Stability of Epinephrine in a Normal Saline Solution

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Objective: Dilution of concentrated epinephrine prior to intravenous use during clinical emergencies can delay urgent interventions. The objective of this study was to determine whether diluted epinephrine remains stable and sterile over time in common hospital settings.

Methods: Epinephrine samples were prepared by clinically relevant double dilution techniques. Samples were stored in 10-mL syringes and incubated under 1 of 4 simulated hospital environments with a mixture of lighting and temperature settings: 4°C/20°C, with or without fluorescent lighting. Samples were incubated for 0, 15, 30, 60, or 90 days. Capillary zonal electrophoresis was used to quantify the concentration of epinephrine and/or presence of any degradation products. All samples were tested for the presence of bacterial growth using blood agar cultures.

Results: Diluted epinephrine samples remained stable for up to 90 days in all 4 simulated clinical storage conditions. No bacterial colony-forming units were detected in any of the environmental samples regardless of incubation duration, light, or temperature conditions.

Conclusion: Diluted epinephrine for anticipated clinical emergencies may remain clinically useful for up to 90 days, thus improving patient safety, access to medications, and overhead costs by reducing waste.

Key Words: Epinephrine; Safety; Emergency; Stability; Normal saline.

Epinephrine is a small endogenous catecholamine with multiple uses in emergencies. In most clinical settings, epinephrine comes packaged in 2 forms: a 1:1000 (1 mg/mL) ampule or vial that must be diluted before intravenous (IV) use, and a 1:10,000 (1 mg/10 mL; 100 µg/mL) prepackaged syringe that is ready for IV use.[1] In true emergency situations requiring epinephrine, 100 µg/mL solutions of epinephrine are typically used during advanced cardiac life support for cardiac arrest.[2] During more urgent situations, such as mild refractory hypotension, bronchospasm, bradycardia, and allergic reactions, epinephrine may be used but should be diluted to a lower concentration of 10 µg/mL to help avoid inadvertent overdose.[3]

Such dilutions can make it challenging for a provider to draw up a dose of epinephrine for IV use quickly and accurately, especially under the stress and time constraints of a medical urgency. Current evidence indicates that many drugs remain stable past their labeled pharmaceutical expiration dates.[4,5] In addition, previous reports have shown that epinephrine is stable well beyond the US Food and Drug Administration (FDA) guidelines for storage.[6–11] However, a gap in knowledge exists regarding epinephrine stability in common hospital conditions for up to 90 days. Such information could potentially encourage manufacturers to create a prefilled low-dose (10 µg/mL) epinephrine product that meets FDA standards for storage. Currently, a 10 µg/mL epinephrine product is not commonly available and would require a double serial dilution of the 1 mg/mL solution or single dilution of the 100 µg/mL solution.

The primary objective of this study was to determine the stability of 1 mg/mL epinephrine in normal saline after clinically relevant double dilution and storage in a 10-mL syringe under standard hospital setting environments for up to 90 days. The secondary objective of this study was to determine the sterility of 1 mg/mL epinephrine in normal saline after clinically relevant double dilution and storage in a 10-mL syringe under standard hospital setting environments for up to 90 days.

Received March 16, 2023; accepted for publication October 9, 2023.

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Anesth Prog 71:109–114 2024 | DOI 10.2344/998301

METHODS

The syringes (BD PosiFlush, Becton Dickinson) used in this study were prepackaged 10-mL syringes of sterile 0.9% saline without any bacteriostatic additives or preservatives. During preparation, 1 mL was discarded from the syringe prior to the addition of the 1:1000 epinephrine (1-mL vial; Adrenalin, epinephrine injection, USP, Par Pharmaceutical) to achieve a total dilutional volume of 10 mL of 1:10,000 epinephrine (100 mcg/mL). Following the first dilution, 1 mL of the previous 100 μg/mL epinephrine sample was diluted again by adding it into a second saline syringe with 9 mL to yield a final dilution of 1:100,000 epinephrine (10 μg/mL). All epinephrine vials originated from the same lot. Alcohol swabs were used to disinfect the epinephrine vials prior to puncturing with a blunt-tip, 18-gauge needle. For both dilutions, mixture was accomplished by inverting the syringes several times. Nonsterile gloves and a procedural, level 1 mask were worn during the serial dilutions.

The clinically relevant double-dilution technique described above was used to produce epinephrine solutions of approximately 10 μg/mL. A total of 3 samples were made for each of the 4 testing environments that were analyzed at 5 time points (0, 15, 30, 60, 90 days) yielding 60 total samples. To ensure consistency, all double dilutions were performed by the same individual. Samples were prepared in sterile, 10-mL syringes and incubated under 4 different common hospital environments.

The 4 standard hospital environments were emulated with a mixture of lighting and temperature settings, and 3 syringes containing 10 μg/mL epinephrine solutions were placed into each of the following settings: refrigerated (4°C) with fluorescent lighting (light), refrigerated (4°C) with no light (dark), ambient temperature (20°C) with fluorescent lighting (light), ambient temperature (20°C) with no light (dark).

Capillary Zonal Electrophoresis

Samples were frozen after storage and kept at −20°C until analysis by capillary zonal electrophoresis (CZE), which was used to measure the present levels of epinephrine. CZE assays for epinephrine were based on previously published methods[12,13] that used a buffer system of 25 mM Tris (pH 2.5), 20% MeOH (v/v), and 15 mM heptakis-β-cyclodextrin. In the CZE assays, an electrical charge was used to separate epinephrine and related isomers based on the charge-to-mass ratios of the molecules. Epinephrine was detected and measured using its spectral absorbance (ie, ability to absorb specific wavelengths of light). Analysis of epinephrine standards confirmed the linearity of response for the CZE chromatography. The absorbance of light (measured in absorbance units) was directly proportional to the amount of epinephrine present in the samples across the range of concentrations used in this study. CZE measurements were performed using a Beckman-Coulter P/ACE MDQ unit at the Ohio Agricultural Research and Development Center Metabolite Analysis Cluster. The investigator performing the CZE measurements was blinded to the experimental conditions. Concentrations of epinephrine were determined using 8-point concentration curves generated with authentic epinephrine standards from a 1-mg/mL epinephrine vial (stored at ambient temperature) from the same lot as the experimental group.

Sterility Testing

To address sterility concerns with storing diluted epinephrine, all samples were tested for the presence of bacterial growth using blood agar cultures. Sterility testing was performed by streak-plating under aseptic conditions with a BSL-2 medical hood. Disposable, sterile needles were used to streak plate approximately 0.1 mL of the double-diluted 10-μg/mL epinephrine samples across agar plates (Thermo Scientific Blood Agar, Fisher Scientific). Agar plates were then transferred to a 37°C incubator for 48 hours.

Positive controls consisting of inoculating organisms from nonsterile media and negative controls consisting of sterile media without inoculating organisms were tested in parallel. Both control groups were added to validate the growth of test species in positive controls and the absence of test species in negative controls for this sterility assay. After 48 hours, the agar plates were analyzed for the presence of microbial growth using ImageJ with the Colony Counter plugin (ImageJ Version 1.52a, National Institutes of Health and the Laboratory for Optical and Computational Instrumentation at the University of Wisconsin).

Statistical Analysis

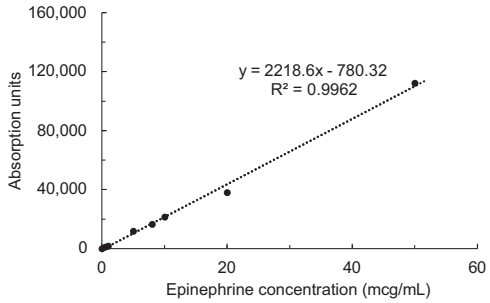
All data are expressed as averages ± standard deviation. To determine significant main effects and interactions between main factors, data were analyzed using analysis of variance (ANOVA) multifactor using RStudio version 1.1.456 (Posit Software). The threshold for statistical significance was set at $P < .05$.

RESULTS

Stability

Epinephrine levels were quantified using CZE with diode array detection. When using any method for analytical quantification of a molecular species in solution, it is critical to demonstrate that the method retains linearity of

Figure 1. CZE Concentration Response Curve



Representative concentration-response curve for CZE analysis of epinephrine. Epinephrine levels were quantified using diode array detection (DAD) at a wavelength of 205 nm. A stock solution of epinephrine was used to generate an 8-point standard curve, and the results of this concentration curve are shown here. Linearity of response, which is critical for quantification of epinephrine in solution, was demonstrated to be achievable across the range of epinephrine concentrations encountered in this study. The best-fit line for the standard curve shown here had an r^2 value of 0.9962, indicating a high degree of linearity and a strong correlation between concentration and absorbance unit response (peak area) across the concentrations of epinephrine used in subsequent experiments. The limit of detection (LOD) for epinephrine solutions used in this study was 1 µg/mL, and the maximum concentration on the standard curve was 50 µg/mL.

response across the concentrations measured in the course of the assay, ensuring that concentration calculations are accurate and precise. Using a standard curve generated using authentic standards, we were able to demonstrate that our CZE method showed linearity of response across all concentrations assayed in the sample sets used in this study (Figure 1).

CZE analysis detected no epinephrine degradation products (ie, only a single peak identical to that seen in pure epinephrine standards) at 15 and 30 days of incubation, regardless of temperature or light exposure. In addition, our analyses indicated that there was not a significant difference in the concentrations of epinephrine observed in samples stored for 0, 15, or 30 days of incubation, regardless of temperature or light exposure conditions (Figure 1; Tables 1 and 2). Across all time points, concentrations of epinephrine ranged between 12 and 19 µg/mL (Figures 1 and 2) under all light (light vs dark) and temperature conditions (4°C vs 20°C) as well as all combinations of light and temperature

Table 1. Epinephrine Absorption vs Environment (0, 15, and 30 Days)

	Peak Area, Mean (SD), Absorbance Units		
Environment	*Day 0*	*Day 15*	*Day 30*
Light/4°C	16,777 (3200)	15,408 (1853)	19,414 (5023)
Dark/4°C	20,700 (2737)	19,358 (3024)	19,971 (3363)
Light/20°C	15,638 (3355)	18,983 (2104)	14,894 (7099)
Dark/20°C	16,862 (1175)	20,051 (3425)	16,083 (5128)

Table 2. Epinephrine Concentration vs Environment (0, 15, and 30 Days)

	Concentration, Mean (SD), µg/mL		
Environment	*Day 0*	*Day 15*	*Day 30*
Light/4°C	15.5 (2.6)	14.4 (1.5)	17.6 (4.0)
Dark/4°C	18.7 (2.2)	17.6 (2.4)	18.1 (2.7)
Light/20°C	14.6 (2.7)	17.3 (1.7)	14.0 (5.7)
Dark/20°C	15.6 (0.9)	18.1 (2.7)	15.0 (4.1)

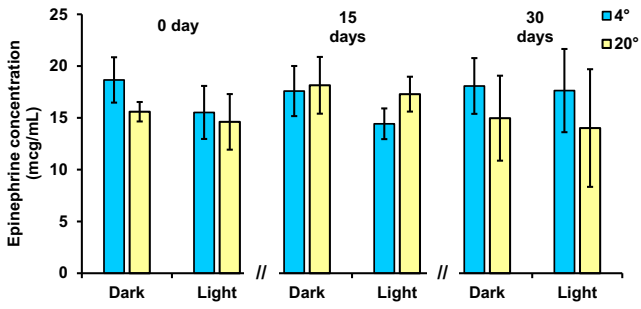
treatments (ie, dark at 4°C, dark at 20°C, light at 4°C, and light at 20°C).

ANOVA analyses indicated no significant differences in epinephrine concentrations in a single factor (day, $P = .867$; light, $P = .146$; temperature, $P = .33$), two-factor (day-light, $P = .844$; day-temperature, $P = .119$; light-temperature, $P = .522$), and three-factor (day-light-temperature, $P = .879$) interactions. These findings indicate that degradation of epinephrine was minimal and that the concentration of intact epinephrine was maintained for at least 30 days under all temperature and light storage conditions.

Stability Over Time: Epinephrine Concentration between 0 and 90 Days

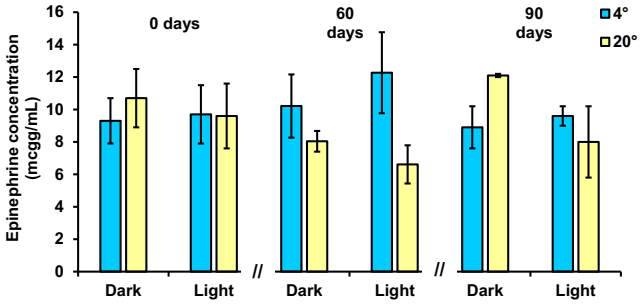
No chemical epinephrine degradation products (ie, no additional peaks on the capillary electrophoresis chromatogram) were detected at 60 and 90 days of incubation under all temperature and light storage conditions. Furthermore, as with the 0-, 15-, and 30-day samples, there was not a significant difference in epinephrine concentration between 0, 60, and 90 days of incubation regardless of temperature or light exposure or combination of light and temperature, indicating that there was little degradation of the target epinephrine molecule (Figure 3; Tables 3 and 4). Similarly, ANOVA analyses indicated no significant differences in epinephrine concentrations in single

Figure 2. Epinephrine Concentration Between 0 and 30 Days



The relatively uniform concentrations of epinephrine observed in samples across all day, light, and temperature treatments indicate that little or no degradation of epinephrine occurred in samples, regardless of the storage conditions. Bars represent average ± SD.

Figure 3. Epinephrine Concentration Between 0 and 90 Days



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factor (day, $P = .867$; light, $P = .146$; temperature, $P = .33$), two-factor (day-light, $P = .844$; day-temperature, $P = .119$; light-temperature, $P = .522$), and three-factor (day-light-temperature, $P = .879$) interactions. These data suggest that diluted epinephrine remained stable for up to 90 days regardless of temperature or light storage conditions.

Sterility

No bacterial colony-forming units (CFUs) were detected on any of the experimental samples regardless of incubation duration, temperature, or light conditions. Positive controls created from environmental swabs produced greater than 400 bacterial CFUs (Figure 4).

DISCUSSION

This study aimed to determine whether diluted epinephrine remains stable and sterile over time (0–90 days) in common hospital environments. Incubation duration, temperature, or light had no significant effects on epinephrine levels over the course of 90 days in terms of stability or sterility. Data from this study support epinephrine having a relatively high degree of stability when diluted in a normal saline solution with minimal degradation observed across all 4 storage environments.

Table 3. Epinephrine Absorption vs Environment (0, 60, and 90 Days)

	Peak Area, Mean (SD), Absorbance Units		
Environment	*Day 0*	*Day 60*	*Day 90*
Light/4°C	23,237 (4532)	29,682 (6245)	22,983 (1413)
Dark/4°C	22,339 (3448)	24,548 (4872)	22,138 (3207)
Light/20°C	22,994 (5078)	15,549 (2944)	18,977 (5409)
Dark/20°C	25,670 (4468)	19,109 (1597)	29,191 (345)

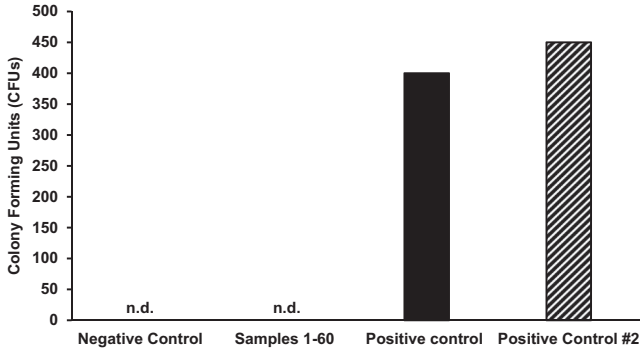
Table 4. Epinephrine Concentration vs Environment (0, 60, and 90 Days)

	Concentration, Mean (SD), µg/mL		
Environment	*Day 0*	*Day 60*	*Day 90*
Light/4°C	9.7 (1.8)	12.3 (2.5)	9.6 (0.6)
Dark/4°C	9.3 (1.4)	10.2 (1.9)	8.9 (1.3)
Light/20°C	9.6 (2.0)	6.6 (1.2)	8.0 (2.2)
Dark/20°C	10.7 (1.8)	8.0 (0.6)	12.1 (0.1)

Interestingly, although no significant differences were observed following temperature and light treatments for our 90-day study, we did note that samples in this data set showed within-group, sample-to-sample variation, specifically a low outlier of 6.6 µg/mL epinephrine for one of the samples (60-day/20°C/light) with the next lowest sample in this treatment group being 8.0 µg/mL. Since reduced concentrations of epinephrine were not detected in the later time points (ie, 90-day samples all had higher concentrations of epinephrine), this likely indicates that the low concentrations found in those samples represent an outlier or "false low" that is more likely the result of dilution error or injection error with the analytical equipment (ie, analysis variance) rather than actual epinephrine degradation.

As previously mentioned, precision instrumentation for dilution was not used in this study to replicate practical clinical application. Samples for analyses were prepared using gross approximation with prefilled saline syringes, blunt-tip needles, and highly concentrated epinephrine (1:1000, 1 mg/mL). The expected epinephrine concentration after double dilution was 10 µg/mL, but our final concentration ranged from 6.6 to 18.7 µg/mL (66%–187% of expected; Figures 2 and 3). Any error during sample preparation would likely be multiplied, as each sample required

Figure 4. Sterility Testing



Colony-forming units (CFUs) represent contamination as a function of the number of microbial cells present in the indicated samples. Samples 1 to 60 and the negative control sample did not show evidence of contamination (n.d. = no difference) due to absence of microbial cells. Positive controls showed evidence of contamination as expected.

the use of 2 prefilled saline syringes: one for the initial 1 mL of the 1:1000 (1 mg/mL) epinephrine vial for the first dilution, and a second for the 1 mL of the 1:10,000 (100 μg/mL) epinephrine syringe to complete the final dilution. While variance in sample preparation is the most plausible explanation for the observed within-group, sample-to-sample variance, an alternative hypothesis for the observed range of concentrations is that storing samples at −20°C may have induced some sample degradation prior to analysis. However, this is an unlikely explanation as it should have resulted in a consistent underrepresentation of epinephrine concentrations in samples with across-the-board reductions in peak area, rather than the stochastic variance observed across samples at all time points.

Finally, observed variability in the samples may have resulted from the variance present in the epinephrine solutions used to generate samples. Medications found in the vial prior to dilution may not have equivalent concentrations, as United States Pharmacopeia manufacturer standards state drug products must contain 90% to 115% of the product's noted concentration. This could account for an additional increase in sample intravariability, as any 1-mL vial of 1:1000 (1 mg/mL) epinephrine could possibly have 0.90 mg to 1.150 mg. However, this variance would not completely explain the effect observed in the samples, as our range of 6.6 to 18.7 μg/mL (66%–187% of expected) extends above and below the theoretical double dilution range of 9.0 to 11.50 μg/mL (90%–115% of expected). Interestingly, a previous study showed similar results, finding that the experimentation phase had higher concentrations than those present in control samples.[14] Regardless, this leads to a popular mantra used in clinical settings, "titrate to effect."

In-depth investigations on drug degradation resistance have been performed to preserve valuable resources. For example, brown ultraviolet-protecting bags and tinted vials have been used with epinephrine and other drugs to resist light degradation.[15] Chemical interactions can influence epinephrine degradation as well. For instance, bicarbonate has been shown to cause more rapid epinephrine degradation.[16] However, the addition of bisulfite has been shown to enhance epinephrine stability, especially with direct heat exposure.[17] Regardless, special precautions to ensure epinephrine stability by chemicals or barriers were not used in this study to increase practicality (ie, clinical relevance) and reduce overhead costs.

Epinephrine may remain relatively stable even in nonideal storage conditions.[18] For instance, high-concentration epinephrine drawn up into syringes and carried by anaphylactic-prone individuals while exposed to elevated temperatures and humidity remains relatively stable after 3 months.[19] Interestingly, when epinephrine is stored in high humidity, its concentration remains more stable than when exposed to a drier environment.[20] Epinephrine seems to be more sensitive to degradation when undergoing cyclic elevated temperature changes but does appear to be resistant to repeated freeze-thaw cycles.[14,17] However, the previously mentioned studies do not represent standard hospital settings but do contribute to the notion that epinephrine remains stable in nonfluctuating environments, thus providing further support for the results observed in this study.

In addition to the misconception that diluted drugs are not considered stable, another misunderstanding is that diluted drugs become contaminated over time when they are not stored in their original containers, thus being considered unacceptable for clinical use. As previously mentioned, the only standard aseptic techniques used in the current study included a mask, nonsterile gloves, and disinfection with an alcohol swab to represent practical bedside clinical conditions. Despite these methods, none of the experimental samples exhibited any bacterial growth, regardless of incubation duration, temperature, or light conditions (Figure 4). The presence of CFUs in only the positive controls suggests that diluted epinephrine remained sterile for up to 90 days, despite being stored under dark conditions. The lack of CFUs on the agar plates thus suggests that the samples were indeed sterile. However, not all pathogenic species can grow on blood agar, and the presence of any pathogenic anaerobes could not be excluded by the cultures because of the aerobic conditions used in the present study. Future experiments to address this could include the use of an animal model, where it would be possible to observe signs of infection and sepsis after medication use. These investigations may reveal the presence of an effect in epinephrine's biologic response or other potential health risks after certain storage conditions.

Several limitations exist in our study. An 18-gauge blunt needle is common for clinical practice and thus was used for all experiments in this study. However, we recognize that a smaller needle (larger gauge) would potentially increase dilution accuracy by having decreased dead space and may be a consideration in such practice.

The nature of CZE makes it difficult, if not impossible, to directly compare the concentrations and absorptions of the 0-, 15-, and 30-day trial to the 0-, 60-, and 90-day samples. This is because samples were measured in overlapping batches on different capillary columns, and epinephrine peaks exhibited retention times and concentration-response kinetics specific to each capillary. Changing capillaries between batches is necessary, as the large voltages used in CZE-based separations result in peak "drift" over time and, ultimately, column failure, making it impossible to run the large numbers of samples in the data set in one large, single batch. The need to run samples in batches as well as the time needed for method optimization and to perform CZE system maintenance between batch runs resulted in individual samples being maintained at −20°C for a period ranging from 5 to 6 months. However, as previously mentioned, epinephrine remains stable after multiple freeze thaw cycles, and in this instance, samples were subjected to only a single freeze-thaw event.[14] The overall effect is therefore likely minimal,

especially as all the sample batches were frozen together with their respective 0-day controls.

Another limitation of this study is that it assessed only epinephrine quantity and not quality. Future experiments to address this limitation and investigate the preservation of clinical effects could include analysis of expected increases in cardiac output after epinephrine administration using an animal model. This could be further extrapolated to investigate if significant biologic differences (ie, increase in heart rate or blood pressure and/or duration of action) appear between our range (6.6–18.7 μg/mL) of epinephrine concentrations.

CONCLUSION

The results of this study demonstrate that epinephrine in prefilled 0.9% saline syringes remained stable for at least 90 days in common clinical settings. Changes in epinephrine levels resulting from light, temperature, or incubation duration were less than those resulting from within-group, sample-to-sample variability. Furthermore, no bacterial CFUs were detected from any of the experimental samples, thus suggesting that epinephrine dilutions remained sterile for up to 90 days despite being stored under nonsterile conditions. As increasing evidence emerges, this may signal that the current FDA guidelines may warrant updating or that new concentrations of prefilled epinephrine syringes be available for purchase from drug manufacturers. These changes could result in less medical waste, reduced overhead expenditures, and increased access to medications, especially in parts of the world with limited resources.

ACKNOWLEDGMENTS

This research was supported by the American Society of Dental Anesthesiology Education & Research Foundation issued to Spencer D. Wade.

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