Co., Sichuang, China). The final concentration ranges were 5.0 mg/mL for tramadol hydrochloride and 0.5, 1.0, or 2.0 mg/mL for ketamine hydrochloride. The final dose and concentration of each drug in the study were chosen by taking into consideration those most frequently used for postoperative pain [7–11].

### Sample collection

Three samples of each solution were prepared and stored in the dark at 4°C and 25°C. Samples (5 mL) were transferred from polyolefin bags into glass vials and frozen at –70°C for analysis at a later date. On days 1, 2, 3, 5, 7, 10, and 14, additional samples were similarly collected and frozen.

### Stability study of tramadol-ketamine solutions

In the stability study, samples were removed from each admixture for analysis of appearance, pH, and drug concentration at



**Figure 1.** Structures of (A) tramadol hydrochloride and (B) ketamine hydrochloride.

predetermined times (0, 1, 2, 3, 5, 7, 10, and 14 days). At the specified times, color change, cloudiness, and precipitation were evaluated against light and dark backgrounds. Moreover, at 0 and 14 days, the pH of each mixture was measured by using a digital Crison phs-3c pH meter (Leici Instrument Co., Shanghai, China). On the day of analysis, samples were allowed to reach room temperature and were diluted 1:10 in deionized water before injection into an HPLC system. Samples from each syringe were analyzed in triplicate (total n=3).

### Analysis of data

The percentage of tramadol and ketamine remaining on day 14 was calculated from the concentration on day 14, as determined by linear regression and the concentration observed on day 0, according to the following formula: (concentration on day 14/concentration on day 0) ×100%. Data are expressed as the mean ± standard deviation (SD). The admixtures were considered chemically stable if they retained 90% of the initial value. The changes with time, temperature, or concentration of the remaining drug concentration in solution were analyzed using a 3-way ANOVA analysis. A P-value of less than 0.05 was considered to be significant.

### HPLC assay

#### Chromatographic system

The Dionex HPLC system (UltiMate 3000, GER) consisted of quaternary gradient pump, an ASI-100 auto sampler, a TCC-100 thermostat column oven, and an ultraviolet detector (DAD). Chromatographic data was acquired using Chromeleon software version 6.80. A Zorbax Hypersil ODS Column (150×4.6 mm, 5.0 μm) (Agilent Technologies, China) was used as a stationary phase. The mobile phase consisted of acetonitrile (Agilent Technologies, Shanghai Branch, China) – 0.05 mol/L KH<sub>2</sub>PO<sub>4</sub> (Wuhan Analytical reagent company, Wuhan, China) adjusted to pH 4.5 with triethylamine (25: 75 v/v), with a flow rate of 1.0 ml/min. The λ<sub>max</sub> for UV detection was set at 268 nm. The column temperature was kept ambient and injection volume was 20 μL.

#### Preparation of stock and working solutions

The standard stock solutions were prepared in deionized water in the concentration of 10.0 and 5.0 mg/mL for tramadol hydrochloride and ketamine hydrochloride, respectively. The working standard solutions of tramadol hydrochloride and ketamine hydrochloride were prepared by diluting the stock solutions with deionized water to give final concentrations. Working solutions were prepared daily and stock solutions were stored at –20°C.

### Validation of the method

The method was validated for linearity, accuracy, precision, and stability [12,13]. For evaluating the quantitative applicability of the method, 6 different concentrations and 3 replicates of tramadol hydrochloride and ketamine hydrochloride in a range 0.05–1.0 mg/mL and 0.01–0.5 mg/mL were used to characterize the calibration functions. Linear regression analysis of the calibration data was performed using the equation  $y=mx+b$  where y was the peak area ratio, x the concentration of analytes, and m and b the slope and intercept, respectively, of the curve. Replicate analysis (n=5) of quality control samples at 3 concentration levels (0.25, 0.5, and 0.75 mg/mL for tramadol hydrochloride; 0.05, 0.1, and 0.2 mg/mL for ketamine hydrochloride) was used for determining the precision and accuracy of the assay. Precision was calculated as the coefficient of relative standard deviation (RSD,%) within a single run (intra-day) among different runs (inter-day). The accuracy was calculated by means of the recovery value.

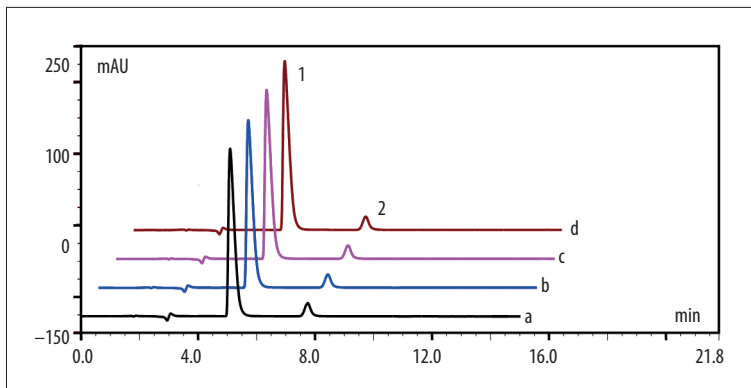
### Degradation of tramadol and ketamine

The tramadol hydrochloride and ketamine hydrochloride mixture was degraded with 0.1 mol/L sodium hydroxide (acidified), 0.1 mol/L sodium hydroxide (alkaline degraded), and 3% hydrogen peroxide (oxidized) for 5 h at 60°C. The chromatogram obtained for the degraded preparation was compared with a chromatogram obtained from the standard curve to confirm separation of the parent molecule from its degradation products.

## Results

### HPLC method validation

A new, simple, and rapid HPLC method was established for simultaneously determining tramadol hydrochloride and ketamine hydrochloride in analgesic mixture samples used in PCA. Under the current chromatographic conditions, tramadol and ketamine were satisfactorily separated. Chromatograms of the degradation samples are shown in Figure 2, demonstrating that the decomposition products were baseline separated from tramadol and ketamine. Retention times were 4.6 min for tramadol and 8.1 min for ketamine. The linearity of tramadol and ketamine were in the range of 0.05–1.0 mg/mL and 0.01–0.5 mg/mL, respectively, with correlation coefficient more than 0.999. The average linear regression equation was represented as  $y=10.91x+3.732$  for tramadol and  $y=4.448x+0.29$  for ketamine. The intra-day and inter-day variations RSD% at 3 concentrations were all less than 2.5% for both drugs. Recovery values for all cases were between 99.0 and 101.0 with RSD <3.0%. These results indicate that the method provides



**Figure 2.** HPLC chromatograms of tramadol-ketamine solutions. a: Freshly prepared sample of tramadol/ketamine solutions. b: Acidified sample of tramadol/ketamine solutions after 5 h at 60°C. c: Alkaline-degraded sample of tramadol/ketamine solutions after 5 h at 60°C. d: Oxidized sample of tramadol/ketamine solutions after 5 h at 60°C. Retention times were 4.6 min for tramadol (peak 1) and 8.1 min for ketamine (peak 2).

adequate accuracy and precision for quality control of tramadol and ketamine in NS.

### Stability of tramadol-ketamine solutions

The earlier established HPLC method was applied to study the stability of tramadol hydrochloride and ketamine hydrochloride in PCA solution. The peak-area of drugs was recorded and the concentrations of the 2 compositions in the compatible dosage were calculated by the calibration equations. The starting concentration of drugs was designed as 100%. Tables 1–3 present the results of this study.

As indicated in Tables 1–3, the percentages of tramadol hydrochloride and ketamine hydrochloride remaining in the drug mixtures were higher than 98.0% with non-statistically significant differences found after 14 days of storage both at 4°C and 25°C ( $p>0.05$ ). No degradation products of tramadol hydrochloride and ketamine hydrochloride were detected in any of the samples.

After 14 days of storage at 25°C or 4°C, there were no notable changes observed in physical appearance or color of the solutions in any of the samples. The pH value increased by only about 0.2 units for all drug mixtures over the 14 days; this change was considered insignificant.

### Discussion

An effective postoperative pain management regimen is vital to patient recovery after surgery. Multi-modal analgesia, using different classes of analgesics, is the currently recommended method to obtain this goal [14]. Of the multi-modal approaches, combining an opioid with other analgesics, such as local anaesthetics, nonsteroidal anti-inflammatory drugs, NMDA antagonists, antiemetic, alpha-2 adrenergic agonists, or glucocorticoid, for the management of severe pain has become an accepted method in reducing the doses of individual drugs, in providing superior pain relief, and in reducing adverse

effects [15]. One such multi-modal protocol is the combination of ketamine and tramadol. Unlugenc et al. [7] showed, in a small trial, that ketamine/tramadol combinations achieved limited improvement in early postoperative analgesia compared with tramadol alone. Chi et al. [8] has reported that ketamine as an adjuvant to tramadol for intravenous PCA in patients with hypohepatia after surgery can improve the effect of analgesia and reduce tramadol consumption. Webb et al. [9] administered a small-dose ketamine infusion with a tramadol infusion and found that ketamine combined with tramadol resulted in superior analgesia, less sedation, and reduced need for physician intervention to manage pain after major abdominal surgery.

Currently, no information is available about the chemical stability of this tramadol/ketamine analgesic mixture. In many cases, combinations of different drugs are administered together, resulting in the possibility of drug incompatibility or loss of stability. Incompatibility might cause drug precipitation or crystallization, resulting in blockage of the cannula, skin irritation, and poor absorption or loss of potency. Thus, it is necessary to establish the stability of these mixtures if we are to use them in such a manner.

Previously, the physical compatibility and stability of ketamine, tramadol, singly or combined with other drugs, has been widely studied. Tramadol combined with a variety of parenteral medications such as ketorolac tromethamine, alizapride, haloperidol, hyosine N-butyl bromide, metoclopramide hydrochloride, droperidol, dexamethasone, metamizole, ropivacaine, or bupivacaine were stable and compatible in the presence of tramadol hydrochloride [16–27]. As for ketamine stability, the previous tests showed that ketamine is stable in various infusion fluids, concentrations, containers, and storage conditions and with some drugs in binary admixtures [28–38]. Unfortunately, no published information is available on the compatibility and stability of tramadol in combination with ketamine in PCA solution. Therefore, the aim of this study was to remedy this lack of information.

**Table 1.** Stability of tramadol (5 mg/mL) and ketamine (0.5 mg/mL) in 0.9% sodium chloride stored in polyolefin bags at 4 and 25°C.

Temperature and drug	Initial conc. (mg/mL)*	Mean ±S.D.% initial conc. remaining*						
		Day 1	Day 2	Day 3	Day 5	Day 7	Day 10	Day 14
4°C								
Tramadol	5.1±0.02	98.5±0.3	99.4±0.1	99.6±0.2	98.8±0.9	100.5±0.4	99.7±0.2	100.6±0.1
Ketamine	0.5±0.04	99.9±0.1	99.5±0.2	99.5±0.2	99.2±0.5	101.1±0.3	99.9±0.2	99.4±0.4
25°C								
Tramadol	5.1±0.03	99.1±0.4	99.6±0.1	99.7±0.7	99.4±0.5	99.9±0.2	100.1±0.1	99.7±0.2
Ketamine	0.49±0.06	99.7±0.1	100.6±0.1	100.6±0.2	100.5±0.7	100.7±0.4	99.8±0.2	99.5±0.1

\* n=3.

**Table 2.** Stability of tramadol (5 mg/mL) and ketamine (1.0 mg/mL) in 0.9% sodium chloride stored in polyolefin bags at 4 and 25°C.

Temperature and drug	Initial conc. (mg/mL)*	Mean ±S.D.% initial conc. remaining*						
		Day 1	Day 2	Day 3	Day 5	Day 7	Day 10	Day 14
4°C								
Tramadol	5.1±0.02	101.2±0.2	99.7±0.3	100.2±0.9	99.3±0.1	100.0±0.4	98.9±0.2	100.1±0.2
Ketamine	1.0±0.02	99.2±0.1	100.6±0.5	99.5±0.8	100.1±0.1	99.8±0.1	100.7±0.2	100.9±0.3
25°C								
Tramadol	5.0±0.01	100.0±0.1	100.1±0.1	100.8±0.5	98.6±1.0	101.1±0.7	99.3±0.1	100.2±0.2
Ketamine	1.1±0.08	100.9±0.1	101.6±0.4	98.8±0.2	100.4±0.2	99.5±0.1	99.6±0.8	101.2±0.2

\* n=3.

**Table 3.** Stability of tramadol (5 mg/mL) and ketamine (2.0 mg/mL) in 0.9% sodium chloride stored in polyolefin bags at 4 and 25°C.

Temperature and drug	Initial conc. (mg/mL)*	Mean ±S.D.% initial conc. remaining*						
		Day 1	Day 2	Day 3	Day 5	Day 7	Day 10	Day 14
4°C								
Tramadol	5.0±0.03	99.4±0.1	102.2±1.2	99.7±0.3	100.0±0.1	99.3±0.1	100.9±0.2	99.6±0.2
Ketamine	2.1±0.05	99.6±0.5	101.8±0.8	100.2±0.4	100.3±0.3	99.7±0.2	100.5±0.6	99.6±0.1
25°C								
Tramadol	5.0±0.1	99.8±0.2	100.1±0.1	99.7±0.1	98.7±0.5	100.2±0.1	100.5±0.6	99.3±0.1
Ketamine	2.1±0.09	100.3±0.5	99.8±0.1	99.6±0.1	99.7±0.2	98.4±0.6	101.2±0.1	99.5±0.1

\* n=3.

In the present study, there were no notable changes in pH or color in any of the solutions stored in polyolefin bags at 4°C or 25°C for 14 days. All formulations of tramadol/ketamine remaining in the drug mixtures were higher than 98.0% of their initial concentration. The results indicate that the drug mixtures of tramadol with ketamine were physically compatible and chemically stable for 14 days when diluted with NS for PCA delivery system use.

When mixing drugs taken from ampoules of sterile solutions, there is also the potential issue of bacterial contamination. In the present study, we have only examined physicochemical stability without taking into consideration microbial contamination. In clinical practice, we should follow the guidelines in the USP (United States Pharmacopeia)/NF (National Formulary) Chapter 797 [39]. In this regulation, the preparation is a low-risk compounding sterile product. It specifies that storage at

room temperature or at refrigerated temperatures for low-risk compounding should not exceed 48 h and 14 days, respectively. Given that sterility can change according to site, equipment, operator, and procedures used, the following cautions are suggested: (1) the preparation should be used by the date at room temperature for 48 h or at refrigerated temperatures for 14 days on the basis of USP specifications; (2) The infusion can be safely prepared and stored in a hospital pharmacy using aseptic technique by licensed central intravenous additive (CIVA) services.

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## Conclusions

Admixtures of tramadol (5.0 mg/mL) combined with ketamine (0.5, 1.0, or 2.0 mg/mL) were stable for 14 days when diluted with NS, packaged in **polyolefin** bags, and stored at either 4°C or 25°C. We conclude that this solution can be safely prepared and stored (in the dark) for up to 14 days in advance by licensed central intravenous additive (CIVA) services.

## Competing interests

None.

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