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Intravenous patient-controlled analgesia: in vitro stability profiles of mixtures containing fentanyl, hydromorphone, oxycodone, nefopam, ondansetron, and ramosetron

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Abstract

Background and objectives: Patient-controlled analgesia often involves combinations of multiple drugs. This study aimed to determine the stability of drug mixtures commonly used for intravenous patient-controlled analgesia.

Materials and methods: We examined four of the most commonly used drug combinations in intravenous patient-controlled analgesia at our institution. Mixtures contained fentanyl (400 μg), either oxycodone (10 mg) or hydromorphone (4 mg), nefopam (20 mg), and either ondansetron (10 mg) or ramosetron (0.3 mg). Each drug mixture was diluted in 0.9% saline and stored in a portable patient-controlled analgesia system at room temperature (24 °C) for 96 h. Physical attributes including color, turbidity, and precipitation were assessed using digital imaging and optical microscopy. Sterility testing was conducted to assess for microbiological contamination. The pH of each mixture was monitored for up to 96 h after mixing. The concentration of each drug in the mixture was also evaluated using high-performance liquid chromatography.

Results: All mixtures remained colorless and transparent with no visible sediment for 96 h. After 14 days of culture, none of the samples showed bacterial or fungal growth. The pH for all mixtures was maintained between 4.17 and 5.19, and the mean pH change in any mixture was less than 0.4 over the study period. The concentration of each drug remained between 90 and 110% of the initial value for 96 h after mixing.

Conclusion: Four drug mixtures commonly used for intravenous patient-controlled analgesia are physiochemically stable and remain sterile for 96 h after mixing.

Keywords: Patient-controlled analgesia, Sterility, pH, Chromatogram, Fentanyl, Hydromorphone, Oxycodone, Nefopam, Ondansetron, Ramosetron

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Introduction

Patient-controlled analgesia (PCA) allows the patient to self-administer a prescribed amount of intravenous (IV) opioid-based analgesia for the management of pain (Grass 2005). PCA is widely used to control postoperative pain and several other types of acute pain, as well as chronic pain associated with cancerous tumors (Buvanendran and Kroin 2007). In addition to reducing postoperative pain, PCA can aid early mobilization, reduce the length of hospital stay, and increase patient satisfaction (Buvanendran and Kroin 2007). Multimodal analgesia, which is the combination of different classes of analgesics, has been increasingly used for PCA (Joshi 2005; Jin and Chung 2001). The use of different types of analgesics decreases overall drug use and reduces complications caused by high doses of opioid analgesics (Vendittoli et al. 2006; Berger et al. 2009).

PCA involves the mixing of several drugs into a single storage pouch, after which the drug mixture is administered to the patient at a constant rate. If the patient is in severe pain or needs additional medication, PCA affords the convenience of providing pain control with the push of a button. Currently, all IV PCA cocktails used at our institution include a low concentration of fentanyl, which has a short onset and duration of action. In addition, PCA cocktails often include either oxycodone or hydromorphone, both of which have a relatively long onset and duration of action. Most cocktails also include nefopam, which has a mechanism of analgesia that is different from that of opioids; the use of this agent helps reduce the dose of required opioids, which in turn reduces opioid-related side effects (Son et al. 2017; Aveline et al. 2009). To further reduce the opioid-induced side effects of nausea and vomiting, antiemetic drugs can be added to IV PCA (Estan-Cerezo et al. 2017). Thus, to create a balanced and effective treatment, PCA cocktails may contain up to four different therapeutic compounds.

To ensure consistent safety and efficacy, PCA cocktails must maintain sterility, remain physiochemically stable without inter-drug interactions, and maintain the original concentrations of all agents. However, when two or more drugs are mixed, physical and chemical changes may occur, resulting in alterations of therapeutic properties and an increase of the risk of side effects (Gikic et al. 2000; Trissel 2011). For example, auto-crystallization can occur when different drugs are mixed (Hwang et al. 2016), and these crystals could potentially clog the IV tubing. Further, it is also possible that such crystals could obstruct blood vessels and cause unexpected side effects.

The purpose of this study was to determine whether these drug mixtures are stable and maintain the original concentration of all agents over time. We mixed some of the more common PCA medications and evaluated their physical stability, concentration, and sterility over 96 h in vitro.

Methods

Preparation of individual drug solutions

Fentanyl (Fentanyl Citrate injection, 50 μg/mL, 2 mL, Hana Pharm Co. Ltd., Seoul, Korea), oxycodone hydrochloride (OxyNorm® injection, 10 mg/mL, 1 mL, Mundipharma Korea Ltd., Seoul, Korea), hydromorphone hydrochloride (Dilid injection, 1 mg/mL, 1 mL, Hana Pharm Co. Ltd., Seoul, Korea), nefopam hydrochloride (Acupan® injection, 10 mg/mL, 2 mL, Pharmbio Korea Inc., Seoul, Korea), ondansetron hydrochloride (Ondansetron injection, 2.5 mg/mL, 4 mL, Hana Pharm Co. Ltd., Seoul, Korea), and ramosetron hydrochloride (Nasea injection, 0.15 mg/mL, 2 mL, Astellas Pharma Inc., Seoul, Korea) were obtained from commercial suppliers (Table 1).

Drug mixtures

The concentrations and combinations of drugs tested were based on the most commonly used PCA mixtures for postoperative pain management in our institution. We created four mixtures using fentanyl (400 μg), oxycodone (10 mg), hydromorphone (4 mg), nefopam (20 mg), ondansetron (10 mg), and ramosetron (0.3 mg). Fentanyl and nefopam were present in all mixtures. In addition, the mixtures contained either oxycodone or hydromorphone as an additional opioid, and either ondansetron or ramosetron as an antiemetic. A total of four drug combinations were evaluated (Table 2).

Drug combinations were diluted in 0.9% saline to produce a total volume of 25 mL. While the drug mixtures were identical to those used in clinical practice, the total volume was half of that used in practice. Each mixture was stored in a portable balloon infusion device (Auto-Fuser pump; ACE Medical Co. Ltd., Seoul, Korea) configured to deliver 0.5 mL per hour. Devices were stored at room temperature (24 °C) and shaded from sunlight. Drug concentrations were as follows: fentanyl, 0.016 mg/mL; oxycodone, 0.4 mg/mL; hydromorphone, 0.08 mg/mL; nefopam, 0.8 mg/mL; ondansetron, 0.32 mg/mL; and ramosetron, 0.012 mg/mL.

Five replicates were prepared for each mixture. Replicates were used for analysis over time. All mixtures were prepared under a hood in sterile conditions by researchers wearing surgical masks, caps, overshoes, gowns, and sterile gloves.

Mixture stability

Physical characteristics

Appearance, clarity, and color Each mixture was examined for color, turbidity, and precipitation. Samples (3 mL) were extracted immediately after mixing and at 24, 48, 72, and 96 h after mixing. Extracted samples were placed in colorless silicate glass test tubes and visually

Table 1 Concentration, chemical formula, molecular weight, and pH of each drug used

Drug	Concentration before mixing (mg/mL)	Chemical formula	Molecular weight	pH
Fentanyl citrate	0.05	$C_{28}H_{36}N_2O_8$	336	5.61
Oxycodone hydrochloride	10	$C_{18}H_{22}ClNO_4$	315	5.05
Hydromorphone hydrochloride	2	$C_{17}H_{20}ClNO_3$	285	3.94
Nefopam hydrochloride	10	$C_{17}H_{20}ClNO$	254	5.23
Ondansetron hydrochloride	2	$C_{18}H_{20}ClN_3O$	294	3.14
Ramosetron hydrochloride	0.15	$C_{17}H_{17}N_3O$	279	4.33

inspected for clarity, color changes, particulate matter, and turbidity (when viewed against white and black backgrounds). Fine crystal formation was assessed using an optical microscope (Olympus BX51 microscope; Olympus, Germany). Physical stability was defined as retention of the transparent, colorless, particle-free appearance of the original solution (Trissel and Martinez 1993).

Microbiological stability

Sterility Four 2 mL samples were extracted from each drug mixture 96 h after mixing. To determine whether aerobic bacteria or *Candida albicans* could be cultured, two samples were seeded into two trypticase soy broth (TSB) culture dishes, respectively. To determine whether anaerobic bacteria could be cultured, two samples were seeded into two thioglycolate broth (TGB) culture dishes, respectively. One TSB plate and one TGB plate were incubated at 24 °C for 14 days, while the other TSB and TGB plates were incubated at 36 °C for 14 days. For a negative control, 2 mL of sterile distilled water was added to one TSB plate and one TGB plate. This analysis was performed for all four mixtures and repeated five times per mixture. The aforementioned incubation times and temperatures were chosen because the European Pharmacopoeia recommends an incubation time of 14 days at a temperature of between 20 and 36 °C to allow for the development of bacteria and fungi from these types of samples (European Pharmacopoeia 2005).

Chemical stability

pH pH was measured immediately after mixing and 24, 48, 72, and 96 h afterwards. pH measurement was performed using a digital pHs-3c pH meter (Orion Star A212; Thermo Scientific, Melbourne, Australia). At each time point, measurements were repeated five times for each mixture, and mean and standard deviation were then calculated. A change in pH was thought to indicate a change in chemical properties over time.

Drug concentrations The concentration of each drug in each mixture was evaluated using high-performance liquid chromatography (HPLC). Before analysis of the mixtures, HPLC was used to create a baseline chromatogram for each of the individual drugs. Owing to detector saturation, we were unable to accurately calculate the peak area for oxycodone, nefopam, and ondansetron. Therefore, to support accurate calculation of drug concentrations, mixtures 1B, 2B, 3B, and 4B were prepared based on the maximum concentrations of oxycodone, nefopam, and ondansetron that would not result in saturation. The concentrations of drugs in these B mixtures were as follows: fentanyl, 0.016 mg/mL; oxycodone, 0.1 mg/mL; hydromorphone, 0.08 mg/mL; nefopam, 0.08 mg/mL; ondansetron, 0.04 mg/mL; and ramosetron, 0.012 mg/mL. The B mixtures were prepared as previously described. Five replicates were prepared for each mixture.

Samples (100 μL) of the B mixtures were obtained immediately after mixing and 24, 48, 72, and 96 h afterwards. Using HPLC, we were able to confirm whether the concentration of each drug was maintained over time. By comparing the chromatograms from the B mixtures to the baseline individual drug chromatograms, we could determine whether drug degradation had occurred. The presence of degradation products could potentially interfere with the quantification of drug concentrations based on measurements taken more than 24 h after mixing.

The concentration of each drug measured immediately after mixing was defined as 100%, and the concentration relative to this was calculated for each time point. Using

Table 2 Drug combinations evaluated in this study

	Opioid	Additional opioid	Non-opioid analgesic	Antiemetic
Mixture 1	Fentanyl 400 μg	Oxycodone 10 mg	Nefopam 20 mg	Ondansetron 10 mg
Mixture 2	Fentanyl 400 μg	Oxycodone 10 mg	Nefopam 20 mg	Ramosetron 0.3 mg
Mixture 3	Fentanyl 400 μg	Hydromorphone 4 mg	Nefopam 20 mg	Ondansetron 10 mg
Mixture 4	Fentanyl 400 μg	Hydromorphone 4 mg	Nefopam 20 mg	Ramosetron 0.3 mg

five replicates, we calculated the mean and standard deviation for the change in concentration of each drug in each mixture at each time point. Stability of drug concentration was defined as maintaining 90–110% of the initial drug concentration, as stated in the current US Pharmacopeia (United States Pharmacopeial Convention 2007).

HPLC equipment and chromatography conditions A YL9100 HPLC system (Younglin Instrument Co., Ltd., South Korea) was used for reverse-phase HPLC. The YL9100 HPLC system consists of a YL9110 quaternary pump, a YL9101 vacuum degasser, and a YL9120 UV/Vis Detector run with the YL Clarity software program. HPLC separation was performed on a Vydac C18 column (250 × 7.6 mm internal diameter). Gradient elution was performed using a solution of 0.05% trifluoroacetic acid in water and a solution of 0.05% trifluoroacetic acid in acetonitrile. The flow rate was 1.5 mL/min (flow conditions: 0–50 min—increasing concentration of acetonitrile from 10 to 70%; 50–60 min—water 30%, acetonitrile 70%). The UV/Vis detector wavelength was set between 214 and 254 nm. The column was maintained at room temperature, and the injection volume was 100 μL.

Validation of analyses

According to the guidelines established by the International Conference on Harmonization (International Conference on Harmonization 1996), validation of analytical techniques includes the demonstration of linearity, accuracy, and repeatability.

Linearity

The relationship between the peak area for each drug and the amount of drug added was determined using linear regression analysis over a previously defined range. Calibration for each drug standard was achieved by completing this analysis four times at four different concentrations.

Accuracy

Accuracy was assessed using the relative standard deviation (RSD) or coefficient of variation of accuracy (CVa = RSD × 100), calculated using the mean and standard deviation of the theoretical and experimental concentrations measured four times for each of four drug concentrations. The CVa for each drug was calculated for mixtures 1B, 2B, 3B, and 4B.

Repeatability

The analysis of the concentration of drugs in each mixture was repeated in the same way five times. Repeatability is expressed in terms of RSD or the coefficient of variation of repeatability (CVr) using the mean and standard deviation of the values from the five repeats. The CVr for each drug was calculated for mixtures 1B, 2B, 3B, and 4B.

Results

Physical stability

Appearance, clarity, and color

All mixtures were colorless and transparent and did not contain visible particles or sediment in any of the assessments after mixing. No evidence of incompatibility between the agents (precipitation, turbidity, or color change) was observed (Supplementary file 1, 2).

Microbiological stability

Sterility test

None of the 80 mixture samples showed bacterial or fungal growth. No bacterial or fungal growth was observed in the control samples (sterile distilled water) (Supplementary file 3).

Chemical stability

pH

The pH for all mixtures was maintained within the range of 4.17–5.19, and the mean pH value for each mixture changed by less than 0.4 from the initial measurement to the final measurement at 96 h (Table 3; Supplementary file 4).

Concentration

The concentration of each individual drug in each B mixture was calculated by determining the area under the appropriate chromatographic peak through integration (Supplementary file 5). The approximate retention times were as follows: fentanyl, 29.8 min; hydromorphone, 11.8 min; oxycodone, 15.5 min; nefopam, 26.7 min; ondansetron, 23.7 min; and ramosetron, 24.7 min (Fig. 1).

Figure 2 shows the change in concentration of each drug over time. It can be seen that the concentration of each drug in all B mixtures remained between 90 and 110% of the original concentration at each time point (Fig. 2). Linear regression analysis revealed that all drugs

Table 3 pH values for each mixture at all time points

Time after mixing	Mixture 1	Mixture 2	Mixture 3	Mixture 4
Immediately	5.11 ± 0.10	5.04 ± 0.10	4.17 ± 0.06	4.17 ± 0.04
24 h	5.19 ± 0.03	5.08 ± 0.05	4.35 ± 0.02	4.38 ± 0.04
48 h	5.18 ± 0.06	5.04 ± 0.10	4.32 ± 0.02	4.32 ± 0.02
72 h	5.12 ± 0.12	5.04 ± 0.05	4.48 ± 0.08	4.52 ± 0.04
96 h	5.15 ± 0.06	5.02 ± 0.06	4.42 ± 0.08	4.42 ± 0.10

Mixture 1: fentanyl, oxycodone, nefopam, and ondansetron; mixture 2: fentanyl, oxycodone, nefopam, and ramosetron; mixture 3: fentanyl, hydromorphone, nefopam, and ondansetron; mixture 4: fentanyl, hydromorphone, nefopam, and ramosetron. Data are presented as the mean ± standard deviation

remained at over 93% of their initial concentration until 96 h after mixing.

Validation of analyses

Calibration

The calibration function for the concentration of each drug was determined using linear regression analysis (Supplementary file 6). Linear regression equations were as follows: fentanyl, y = 114004 (x) + 142, mean r^2 0.9999; oxycodone, y = 175523 (x) − 807, mean r^2 = 0.9982; hydromorphone, y = 182664 (x) − 1113, mean r^2 = 0.9991; nefopam, y = 210487 (x) − 387, mean r^2 = 0.9992; ondansetron, y = 417090 (x) − 66, mean r^2 = 0.9990; and ramosetron, y = 419025 (x) − 1528, mean r^2 = 0.9962. For all drugs, the relationship between the peak area and concentration was linear with high correlation coefficients (r^2). These equations allowed the determination of the concentration of each drug in the mixture.

Accuracy

The calculated CVa between the calculated theoretical concentration and the observed experimental concentration for each drug was as follows: fentanyl, 3–4.6% (accuracy ≥ 95.4%); oxycodone, 1.7–1.9% (accuracy ≥ 98.1%); hydromorphone, 3.9–4.1% (accuracy ≥ 95.9%); nefopam, 0.2–2.4% (accuracy ≥ 97.6%); ondansetron, 0.2–3.1% (accuracy ≥ 96.9%); and ramosetron, 2.9–4.7% (accuracy ≥ 95.3%). The CVa for all six drugs in all combinations in the B mixtures was less than 5.0%.

Repeatability

The CVr for each drug was calculated using the results obtained from five repetitions for each B mixture. The CVr values were as follows: fentanyl, 0.5–2.5% (accuracy ≥ 97.5%), oxycodone, 1.1–2.5% (accuracy ≥ 97.5%); hydromorphone, 1–1.2% (accuracy ≥ 98.8%); nefopam, 0.7–2.3% (accuracy ≥ 97.7%); ondansetron, 1.0–1.1% (accuracy ≥ 98.9%); and ramosetron, 0.8–1.6% (accuracy ≥ 98.4%). The CVr for all six drugs in all B mixtures was less than 3.1%.

Discussion

We evaluated the physical, chemical, and microbiological stability of four drug mixtures commonly used in our hospital for IV PCA. Each mixture contained four drugs: fentanyl, either oxycodone or hydromorphone, nefopam, and either ondansetron or ramosetron. We found that these mixtures were physiochemically stable and remained sterile for up to 96 h after mixing.

IV PCA with opioid analgesics is the most widely used method for managing acute pain after major surgery (Aveline et al. 2009). However, the use of opioid

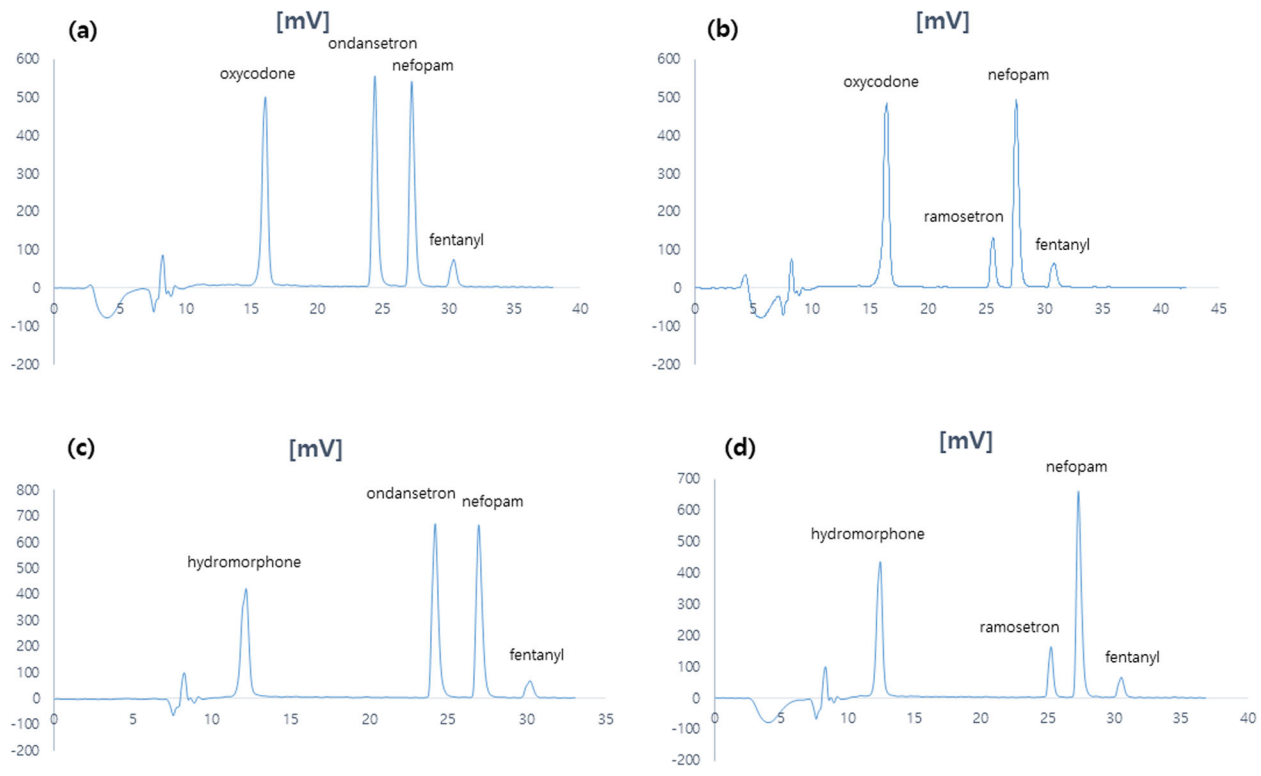

Fig. 1 Chromatograms from samples taken immediately after preparation of the B mixtures. **a** Mixture 1B. **b** Mixture 2B. **c** Mixture 3B. **d** Mixture 4B

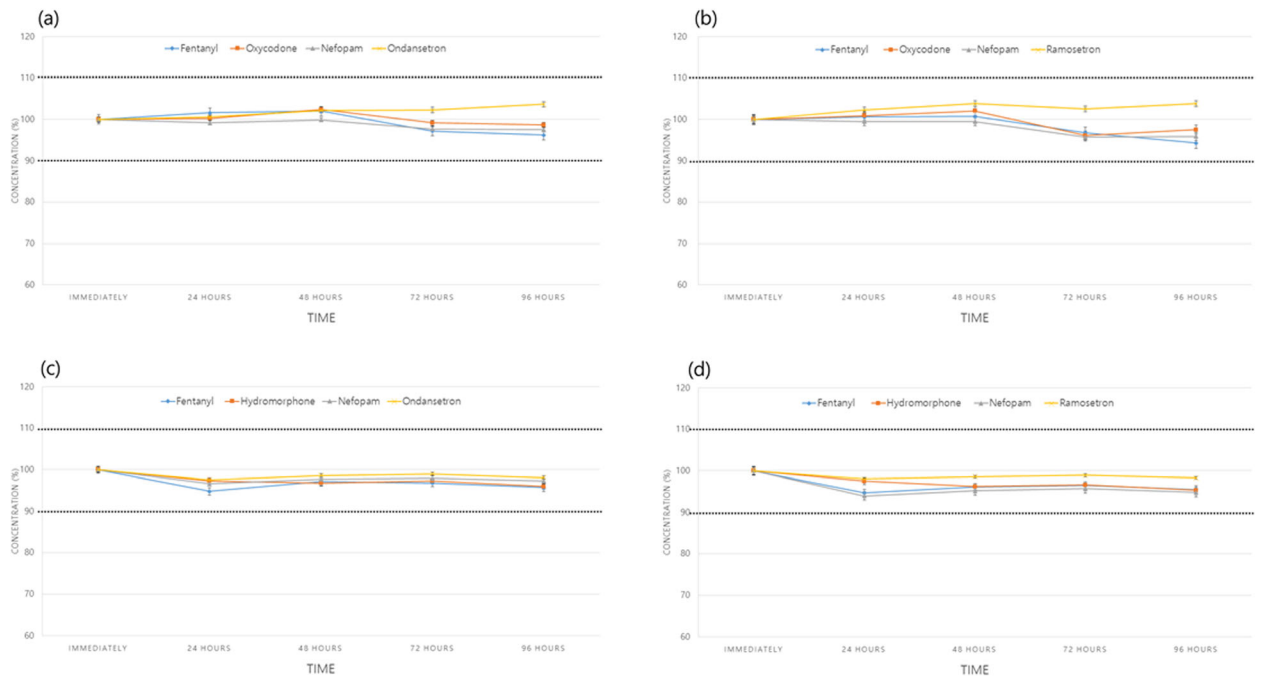

Fig. 2 Changes in the concentration of drugs in B mixtures over time. The concentration measured immediately after mixture preparation was taken to be 100%. **a** Mixture 1B. **b** Mixture 2B. **c** Mixture 3B. **d** Mixture 4B

analgesics has been linked to postoperative nausea and vomiting, dizziness, pruritus, and respiratory depression (Friedman et al. 2008; Woodhouse et al. 1999; Shapiro et al. 2005). Combining opioid analgesics with supplemental analgesics such as nefopam adds an extra mechanism of analgesia. This increases the effectiveness of treatment and reduces the required dose of each individual agent, which in turn leads to a reduction in side effects (Aveline et al. 2009; White 2008). The addition of antiemetic agents to IV PCA decreases the occurrence of nausea and vomiting.

Drug mixtures used in IV PCA are usually prepared while the patient is in surgery. Although the safety of these combinations is supported by years of anecdotal evidence, there is little supporting scientific evidence. It is important to gain reliable information about the compatibility of agents used in these mixtures, as the IV route is often used for pain management after surgery. Therefore, the purpose of this study was to address this lack of information.

The stability of certain drug mixtures has been previously reported. Fentanyl is stable for up to 48 h when mixed with 5% dextrose or 0.9% saline and stored in glass or polyvinyl chloride containers (Kowalski and Gourlay 1990). Moreover, fentanyl is stable when mixed with midazolam and either hyoscine butyl bromide or metoclopramide and stored in polypropylene syringes for 1 week at ≤ 32 °C (Peterson et al. 1998). Solutions of fentanyl diluted with 0.9% saline are stable when stored in a polyvinyl chloride portable infusion pump for 14 or 30 days at 23 °C (Chapalain-Pargade et al. 2006). Oxycodone, either pure or diluted with 0.9% saline, 5% dextrose, or water for injection, is stable when stored at room temperature for 28 days in a PCA device (Amri et al. 2010). Furthermore, oxycodone is physically and chemically stable when mixed with ketamine, diluted in 0.9% saline, and stored at 23 °C for 7 days in a polypropylene syringe or polyvinyl chloride bag (Daouphars et al. 2018). Hydromorphone (100 μg/mL in 0.9% saline) is unstable when stored in a polypropylene syringe for 100 days (Anderson and MacKay 2015). Nefopam is chemically stable for 24 h when mixed with paracetamol or ketoprofen (Troitzky et al. 2008) or ketamine (Hamdi et al. 2009). While these published studies provide useful information regarding the stability of these agents, no previous studies have evaluated the stability of mixtures currently used in IV PCA protocols in the clinic. We, therefore, evaluated the physical, chemical, and microbiological stabilities of mixtures containing fentanyl, either oxycodone or hydromorphone, nefopam, and either ondansetron or ramosetron.

Helin-Tanninen et al. (2013) reported that a significant increase in drug concentration can occur as a result of evaporation through polyester injection bags when drug mixtures are stored at room temperature in the absence of tightly closed secondary packaging. In our study, there was no significant increase or decrease in the concentration of each drug in any of the mixtures up to 96 h after mixing, suggesting that evaporation did not occur from the portable balloon infusion pump used in this study.

Hwang et al. (2016) reported that interactions between acidic and basic drugs can result in precipitation and crystallization upon mixing. All drugs used in this study had a pH of ≤ 5.61 before mixing. The pH for each mixture ranged from 4.17 to 5.11 and remained stable up to 96 h after mixing, suggesting that these drugs were compatible with each other and their chemical properties remained consistent over time.

This study had certain limitations. First, while the drugs used in this study were shown to be chemically and microbiologically stable and physically compatible in vitro for up to 96 h after mixing, this does not automatically guarantee that their pharmacokinetic and pharmacodynamic properties will be stable in vivo. It is, therefore, advisable to conduct clinical trials to evaluate the pharmacokinetic and pharmacodynamic properties of these drug mixtures.

Second, the clinical concentrations of oxycodone, nefopam, and ondansetron in the original mixtures caused saturation of the HPLC detector. Thus, it was not possible to determine the concentrations of these drugs in the original mixtures. We instead used reduced concentrations for the HPLC study; this may have biased the results.

Third, this study conducted a stability study based on the combination of drugs used at our institution only. Further research should be extended to stability studies including other opioids, non-steroidal anti-inflammatory drugs, and other antiemetics commonly used in PCA.

Fourth, in order to eliminate any potential bias caused by the effects of light on drug stability, this study investigated the stability of the PCA device while being shaded for 96 h. However, in practice, when a PCA device is used in a patient, it is often used without shading. Future studies should aim to assess drug stability both when the PCA device is shaded and when it is not.

Conclusions

We evaluated four drug combinations containing fentanyl, either oxycodone or hydromorphone, nefopam, and either ondansetron or ramosetron. These mixtures were prepared by diluting the drugs with 0.9% normal saline in a portable balloon infusion device. We demonstrated that all four mixtures were chemically and microbiologically stable and physically compatible. Further evaluation of these mixtures and mixing conditions in a clinical setting would be necessary to confirm their pharmacokinetic and pharmacodynamic stability in vivo.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40543-020-00230-w.

Additional file 1. Images from the visual observation of all mixtures.

Additional file 2. Optical microscopy images for all mixtures.

Additional file 3. Images of microbiological culture for all mixtures.

Additional file 4. pH values at each time point for all mixtures.

Additional file 5. Concentration values over time for each drug in all mixtures.

Additional file 6. Calibration values.

Abbreviations

PCA: Patient-controlled analgesia; IV: Intravenous; TSB: Trypticase soy broth; TGB: Thioglycolate broth; HPLC: High-performance liquid chromatography; RSD: Relative standard deviation; CVa: Coefficient of variation of accuracy; CVr: Coefficient of variation of repeatability

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Authors' contributions

All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of data analysis. CHL and SSC designed the experiments. All authors were involved in performing the experiments. All authors searched and reviewed the literature and wrote the first draft of the manuscript. CHL and SSC performed a revision of the intellectual content and provided final approval of the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed in this study are available in the [OSF] repository, [https://osf.io/8k2nx/ or DOI 10.17605/OSF.IO/8K2NX]. Datasets are also submitted with manuscript files as additional supporting information files.

Competing interests

The authors declare that they have no competing interests.

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