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THE ADVANCES IN USE OF TOPICAL ANESTHESIA; A REVIEW OF RECENT LITERATURE

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Abstract:

Introduction: *Administrating local anesthetics with injections is associated with much pain and is known to lead to the development of edema of tissues that can negatively affect the surgical wound. The use of topical anesthetics has been increasing in several procedures due to its improved efficacy and decreased pain when compared to injected local anesthetics. Topical anesthetics are generally used in skin procedures, ophthalmological surgeries, minor procedures, and laser treatment modalities, along with other potential uses.*

Aim of work: *In this review, we will discuss the most recent evidence on the use of topical anesthetics in medicine.*

Methodology: *We did a systematic search for topical anesthesia use and updates in medicine, using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). Our search also looked the mechanism of action and adverse effects. All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *Many mixtures have been developed and introduced for different uses. However, despite all developments and improvements in the use of topical local anesthetics, they are still associated with adverse events and toxicity that may be severe in some cases and cause death. Therefore, caution should be applied by physicians when they attempt to use topical local anesthetics along with careful attention to the proper doses and methods of application. In addition, strict caution should be applied with topical local anesthetics are applied in vulnerable patients like neonates, children, elderly, and pregnant females. Further studies are still required to improve the use of topical anesthetics and provide protocols with highest efficacy and minimal adverse events.*

Key words: *Topical anesthetic, surgery, adverse effect*

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INTRODUCTION:

Administrating local anesthetics with injections is associated with much pain and is known to lead to the development of edema of tissues that can negatively affect the surgical wound. Moreover, it is associated with significant increases in rates of needle fear. Topical anesthetics carry the advantages of avoiding these limitations, and thus are becoming more common in the clinical practice.

The term 'topical anesthesia' refers to the loss of superficial sensation of the skin, the mucous membrane layer, or the conjunctiva, which occurs as a result of direct placement of a local anesthetic material like ointments, solutions, sprays, or gels. Cocaine was the first substance to be used as a local anesthetic, after its anesthetic effects were discovered in the year 1860 by Dr. Niemann who isolated cocaine and observed the numbness it causes to the tongue when it is applied [1]. Later in the year 1884, Dr. Koller who was a surgeon discovered that cocaine can be applied during ophthalmic surgeries to lead to anesthesia of the conjunctiva and avoid the need for general anesthesia [2].

Later, ester anesthetics and amide anesthetics were discovered which opened countless possibilities for using topical anesthesia in different types of surgery. in this review, we will review the most recent evidence on the use of topical anesthetics in medicine.

METHODOLOGY:

We did a systematic search for topical anesthesia use and updates in medicine, using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). Our search also looked the mechanism of action and adverse effects. All relevant studies were retrieved and discussed. We only included full articles.
The terms used in the search were: topical anesthetics, anesthesia, surgery, pharmacology, mechanism of action and adverse effects.

Mechanism of Action

Topical anesthetics act by reversibly blocking the conduction of nerves where they are applied. This is achieved by targeting the free endings of nerves which are located in the mucosa or the dermis. As a result, sensation will be temporarily lost in the area of anesthetic application. In addition, permeability of the nerve membrane to ions of sodium will reduce as a result of competition with calcium sites, leading to inhibition of the conduction of nerve impulse. The final consequence of all these changes is the loss of the ability of the nerve to create an action potential.

Pharmacology

Most topical anesthetics belong to the weak bases family, and consist of 3 main parts: the aromatic ring, the intermediate linkage (which is either an ester or an amide), and the amine. The first component, known as ring, is important for solubility in lipids which will allow for the diffusion of the anesthetic through the membrane. [3] The amine portion will then determine the protein binding ability of the topical anesthetic.

Many factors affect the characteristics of the topical anesthetics like the onset, the depth of anesthesia, and duration of anesthetic effect. These factors include the local PH, the level of pKa, solubility of the anesthetic in lipids, the ability of the anesthetic to bind to proteins, and the effects of the anesthetic in inducing vasodilation. Other factors can also be important but to less extent, and include the application site, the surface area, and the duration of use. The application site can play an important role in determining the efficacy due to changes in vascularity of different tissues. For example, topical anesthetic act significantly faster when applied to the mucosa or thin corneum than other sites of the body.
The metabolism of ester anesthetics occurs by the plasma cholinesterase, whereas the metabolism of amide anesthetics can only occur within the liver with microsomal enzymes. Some patients can develop allergic reactions with the use of ester anesthetics, but this is considered rare with amides. [4-5]

Skin Penetration Routes

When using topical anesthetic, the main obstacle for the delivery of the agent is the presence of a thick stratum corneum. Generally, the stratum corneum is penetrated through several routes, these are:[6]

1. The transappendageal route: this route is also known as the shunt pathway, and is present between sweat glands and har follicles openings.
2. The intercellular route: this route is present in the cornified keratinocytes' intercellular spaces.
3. The transcellular route: this route is also known as the paracellular route and is present between the cornified cells.

Sites of mucosal surfaces do not usually have a layer of stratum corneum making the penetration of topical anesthetics easier. These include the genitals, the mouth, and the conjunctiva.

Factors Determining the Dermal Drug Delivery

Drug form

Topical anesthetic are generally free bases which allow them to easily penetrate through lipid membranes and the stratum corneum. On the other hand, salt forms of anesthetics cannot readily penetrate and need special systems for this

Melting point and eutectic mixtures

Penetration is known to be higher when the melting point is lower, and vice versa. Generally, mixtures of two topical anesthetics will generate a new substance that have lower melting and higher penetration than any of the original substances.

Concentration of drug in vehicle

Obviously, penetration is proportionally correlated with the presence off higher concentrations of the anesthetic.

Skin permeation enhancers

Enhancers are substances that are known to improve penetration and permeability through the skin by the temporary induction of reversible environment that allows better penetration of the stratum corneum. Enhancers can be in many types and include:

1. Solvents like alcohols, water, glycerol, silicone, and ethers with low molecular weight [7].
2. Surfactants which can be ionic, non-ionic or bile salts [8].
3. Other miscellaneous substances like anticholinergics and urea [9].

Physical means of enhancing permeation

Some physical measures can be applied to improve the penetration through the skin and these include skin exfoliation, alcohol degreasing, and using nonporous dresses or patches (like micropore) to cover the area of anesthetic application.

Ionotrophoresis can also be used to enhance penetration and was approved by the FDA for this. However, it is associated with several limitations. These limitations include irritation of the skil when applied for long durations [10], polarization of the skin, discomfort and sensation of electrical current through the skin, high costs, the ability to use this technique over small areas only, and electroporation, which is the creation of temporary skin pores [11].

Ultrasound techniques have been found to improve the delivery of anesthetics by causing heating and micro steaming [20]. Ultrasound can be used in both high frequencies or low frequencies to improve penetration. Creating magnetic fields (this procedure is known by magnetophoresis) is also beneficial in improving penetration [12]. Other techniques include increasing heat, pretreatment with laser [13], and pretreatment of the skin with microneedle arrays [14].

Delivery from Lipid Vesicles

Examples of lipid vesicles include transfersomes, liposomes, and noisome. Liposomes are known to be micro-vesicles that contain several bilayers of lipid ordered concentrically and containing a specific number of liquid segments that have to ability to trap both lipid- and water-soluble agents [15] Previous studies that used radioactive techniques have concluded that liposomes have the ability to spread in the stratum corneum without penetrating into deeper structures like the dermis[16]. In another study, the use of tetracaine encapsulated with liposome led to the induction of better superficial anesthetic effects than the use of tetracaine mixed with other agents[17]. However, they also found that liposomes were associated with significant instability and high liability to oxidation.

On the other hand, niosomes are also microvesicles that are somewhat similar to liposomes but consist of nonionic surfactants. Generally, they have smaller diameters when compared to liposomes and can be with one layer or multiple layers. Niosomes have the advantage of being more stable than liposome and can achieve more rapid penetration, but they still cannot go deeper than the stratum corneum.

Eutectic mixture of local anesthetics

Mixtures are known to be compound of several anesthetic substances that will have lower melting point and thus allow for improved penetration of the anesthetic. Following the application of an eutectic mixture, a tegaderm patch is used to cover the skin and allow better stratum corneum penetration. Clear plastic wraps can sometimes be used in the absence of tegaderm patches. The duration of the eutectic mixture application is proportionally correlated with the depth of induced anesthesia. Studies have found that the application of an eutectic mixture for an hour can achieve three-millimeter penetration, and the application of an eutectic mixture for two hours can achieve five-millimeter penetration. Research suggests that the prolongation of the application or three hours will achieve even deeper penetration that can persists for about two hours following the removal of the anesthetic.

However, the penetration of eutectic mixtures through the palms and soles is usually variable and thus is not recommended. Safety studies have found

that eutectic mixtures can be used safely during pregnancy but caution is still required during lactation due to the possible excretion of lignocaine in milk.

Tetracaine, adrenaline (epinephrine), and cocaine (TAC) mixture:
This mixture was the first anesthetic mixture that was developed and used topically to achieve effective anesthesia. It is primarily synthesized using tetracaine, cocaine, and adrenaline in different concentrations, and was first used in treatment of facial lacerations and scalp lacerations. This mixture is applied on the skin through a cotton facilitator that achieves certain pressure, and then kept for about half an hour. Limitations of this mixture included high costs, potential toxicity, and cocaine abused. These limitations led to stopping its use for local anesthesia [18].

Lidocaine, epinephrine, and tetracaine (LET) mixture:
This mixture is considered to be associated with better safety and cost-effectiveness and is consisted of a mix of lignocaine, epinephrine, and tetracaine in different concentrations. The indications for the use of this mixture include skin laceration in which it can be directly placed on the wound. Placement of this mixture is achieved using a cotton facilitator with firm pressure for about half an hour.

This mixture has been safely used in children after the age of two years. However, it has shown relatively lower efficacy when applied on lacerations of the upper and lower limbs. Additionally, the epinephrine part of this mixture can be associated with the development of ischemia and gangrene due to vasoconstriction when applied to digits, which should be, therefore, avoided. Moreover, it can lead to toxicity when applied over contaminated injuries, compound wounds, and large areas. Finally, both this mixture and the TAC mixture are inefficient when used on intact skin layers [18].

Bupivanor:
This mixture is created by combining bupivacaine with norepinephrine and provides acceptable efficacy and safety. It is generally used during repair of facial lacerations and scalp lacerations [19].

ELA-max
This mixture is created by encapsulating lignocaine cream within a matrix of liposomes, and got the FDA approval for decreasing the pain associated with abrasions and small wounds. It can sometimes be also used to decrease pain in the anorectal area. ELA-max is generally placed on the site of pain for about forty minutes, which will result in pain relief for a relatively long duration. However, it should not be applied over an area that is larger than six hundred cm2, and it should not be used in under-weight children over an area that is larger than one hundred cm2, due to possible toxicity [20].

Betacaine-LA:
This mixture consists of prilocaine, phenylephrine, and lignocaine and is known to achieve relatively high efficacy. However, it was found to be associated with toxicity when applied over large areas or applied in children[20].

4% tetracaine (amethocaine):
This ester compound is mixed with a gel base of lecithin to provide a long-acting anesthetic that can be generally used with occlusive dressing. It is recommended to be applied for about half an hour with a dose that is less than fifty mg to avoid toxicity [20].

Topicaine
Topicaine is 4% lignocaine in a gel microemulsion drug delivery system. The recommended application time by the manufacturers is 30-60 min. The maximum area of application is 600 cm2 in adults and 100 cm2 in children.

S-Caine Patch™ and local anesthetic peel:
This patch was designed to contain an eutectic mixture of lignocaine and tetracaine used along with a heating element that is activated by oxygen. This heating element was added to improve the cutaneous delivery of the anesthetic that will improve anesthetic activity [21,22].

Lidoderm patch:
This patch is synthesized using an adhesive substance that contains lignocaine placed in a liquid basic material. The use of this patch has been recently recommended in the relief of postherpetic neuralgia pain.

Proparacaine or proxymetacaine:
This anesthetic is generally used in ophthalmic procedures. It comes as eye drops and can induce anesthesia within half a minute following a drop into the eye. The highest efficacy is achieved within five minutes following the drop, and will last for fifteen minutes and up to half an hour in some cases.

Safety considerations when using topical local anesthetics:
Patients who are known to have PABA allergy are

contraindicated to use any ester anesthetic as is can potentially provoke severe allergic response. This also applies to any patients with allergy to hair dyes and sulfonamides. A common adverse event following the use of topical anesthetics is the development of skin irritation that can sometimes be severe and cause burning. The use of some anesthetics can be associated sometimes with toxicity, especially during the treatment of relatively large skin areas. The repeated use of topical anesthetics in vulnerable groups (like young or old patients) has also been associated with the development of systemic toxicity.

Other possible adverse events include the development of metallic taste, numbness, dizziness, diplopia, and tinnitus. Some topical anesthetics have also been associated with the development excitation of depression of the central nervous system leading to the development of a wide range of neurological manifestations including anxiety, seizures, twitching of muscles, restlessness, altered mental status, respiratory depression, and coma in severe toxicity.
Cardiovascular manifestations associated with topical anesthetic toxicity can also develop and these include increased blood pressure, increased heart rate, development of arrhythmias, and coronary artery events. Cases of Methemoglobinemia have been reported with the use of benzocaine and prilocaine [23]. Methemoglobinemia should be suspected when the patient develops cyanosis, shortness of breath, general fatigue with headache, altered mental status, and dizziness. The arterial blood will become brown colored, which is characteristic of the condition. Severe cases of Methemoglobinemia can lead to the development of arrhythmias, seizures, and coma. When Methemoglobinemia is suspected, immediate oxygen therapy and exchange transfusion are required along with the administration of methylene blue, which will reverse the condition [24].

The development of these manifestations and adverse events, which can be severe sometimes, make it essential for physicians to be able to properly use topical anesthetic in methods and doses that will decrease adverse events and improve efficacy.

CONCLUSION:

The use of topical anesthetics has been increasing in several procedures due to its improved efficacy and decreased pain when compared to injected local anesthetics. Topical anesthetics are generally used in skin procedures, ophthalmological surgeries, minor procedures, and laser treatment modalities, along with other potential uses. A wide variety of topical anesthetics has been discovered and developed with varying efficacy, safety, and uses. The most challenging step when using a topical anesthetic is the penetration of the corneum. Therefore, better anesthetics are associated with improved corneum penetration. The use of combination anesthetics has been found to lead to significant improvements in the efficacy and penetration of the anesthetics. Many mixtures have been developed and introduced for different uses. However, despite all developments and improvements in the use of topical local anesthetics, they are still associated with adverse events and toxicity that may be severe in some cases and cause death. Therefore, caution should be applied by physicians when they attempt to use topical local anesthetics along with careful attention to the proper doses and methods of application. In addition, strict caution should be applied with topical local anesthetics are applied in vulnerable patients like neonates, children, elderly, and pregnant females. Further studies are still required to improve the use of topical anesthetics and provide protocols with highest efficacy and minimal adverse events.

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