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Stability and beyond-use date of anesthetic agents used in surgical procedures: a review

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Abstract

Background: Anaesthesia drugs are often divided into other syringes to be soluted or mixed with other medications to share with other patients for the sake of efficiency.

Objectives: This study aims to know the stability of anesthetic agents and the compatibility with co-simultaneous drugs used.

Methods: This review was conducted by searching literature through the following databases: PubMed, Science Direct, and Google Scholar. The keywords used in the search for articles were "stability," "beyond use date," "anesthetic drug," and "intravenous."

Results: The data showed that mixing fentanyl with levo-bupivakain or epinefrin is relatively stable up to one month, but it decreases only for 72 hours in dextrose 5% or normal saline (NS). Pethidin can be mixed with acetaminophen and metoclopramide using dextrose, NS, or water and stored up to 24 hours. Midazolam diluted in dextrose 5% (D5) or mixed with other medications maintains for stability up to 14 days or more. Stability of ketamine is 24 hours longer whether it is mixed in solvent or acetaminophen. Mixing with propofol induces instability because of the emulsion form of propofol.

Conclusion: In general, the anesthetic drugs of fentanyl, pethidine, midazolam, and ketamine are stable and safe for preparation and administration in more than 24 hours. These four medications are compatible with NS and D5 and all tested medications during 24 hours.

Keywords: stability, beyond use date, anaesthesia drugs, intravenous

1. Introduction

The administration of anesthetic medications is an integral component of surgical procedures. Their utilization aims to ensure the patient is pain-free and as comfortable as possible throughout the procedure. Accuracy of the dose and concentration of the drug plays a pivotal role to achieve this goal. However, the amount of injection drug concentration can change under conditions of instability; decrease of stability may decrease effectivity including the hemodynamic instability (Bedocs *et al*., 2019).

It is essential to recognize that anesthetics do not utilize a one-size-fits-all approach. Therefore modification such as dilution or mixing cannot be avoided for achieving personalised goal. Anesthetis often need to open, divide and store for several hours before administration. Sharing one dosage form for some patients and giving several medications at once can result in efficient anesthetic care (Bedocs *et al*., 2019). In addition, multidrug administration strategy often also can not be avoided in practical setting because of venous access limitations. Co-administration of anesthetic and other drugs in one pack may change the stability.

The stability of these anesthetic drugs including the "beyond use date" (BUD) is the date set on an opened sterile product when the state of the product is still within the stable range and can be delivered to the patient. When a sterile product is unsealed, it is exposed to the surrounding

environment and will change the stability (Herawati, 2012). The BUD is an indispensable metric in medical practice which is denotes the specific date set on an opened sterile product, signifying the period during which the product remains stable and can be administered safely to patients. This date is not chosen arbitrarily; it is based on extensive research establishing the period during which the product retains its efficacy and safety profile.

When the seal on a sterile product is opened, the product becomes susceptible to contamination from the surrounding environment. Humidity, light exposure, and ambient temperature can significantly impact a drug's stability. The BUD functions as a safeguard against the possible degradation of a drug's efficacy and safety, ensuring that patients receive medications that are both effective and free of contamination. Thus, the BUD serves multiple purposes. It does not only provide healthcare professionals with a clear guideline for the safe use of opened sterile products, but it also supports the overarching objective of medical practice, ensuring patient safety and providing optimal care. Adherence to the BUD and comprehension of its implications are essential for preserving the efficacy of medical treatments and ensuring patients' outcome.

As long as the medication is stored until the patient uses it, it is said to be stable if its properties have not altered physically, chemically, therapeutically, microbiologically, or toxicologically from those specified by the manufacturer (Noviani & Arrang, 2021). By selecting the right ingredients, compatible solvents, a secure storage location, and the ideal administration period, the risk of instability can be reduced (Husna *et al*., 2021). As a result, understanding the stability and BUD is critical for developing a safe anesthetic drug administration strategy. No publication has yet reviewed data on the stability and BUD of anaesthesia drug injection, to the best of the researchers' knowledge.

Understanding medications' stability and BUD is crucial, particularly when developing drug administration strategies. It is especially true for anesthetic medications, where even the smallest variation in stability can have significant clinical consequences. Notably, the stability and BUD are crucial for ensuring the safe and effective administration of anesthesia, given the importance of the surgeries and procedures that these medications facilitate. Surprisingly, despite the significance of this topic, no exhaustive literature review or publication has addressed the stability and BUD of anesthesia drug injections systematically. This research emphasizes the need for rigorous studies in this field to bolster the existing body of knowledge and establish best practices for anesthetic drug administration.

2. Method

2.1. Search strategy

Literature search had been done by using electronic sources or databases such as PubMed, Science Direct, and Google Scholar to find relevant literature, regardless of year. By selecting articles with an English language, a literature search was conducted. The keywords used in the search for

articles were "stability," "beyond use date," "anesthetic drug," and "intravenous." The literature search technique uses a combination of keywords with the boolean operators "OR" and/or "AND".

In order to facilitate an exhaustive review of the topic, a thorough literature search was conducted across multiple electronic databases, such as PubMed, Science Direct, and Google Scholar. The search strategy was not limited by publication date, ensuring that both classic and contemporary studies were proportionally considered. For ensuring consistency and clarity in the analysis, priority was given to articles predominantly composed in English. A keyword-driven search was conducted using terms such as "stability," "expiration date," "anesthetic drug," and "intravenous." The strategic use of boolean operators further improved the precision of the search: combining keywords using "OR" enabled the acquisition of a broader range of relevant literature, while the use of "AND" ensured the intersection of the primary themes under investigation. This methodological approach ensured a comprehensive and pertinent selection of articles to the subject of anesthetic drug stability and beyond-use dates.

2.2. Selection criteria

The inclusion criteria were articles that had been published in English and were available in full text; *in vitro* studies that discussed the stability of injections of anaesthesia drugs in combination with other drugs and solvents in certain storage conditions. The exclusion criteria were articles that did not include data on anesthetic drugs, solvents, other drug combinations, storage, and BUD.

In order to ensure the study's relevance and the collection of data, a precise set of inclusion and exclusion criteria was outlined. In terms of inclusion, the emphasis was placed on English-language articles, allowing for greater accessibility and comprehension among the research community. In addition, only complete studies were considered, allowing for a comprehensive analysis without the danger of omitted information. The emphasis was placed on *in vitro* studies as we delved deeper into the content details. These studies should focus on the stability nuances of anaesthesia drug injections, particularly when merged or combined with other substances or solvents. As this parameter plays a pivotal role in determining the drug's stability, particular storage conditions were also emphasized. In contrast, the exclusion criteria were developed to exclude articles that could dilute the review's focus. Articles were disregarded if they failed to provide data concerning anaesthetic drugs, their corresponding solvents, other potential drug combinations, and the conditions in which they were stored. In addition, articles that did not discuss the BUD of these anaesthetic drug mixtures were deemed extraneous and excluded. These stringent criteria aimed to collect a comprehensive, focused, and relevant dataset for the review. From the process of selection results the data as seen on **Figure 1**.

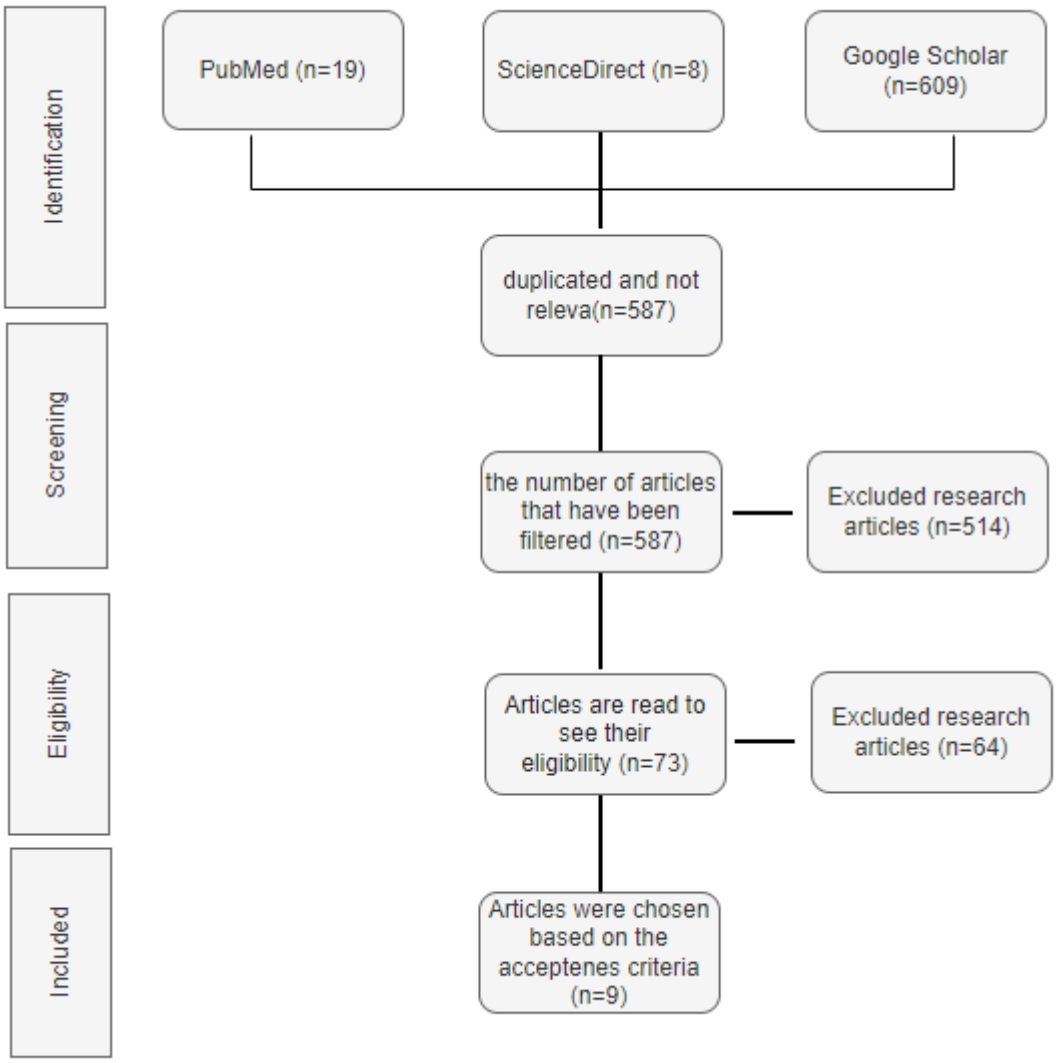

Figure 1. Diagram of retrieved studies

3. Results and discussion

The stability of the medication is a crucial factor in ensuring the safety and efficacy of the administered treatment. A drug is considered stable if its physical, chemical, therapeutic, microbiological, and toxicological properties do not deviate from the manufacturer's specifications during storage and up until the point of administration to the patient. The foundation for attaining this stability is frequently comprised of multiple factors. These include the careful selection of ingredients, the selection of compatible solvents, the designation of a storage environment that safeguards the drug from harmful external factors, and the determination of the optimal administration window. These measures guarantee the drug's efficacy and mitigate any potential risks associated with its instability

Selected research on the stability of anesthetic medications included 9 articles. Of these nine articles reported more than one medicine stability. Table 1 shows the stability of fentanyl identified from 4 articles. Meanwhile, the stability of pethidin was analysed from 3 articles as seen on **Table 2**. Then, midazolam stability was found in 4 articles and ketamine in 4 articles as shown on **Table 3** and **4** respectively.

Table 1. Stability of fentanyl with other drugs and solvent

No	Author, year	Drug	Solvent	Temperature	Duration assay	Stability
1	(Wilson *et al*., 1998)	Fentanyl (50µg/ml)	Sodium chloride 0,9%	5-38°C	7 days	7 days
2	(Wilson *et al*., 1998)	Fentanyl Midazolam	-	22-38°C	7 days	4 days
3	(Chen *et al*., 2020)	Fentanyl citrate (20 µg/ml) Naloxone hydrocloride (4 µg/ml)	Sodium chloride 0,9%	4°C or 25°C	72 hours	72 hours
4	(Helin-Tanninen *et al*., 2013)	Levo-bupivakaine Fentanyl Epinefrin	-	6°C	60 days	60 days
5	*(Helin-Tanninen et al*., 2013)	Levo-bupivakaine Fentanyl Epinefrin	-	22°C	60 days	40 days
6	(Helin-Tanninen *et al*., 2013)	Levo-bupivakaine Fentanyl	-	6°C	60 days	60 days
7	(Helin-Tanninen *et al*., 2013)	Levo-bupivakaine Fentanyl	-	22°C	60 days	40 days
8	(Hanifah *et al.*, 2020)	Fentanyl	Dextrose 5%	26-28°C	7 days	72 hours

Table 2. Stability of pethidine with other drugs and solvent

No	Author, year	Drug	Solvent	Temperature	Duration assay	Stability
1	(Hor *et al*., 1997)	Pethidine Metoclopramide	WFI	32°C	48 hours	48 hours
2	(Hor *et al*., 1997)	Pethidine Metoclopramide	Sodium chloride 0,9%	32°C	48 hours	48 hours
3	(Hor *et al*., 1997)	Pethidine Metoclopramide	Dextrose	32°C	48 hours	48 hours
4	(Hanifah *et al*., 2020)	Pethidine Acetaminophen	-	24-28°C	24 hours	24 hours

Table 3. Stability of midazolam with other drugs and solvent

No	Author, year	Drug	Solvent	Temperature	Duration assay	Stability
1	(Hanifah *et al*., 2020)	Midazolam Acetaminophen	-	24-28°C	24 hours	24 hours
2	(Xia & Chen, 2020)	Midazolam hydrocloride 0,5 mg/100mL Ramosetron hydrocloride 0,3mg/100mL	Sodium chloride 0,9%	4°C	14 days	14 days
3	(Xia & Chen, 2020)	Midazolam hydrocloride 0,5 mg/100mL Ramosetron hydrocloride 0,3mg/100mL	Sodium chloride 0,9%	25°C	14 days	14 days
4	(Hanifah *et al*., 2020)	Midazolam	Dextrose 5%	26-28°C	30 days	30 days

Table 4. Stability of ketamine with other drugs and solvent

No	Author, year	Drug	Solvent	Temperature	Duration assay	Stability
1	(Bedocs *et al*., 2019)	Propofol Ketamine	-	37°C	24 hours	24 hours
2	(Beiler *et al*., 2020)	Ketamine hydrochloride 2,5mg/mL	Sodium chloride 0,9%	28°C	48 hours	48 hours
3	(Hanifah *et al*., 2020)	Ketamine Acetaminophen	-	24-28°C	24 hours	24 hours
4	(Hanifah *et al*., 2020)	Ketamine	Dextrose 5%	26-28°C	7 days	7 days

General anesthesia is a medical state in which a patient is induced to become unconscious, lose sensation, and lose memory during surgical procedures or other medical interventions. It is a controlled and reversible condition that ensures the patient does not feel pain, discomfort, or become aware while undergoing a potentially painful or disturbing surgery (Brown *et al*., 2018).

Anaesthesia can successfully alleviate surgical pain. In a scenario with limited resources, using a single medicine to treat postoperative pain can help save money. Among the several advantages of anaesthetic include less post-operative bleeding, rapid gut function recovery, intact airways, and early detection of problems in awake patients (Arjumand et al., 2022).

Several research have used various combinations of solvents and storage temperatures to provide answers regarding the stability of anesthetic medicines. According to this study, anesthetic medications that have been opened frequently experience instability.

3.1. Stability of fentanyl with other drug and solvent

Fentanyl, like most therapeutically utilized opioids, exerts its pharmacological effects by activating the mu opioid receptor (MOR), which has a low affinity for the delta and kappa opioid receptors. Unlike morphine, which is an alkaloid produced from the opium plant, fentanyl is a synthetic, lipophilic phenylpiperidine opioid agonist. Fentanyl is a highly effective MOR agonist, with a binding affinity (Ki) of 1.35 nM for recombinant human MORs (Comer & Cahill, 2019a).

The use of fentanyl in surgery is often combined with various drugs. The combination of fentanyl with midazolam is often done by anaesthetists to achieve sedation and analgesia during surgery. Midazolam was discovered to work in tandem with fentanyl to induce anaesthesia (Ben-Shlomo *et al*., 1990). Fentanyl is frequently coupled with naloxone hydrochloride, with the goal of reducing fentanyl overdose use by reversing the effects of fentanyl-induced respiratory depression (Comer & Cahill, 2019b). When fentanyl is mixed with levobupivacaine, it causes an early start and prolonged duration of sensory and motor block, as well as surgical analgesia with stable haemodynamics and minimum side effects (Attri *et al*., 2015). Adrenaline, often known as epinephrine, has the potential to be utilized as an adjuvant in digital nerve blocks to expedite and prolong analgesic effects (Edinoff *et al*., 2021). Thus, mixing fentanyl, levo-bupivacaine and epinephrine is an alternative drug combination during surgery.

The stability of fentanyl is impacted by interactions with other medications, solutions, and temperatures. The longest stability at 6°C is 60 days for fentanyl with levo-bupivacaine, fentanyl, and epinephrine. The shortest stability is 3 days when fentanyl and naloxone hydrochloride are combined.

3.2. Stability of pethidine with other drug and solvent

Pethidine is the only opioid with adequate local anaesthetic activity to be used as the sole drug for spinal anaesthesia.The combination of opioid and local anaesthetic activity offers the ability to deliver surgical anaesthesia comparable to that obtained with traditional local anaesthetic drugs, as well as early postoperative analgesia that may be superior (Kee, 1998). The combination of pethidine with metoclopramide is often used during surgery. Metoclopramide is a well-known antiemetic that is widely used in PONV (Ilyas *et al*., 2017).

Similarly, the combination of pethidine and acetaminophen is frequently used in anaesthetic prescription drugs. Acetaminophen (N-acetyl-p-aminophenol, AAP), generally known as paracetamol, is a widely used antipyretic and analgesic that is widely regarded as an effective medication for pain and fever relief in adults and children (Park *et al*., 2014; Bateman *et al*., 2014; Jackson & Kapp, 2011).

The results of the pethidine-metoclopramide combination research dissolved with multiple different solvents, such as aqueus, sodium chloride 0.9%, and dextrose at 32°C temperature storage, with a test period of 48 hours, the results were stable 24 hours even with varied solvents. Pethidine-

acetaminophen combination at 24 – 28°C at 24 hours test duration without solvent, remained stable 24 hours.

3.3. Stability of midazolam with other drug and solvent

Midazolam is administered orally, intravenously, intranasally, and intramuscularly for sedation prior to diagnostic and therapeutic medical operations (Conway *et al*., 2021). Midazolam is a medicine used as an addition to regional and local anesthetic for a variety of diagnostic and therapeutic procedures, and it is well tolerated by both patients and physicians (Reves JG *et al*., 1985). A combination of midazolam and acetaminophen is often used in surgery, with the aim of achieving a sedative effect and controlling postoperative pain. While the combination of midazolam with ramosetron serves to obtain a sedative effect and reduce the onset of vomiting. Based on the results of the combination of midazolam with acetaminophen with a stable temperature of 24 - 28°C at a test duration of 24 hours, the combination of midazolam hydrochloride with ramosetron hydrochloride dissolved with sodium chloride 0.9% at a test duration of 14 days with storage temperatures of 4°C and 25°C remained stable for 14 days.

Midazolam's stability in the same solvent with various storage temperatures did not influence it, however midazolam's stability with various medication combinations did. Each drug has different storage temperature specifications; if the placement is not appropriate, it will affect the stability of the pharmaceutical preparation (Noviani & Arrang, 2021).

3.4. Stability of ketamin with other drug and solvent

Ketamine is a phencylidine class intravenous anaesthetic drug that stimulates the central nervous system. The use of ketamine at low doses is effective for standard opiod regimens and local anaesthesia (Riddell *et al*., 2019). Ketamine is a dissociative anesthetic drug that suppresses neuronal function in the cortex and thalamus and causes abnormal excitatory activity in the limbic system, including the hippocampus, resulting in electroencephalographic changes unique from those generated by anesthetics (Brown *et al*., 2010).

The use of ketamine is often combined with propofol, and acetaminophen. In surgery, the combination of ketamine and propofol seeks to improve anaesthesia. The combination of ketamine and propofol for procedural sedation and analgesia may be beneficial in theory, with the rationale being that using lower doses of each agent may result in a reduction of both agents' undesirable side effects while maintaining optimal conditions for performing procedures (Slavik & Zed, 2007). The combination of propofol and ketamine has the potential to produce superior sedation while being less harmful than either drug alone (Mortero *et al*., 2001). While the combination of ketamine and acetaminophen is to strengthen the pain of surgery. Acetaminophen is one of the most commonly utilized painkillers in operating rooms (Rahimzadeh *et al*., 2013).

The combination of these drugs, at a test duration of 24 hours, was observed to maintain its stability for 24 hours, even with different temperature storage. Different results when ketamine is only dissolved with 0.9% sodium chloride, with a test duration of 48 hours, the stability is maintained for the duration of the test.

3.5. Strength and limitation of the study

The review utilized a broad search strategy, including but not limited to PubMed, Science Direct, and Google Scholar, among other prestigious databases. This rigorous methodology was crucial in ensuring the extraction of relevant and comprehensive literature, paving the way for a comprehensive understanding of the topic. This exhaustive curation was further augmented by a detailed analysis illuminating the myriad factors contributing to drug stability. Elements such as storage temperatures, the nature of solvent mixtures, and various drug combinations were dissected to provide readers with a multifaceted understanding of the stability dynamics of anesthetic drugs. This investigation, with its theoretical and practical aspects, is of considerable importance. Understanding the subtleties of drug stability becomes crucial in surgical procedures, where anesthetic agents are indispensable. This research does not merely add to the body of knowledge; it also fills a glaring gap in the current literature by focusing on the stability and complex interactions of anesthetic agents, an area with significant clinical implications.

However, while the methodology and purpose of the study merit recognition, they have limitations. Primarily, the restriction to particular databases may introduce an unintended bias. The exclusive reliance on PubMed, Science Direct, and Google Scholar may overlook relevant studies that may exist in other academic repositories. In addition, the decision to limit the scope of the study to 17 anesthetic drugs raises an additional concern. Many medications are utilized in surgical contexts, and narrowing the focus could unintentionally limit the scope of the study's findings. In addition, there is the inherent difficulty of generalizing the study's results. Due to the study's limitations, caution must be exercised when applying its findings to various surgical environments, particularly in geographical regions with varying environmental variables. The lack of experimental validation is a significant and potential area for future research. Incorporating empirical validations would have added a tangible and more reliable dimension to evaluating drug stability and interactions despite the undeniable value of the insights gleaned from existing literature.

Conclusion

The anesthetic drugs of fentanyl, pethidine, midazolam, and ketamine are stable for 7 days, 2 days, 40 days, and 7 days respectively. This stability of anesthetic medicines may be impacted by medication also be impacted by the solvent used to dilute it. The results of compatibility study of fentanyl are safe to mix with NS, D5, Levo-bupivakain, and midazolam. Pethidine is compatible with

WFI, NS, D5, metoclopramid and midazolam. Midazolam is compatible with NS, D5, ramosetron and acetaminophen, and compatible is compatible with acetaminophen and propofol.

Conflict of interest

All researchers have stated that there are no potential conflicts of interest with this research, its authorship, and/or its publication.

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