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Original Article

In-use Stability of Hydrocortisone Injection Preparations at a Regional Referral Hospital in Central Java

In-Use Stability Sediaan Injeksi Hidrokortison di Rumah Sakit Rujukan Daerah Jawa Tengah

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Abstract

Hydrocortisone Sodium Succinate 50mg injection is widely used in perinatology wards. These wards cater to newborns (0-28 days), low birth weight (<2.5 kg), or premature babies (<37 weeks), requiring special handling. The use of this injection requires a very small dose, so one vial of hydrocortisone injection can be used for more than one patient. Therefore, the remainder of this hydrocortisone injection is often stored for 24 hours in the refrigerator which will later be reused on other patients. This study aims to determine the in-use stability of hydrocortisone injection stored for 24 hours at 4°C and 25°C. This is certainly to improve patient safety. The data collection technique uses an observational method on hydrocortisone injection samples with 3 replications. In-use stability is assessed from the results of organoleptic tests, pH tests, viscosity tests, determination of drug levels using UV-VIS spectrophotometry and sterility tests. Testing was conducted on days 0, 1, 2, 3, 7, 14 and 30. The results of the study showed that hydrocortisone injection preparations stored for 1 day at 4°C or 25°C in the perinatology ward were no longer physicochemically stable (concentration). Chemical degradation began on day 1, then microbial contamination occurred immediately after completion of compounding in the ward (day 0). This is because reconstitution was not carried out in a clean room in accordance with USP <797>. It can be concluded that hydrocortisone injection preparations prepared in this hospital are not recommended for administration to patients after 1 day of storage and must be compounded in a clean room.

Abstrak

Injeksi Hidrokortison Sodium Succinate 50mg banyak digunakan pada bangsal perinatologi. Bangsal ini merupakan bangsal dengan kondisi pasien bayi yang baru lahir (0-28 hari), berat badan lahir rendah (<2,5 kg) atau bayi premature (<37 minggu) sehingga membutuhkan penanganan khusus. Penggunaan injeksi ini membutuhkan dosis yang sangat kecil, sehingga satu vial injeksi hidrokortison dapat digunakan untuk lebih dari satu pasien. Oleh karena itu, sisa dari injeksi hidrokortison ini seringkali dilakukan penyimpanan selama 24 jam di refrigerator yang nantinya akan digunakan kembali pada pasien yang lain. Penelitian ini bertujuan untuk mengetahui *in-use stability* injeksi hidrokortison yang disimpan selama 24 jam pada suhu 4°C dan 25°C. Hal ini tentunya untuk meningkatkan keselamatan pasien. Teknik pengumpulan data menggunakan metode observasional terhadap sampel injeksi hidrokortison dengan replikasi 3 kali. I*n-use stability* dinilai dari hasil uji organoleptis (warna dan bau), uji pH, uji viskositas, penetapan kadar obat menggunakan spektrofotometri UV-VIS dan uji sterilitas. Pengujian dilakukan pada hari ke 0, 1, 2, 3, 7, 14 dan ke 30. Hasil penelitian menunjukkan bahwa sediaan injeksi hidrokortison yang disimpan selama 1 hari pada suhu 4°C atau 25°C di bangsal perinatologi sudah tidak stabil secara fisikokimia (viskositas, kadar). Degradasi kimia mulai terjadi pada hari ke-1, kemudian kontaminasi mikroba langsung terjadi setelah selesai peracikan di bangsal (hari ke-0). Hal ini karena rekonstitusi tidak dilakukan di ruang bersih sesuai dengan USP <797>. Dapat disimpulkan bahwa sediaan injeksi hidrokortison yang disiapkan di rumah sakit ini tidak direkomendasikan untuk diberikan kepada pasien setelah 1 hari penyimpanan dan harus diracik pada ruang bersih.

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INTRODUCTION

Hospital patients require diverse injection preparations, often necessitating compounding, so that a process of preparing or mixing injection preparations with each other is still required to meet patient needs.[1] The process of mixing injection preparations requires special attention, especially in several important aspects such as personnel, correct aseptic procedures and facilities so that the mixed preparations do not experience microbial contamination.[2,3] Microbially contaminated preparations can have a very fatal impact on patients, especially neonates.[4] Neonates are a population at high risk of infections (HCAIs). This is because their immune systems are immature, and they often come into contact with healthcare workers in the hospital environment. HCAIs that commonly occur include central-line-associated bloodstream infections, healthcare-associated pneumonia, soft tissue infections, and candidaemia. HCAIs can be minimized by improving hand hygiene.[5,6]

Dewi (2018) reported bacterial contamination in 2.3% of 43 tested IV admixtures. The frequency of contamination prepared in the ward was higher compared to preparations prepared in the pharmacy environment.[2] To avoid contamination, the mixing process for injection preparations should refer to existing guidelines such as the United States Pharmacopeia (USP) chapter 797.[7] Meanwhile, Indonesia also has basic guidelines that discuss and regulate the dispensing of sterile preparations which include all aspects starting from human resources, rooms and equipment, aseptic techniques, storage, distribution and documentation.[8,9] Furthermore, these aspects have been proven in research to have an influence on the quality of the preparation. This research has been stated in the basic guideline for the preparation of non-cytostatic sterile products.[9]

In a study conducted by Rambe (2023), the procedures for mixing sterile preparations did not comply with the guidelines for mixing injectable drugs. Incompatibility can occur if the process of mixing sterile preparations does not comply with aseptic techniques.[10] Then, if incompatibility occurs, it can affect the safety, medication, stability, dose changes and efficacy of the drug.[10] Then, research conducted by Genatrika (2022) stated that one of the hospitals in Purwokerto had not yet met the United States Pharmacopedia (USP) <797> guidelines and basic guidelines related to dispensing in preparing sterile preparations.[11] This research is also supported by the results of research conducted by Putri and Yuliani (2018), namely that the preparation of injection preparations in one of the hospitals in Semarang is still not in accordance with the Basic Dispensing Guidelines for Sterile Preparations and Guidelines for Mixing Injectable Drugs and Cytostatics.[12]

This Referral Hospital is a type B hospital located in Banyumas Regency, which has been accredited PARIPURNA in 2019 by the Hospital Accreditation Commission. This Referral Hospital provides friendly and good service, besides that this hospital has enough general practitioners and specialist doctors so that it is the choice of the Banyumas community. Many inpatients at this hospital receive sterile preparations that require reconstitution or mixing of drugs. One of the preparations is hydrocortisone injection. From data obtained from Banyumas Regional Hospital, the use in the last 3 months for hydrocortisone injection was 291 vials.

Hydrocortisone injections are administered in a perinatology ward that specializes in the care of newborns with conditions requiring intensive or specialized treatment. Therefore, hydrocortisone injections used in the perinatology ward are always in small doses so that the use of one vial of hydrocortisone injection can be used for more than one patient. This is what causes hydrocortisone injections to be stored if there is any leftover. The remaining reconstituted hydrocortisone injection is stored for 24 hours in the refrigerator which will then be reused on other patients if the storage is still under 24 hours. Every drug that has been opened from its primary packaging has a certain shelf life called the beyond use date (BUD). Although this BUD has been regulated by USP <797>, the BUD in this regulation is not specific to certain active substances and/or brands.[7]

Leanpolchareanchai et al. (2022) stated that hydrocortisone injection in NaCl 0,9% has stability in use for up to 48 hours when stored at room temperature or in the refrigerator. That study was conducted in Thailand, where the hydrocortisone injection preparation and solvent used were different from those used in this study.[13] Furthermore, a solution of dezocine 0.4 mg/ml mixed with 0.05 mg/ml tropisetron hydrochloride

in 0.9% NaCl has stability in use for 14 days when stored in a polyolefin bag or glass bottle.[14] Based on the descriptions above, this study aims to evaluate the in-use stability of hydrocortisone injection preparations which are often stored in the refrigerator with physical, chemical and microbiological quality parameters.

RESEARCH METHODS

Study Design

This research design is a non-experimental study to determine the in-use stability of hydrocortisone injection used in the Perinatology ward. This study has obtained ethical permission from the health ethics committee with number 286/KEPK-RSUDBMS/I/2024. In-Use Stability is determined based on the results of physical, chemical and microbiological stability tests. The physical stability tests carried out were organoleptic and viscosity tests, chemical stability tests were seen from the pH test and determination of drug levels. Furthermore, microbiological stability was seen from the sterility test of the preparation.

Sampling

The sample used was hydrocortisone injection prepared in the Perinatology Ward. Preparation was performed in the nurses' room using Laminar Air Flow (LAF). This room does not meet USP <797> standards. The reconstituted product will be sent to the microbiology laboratory for sterility testing.

Organoleptic Test

The reconstituted hydrocortisone injection preparation was stored in two different places, namely a room with a temperature of 25 ℃ and a temperature of 4 ℃. Then the change in the color of the hydrocortisone injection preparation will be seen for 30 days, replication 3 times. Furthermore, the changes will be seen on day 0, day 1, day 2, day 3, day 7, day 14 and day 30.[7]

Viscosity Test

The reconstituted hydrocortisone injection preparation will be stored in two different places, a room with a temperature of 25 ℃ and a room with a temperature of 4 ℃. Furthermore, the viscosity value was measured on days 0, 1, 2, 3, 7, 14 and 30 using a calibrated Brookfield DV2T Viscometer.[7(p20)] In this test, replication was carried out 3 times.

pH Test

The reconstituted hydrocortisone injection preparation will be stored in two different places, namely a room with a temperature of 25 ℃ and a temperature of 4 ℃. Furthermore, the pH value will be measured on day 0, day 1, day 2, day 3, day 7, day 14 and day 30 using a calibrated pH meter (OHAUS).[7(p20)] In this test, replication was carried out 3 times.

Hydrocortisone Level Determination

Determination of the levels of hydrocortisone injection samples using UV VIS Spectrophotometry. The sample with a concentration of 10 µg/mL were taken 10 µl, then put into a 10 ml measuring flask and Water for Injection (WFI) was added to the mark on the measuring flask. Next, 1 ml was taken and put into a 5 ml measuring flask then WFI was added to the mark on the measuring flask.[15] The sample that has been prepared is then read for absorbance at a wavelength of 248 nm and the concentration is calculated using the equation y = 0.0366x-0.024. This concentration determination will be carried out for 30 days, namely on day 0, day 1, day 2, day 3, day 7, day 14 and day 30.[7]

Sterility Test

Sterility testing was performed using Fluid Thioglycolate Media (FTM) and Soybean Casein Digest (SCD) media. Hydrocortisone injection samples prepared by staff at the perinatology ward of this referral hospital were directly inoculated into both FTM media and SCD media and incubated for 14 days, with three replicates, for FTM media at 30-35°C and SCD media at 20-25°C. If bacterial growth is observed within 14 days, the hydrocortisone injection can be said to be non-sterile.[16]

Data Analysis

The data obtained were analyzed descriptively and compared with the quality specifications for each quality parameter of Hydrocortisone injection.[16] Then, the chemical quality parameters (content) were analyzed using a two-way ANOVA test with the help of the IBM SPSS Statistics application.

RESULT AND DISCUSSIONS

Hydrocortisone Na Succinate injection samples experienced a color change on the 30th day stored at a temperature of 25°C, as seen in **Table 1**.

Table 1. Organoleptic Test Results

Day to	Organoleptic Observation	
	Temperature 4°C	Temperature 25°C
0	Clear, colorless	Clear, colorless
1	Clear, colorless	Clear, colorless
2	Clear, colorless	Clear, colorless
3	Clear, colorless	Clear, colorless
7	Clear, colorless	Clear, colorless
14	Clear, colorless	Clear, colorless
30	Cloudy, there are white particles	Cloudy, there are white particles

Hydrocortisone injections were known on day 0 to day 14 did not experience any color change and was not cloudy, both stored at 4°C and at 25°C. Then, on the 30th day the sample stored at 4°C was still clear, while the sample stored at 25°C had changed color, was cloudy and contained white particles. These results are in line with research conducted by Sagitha, et al (2023) which showed that the stability test of ampicillin sulbactam preparations after reconstitution was more stable when stored in the refrigerator.[17] Furthermore, for the viscosity test on the sample increased every day, the data can be seen in **Table 2**.

Table 2. Viscosity Test Results

Day to	Viscosity Value	
	Temperature 4°C	Temperature 25°C
0	62,08 cP	73,16 cP
1	60,88 cP	73,98 cP
2	63,56 cP	84,06 cP
3	65,88 cP	86,52 cP
7	78,56 cP	96,56 cP
14	86,64 cP	103,73 cP
30	96,56 cP	113,57 cP

The results of the viscosity test on day 0 to day 30 stored at a temperature of 4°C were in the range of 62-96 cP and stored at a temperature of 25°C were in the range of 73.16-113.567 cP. Berteau, et al (2015) stated that the viscosity that can be tolerated for subcutaneous administration is in the range of 15-20 cP.[18] Another study conducted by Ko Eunji, et al (2022) also stated that the viscosity of intravenous fluids, such as 0.9% physiological saline solution and Hartmann's solution usually ranges from 1.07-1.12 cP, and thick solutions, such as 6% hetastarch and 5% albumin have a viscosity of 2.77-1.86 cP respectively. Therefore, the viscosity value of this hydrocortisone injection is still too high when given intravenously or subcutaneously.[19] This is because the strength of the preparation affects the viscosity value of the solution, the higher the strength of the preparation, the higher the viscosity.[18–20] The viscosity values stored for 30 days at temperatures of 4°C and 25°C did not differ significantly ($p>0.05$), so it can be concluded that temperature does not affect the viscosity value. The solution for administering this preparation is to dilute it before giving it to the patient so that it is not too thick.

The chemical stability study in this study was seen from the pH parameters and drug levels. The pH value obtained was still within the range recommended by the Indonesian Pharmacopoeia, which is around 5-7,[16] as seen in **Table 3**.

Table 3. pH Test Results

Day to	pH value	
	Temperature 4°C	Temperature 25°C
0	7,34	7,31
1	7,41	7,33
2	7,32	7,26
3	7,29	7,26
7	7,25	7,15
14	7,25	6,96
30	7,32	6,87

The pH value produced after being stored for 30 days at a temperature of 4°C and at a temperature of 25°C is known to be in the range of 6 to 7, where according to the Indonesian Pharmacopoeia edition VI, the pH value required for hydrocortisone injection is between 5 and 7.[16] The pH value in this study still meets the pH range for hydrocortisone injection. The appropriate pH will help the safety of using injection preparations, such as if the pH is too low (below 3) it can cause pain when injected, while the pH is too high (more than 9) can cause tissue necrosis.[21] The pH value of injection preparations stored at 4°C and 25°C did not differ significantly (p> 0.05), so it can be concluded that temperature does not affect the pH value.

Then, this injection sample experienced a change in content and did not match the range specified by the Indonesian Pharmacopoeia (90-110%) after storage for 24 hours at both 4°C and 25°C.[16] The percentage of levels increased more than 110% after 24 hours of storage, this indicates that this injection is unstable after being stored for 24 hours at both temperatures. The results of this study are in line with research conducted by Leanpolchareancha et al (2022) which stated that hydrocortisone injection reconstituted using Water for Injection was stable for up to 24 hours at refrigerator temperatures (4±2°C), ICU temperatures (25±3°C), and room temperatures (30±2°C).[22] The data of hydrocortisone levels can be seen in **Table 4**.

Table 4. Results of Level Determination Test

Day to	Hydrocortisone Level (%)	
	Temperature 4°C	Temperature 25°C
0	100,728	98,816
1	155,373	132,695
2	138,888	114,663
3	146,357	150,364
7	145,719	150,455
14	148,360	151,548
30	134,244	119,854

Hydrocortisone injection stored for 24 hours was also determined for its active substance content. The results on day 0 showed that the content of hydrocortisone injection that had been reconstituted with WFI and would be stored at a temperature of 4°C was 100.728%, while that which would be stored at a temperature of 25°C was 98.816%. According to the Indonesian Pharmacopoeia edition VI, the content of the active substance hydrocortisone in injection is not less than 90.0% and not more than 110.0%.[16] The injection that will be stored at different temperatures can be said to be chemically stable on day 0. Then, after 24 hours to 30 days, it shows the level of active substances that have exceeded the levels required by the Indonesian Pharmacopoeia Edition VI (> 110%). This shows that the hydrocortisone injection that has been reconstituted with WFI is no longer stable after being stored for 24 hours. Then, the levels of hydrocortisone at each storage temperature were analyzed and a p value of 0.805 was obtained. It can be concluded that the levels of hydrocortisone stored at temperatures of 4°C and 25°C are not significantly different (p> 0.05).

The results of this study are consistent with those of Leanpolchareancha et al. (2022), which stated that hydrocortisone injection reconstituted using Water for Injection and 0.9% Sodium Chloride (1 mg/mL) was not affected by temperature.[22] The injection remained stable for 24-48 hours at refrigerator temperature (4±2°C), ICU temperature (25±3°C), and room temperature (30±2°C). However, this is inconsistent with other studies,

such as those conducted by Yusefa (2024), which stated that temperature can affect the levels of active substances with a difference in levels of 10.95%.[15,23]

Temperature changes are one of the external factors that cause instability in pharmaceutical preparations. Storing drugs in very hot conditions, high room humidity, and exposure to light can damage drug quality.[24] In this study, humidity is the factor suspected of influencing hydrocortisone stability. Humidity is closely related to water; the presence of water can cause hydrocortisone to degrade or undergo hydrolysis, particularly to 21-aldehyde.

Microbiological stability studies can be determined based on the presence or absence of bacterial growth. Samples inoculated into both test media showed bacterial growth, the results can be seen in table 5.

Table 5. Sterility Test

Day to	Bacterial Growth	
	Temperature 4°C	Temperature 25°C
0	+	+
1	+	+
2	+	+
3	+	+
7	+	+
14	+	+
30	+	+

Microbiological stability parameters also need to be tested to ensure that the injection preparations given to patients are not contaminated by microbes. To prove this, a sterility test was carried out on the hydrocortisone injection that had been reconstituted in the perinatology ward. The results showed that there had been microbial contamination of the injection. This is because the room used to prepare parenteral preparations in this referral hospital does not meet ISO standards and those required by USP <797).[7] If the microbially contaminated preparation is still given to the patient, it can endanger the patient, such as bloodstream infections, surgical site infections, ventilator-associated pneumonia, and urinary tract infections. Bloodstream infection and ventilator pneumonia can cause death.[25–27]

The limitation of this research lies in the lack of support from the government regarding this topic, so that researchers could only collect data from the perinatology ward because there were parties who did not agree with this at this referral hospital.

CONCLUSION

Hydrocortisone injection can only be stored for up to 24 hours at 4 °C and 25 °C based on physicochemical quality parameters, including organoleptic properties, viscosity, pH, and hydrocortisone content. However, this injection is not recommended for use in this hospital according to microbiological quality parameters (sterility), as contamination occurred on day 0. Hospitals must have a clean room that complies with USP <797> standards for the preparation of parenteral products to prevent microbial contamination. If microbial contamination does not occur, this hydrocortisone injection may be administered repeatedly within the 24-hour storage period. Implementing proper sterile compounding standards could significantly improve medication safety and resource efficiency in hospital settings.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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