Comparative Studies of The Effects of Three Topical Anaesthetics on Tear Quality and Tear Quantity

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Abstract- Purpose: ***This study compared the effects of three different topical anaesthetics agents on tear quantity and tear quality.***
Methods: ***To establish this, 51 healthy subjects aged 18 – 35 years with mean age of 20.02±1.82 years who do not have any ocular diseases were used. The study sample consisted of 25 males and 26 females of the University of Benin, Nigeria. The tear quantity and quality were measured for each subject before and after instillation of each topical anaesthetic agents. The anaesthetics used were 2% Lidocaine hydrochloride, 0.5% Proparacaine hydrochloride and 0.5% Tetracaine hydrochloride. Schirmer's tear test was used to assess the quantity of tears while tear quality was assessed with the Non-Invasive Tear Break-Up-Time (NIBUT).***
Results: ***The result obtained showed that 0.5% Proparacaine hydrochloride had a statistically significant decrease in tear quantity produced after its instillation, using the one-way analysis of variance, ANOVA (F = 6.930, P< 0.05). 0.5% Proparacaine hydrochloride also had a statistically significant decrease on tear film stability time (F = 5.071,P< 0.05) while 2% Lidocaine hydrochloride had the least effect on tear quantity and 0.5% Tetracaine hydrochloride had the least effect on tear quality.***
Conclusion: ***It was discovered that of these three topical anaesthetic agents, 0.5% tetracaine hydrochloride may be the preferred choice in optometric practice particularly in patients with evaporative dry eye while 2% Lidocaine will be the drug of choice particularly in patients with aqueous deficient dry eye. The use of proparacaine should be discouraged in patients with dry eye syndrome to avoid more complications.***

Indexed Terms- ***Anaesthetics, Non-Invasive Tear Break-Up Time, Schirmer's test, Dry eye Disease, Proparacaine, Lidocaine, tetracaine.***

I. INTRODUCTION

Anaesthetics are drugs which bring about the state of anaesthesia. Anaesthesia is a measure which produces insensitivity to external expression or a reversible lack of awareness which can be general or local.[1] General anaesthetics act on all parts of the body while local anaesthetics act on some parts of the body or a part of the body. When applied in an effective concentration to nerve tissue, local anaesthetics reversibly block the conduction of impulses through nerve fibres. The primary action is to prevent impulses conduction. However, they will also block motor nerves in higher concentrations than are normally obtained by topical instillation. Local anaesthetics are made mostly from amino-esters and amino-amides. Proparacaine and tetracaine are the most common forms of amino-esters. Ester anaesthetics produce an almost instantaneous and significant anaesthetic effect when applied to the pain sensitive cornea but they are relatively "short-lived". This is because plasma cholinesterase agents in the blood rapidly metabolize esters. Lidocaine is prototype of amide-linked agents, which are metabolized by liver and are longer acting.[2] Anaesthetics can be given topically , intravenously, intramuscularly, or intrathecally.

Topical anaesthetics are types of local anaesthetic that are used by the optometrists and eye care practitioners to numb the surface of the eye (conjunctiva and cornea) during some ocular procedures such as applanation tonometry, foreign body removal, ocular irrigation, ocular surgeries etc. Topical anaesthetics have been reported as been detrimental to the ocular surface and also causing reduction in tear production.[3] This study was aimed at determining the actual effect of anaesthetic on tear production. It also compared their effect on tear production and tear film stability before and after the instillation of the three topical anaesthetics (proparacaine, tetracaine and lidocaine). The result of this research will enable ocular health workers to know the exact effect of these anaesthetics

on tear quality and stability and take necessary precaution on their use particularly in people at the risk of having dry eye or those with dry eye syndrome.

A. Tears

The tear is the interface between the external environment and the ocular surface. It forms a smooth refractive surface over the corneal surface, lubricates the eyelids and maintains the optimal extracellular environment for the epithelial cells of the cornea and the conjunctiva tissues.[4] The tear film is a hydrated mucous gel covered by a lipid layer. Mucins are secreted from the cornea and the conjunctiva,[5] The aqueous component of the tear film is secreted by the main and accessory lachrymal glands whereas the meibomian glands secrete the outermost lipid layer which is thought to play a major role in retarding evaporation of the aqueous components of the tears.[6,7] Tears are a mixture of secretions from the major and minor accessory lacrimal glands, the goblet cells and the Meibomian glands. It covers the anterior surface of the globe and it is about 34 to 45 micrometre thick. It is composed of 3 layers namely:

- A superficial lipid layer which is derived from the Meibomian gland secretion. This function retards the evaporation of the aqueous layer.
- A middle layer which is secreted by the major and minor lacrimal glands and contains water soluble substances examples salts, proteins and an enzyme called lysozyme that actually protects and nourishes the eye.
- A deep mucous layer composed of glycoprotein mucin which overlies the corneal and conjunctival epithelial cells. these layers function to cause the adherence of the tears to the eye.[8,9]

1. *Functions of Tears*

The tears keep the surface of the globes moist and serve as a lubricant between the globes and the eyelids.

- It traps debris and helps remove sloughed epithelial cells.
- It provides a smooth refractive surface for optimum optical function. It contains antibacterial substances lysozymes, beta-lysine and IgA to help protect against infection.
- It helps to maintain corneal hydration by changes in tonicity that occurs with evaporation.
- It is a primary source of atmospheric oxygen for the cornea.

It is very important to maintain the tear quantity and quality to prevent dry eye (keratoconjunctivitis sicca). Blinking is required for the periodic resurfacing of the tear film. Blinking occurs involuntarily (reflex blink) as a response to external stimuli or voluntarily which involve the movement of the upper and the lower lids to close the palpebral fissure.

Production of the tears is a highly complex process. It is mainly controlled by the lacrimal functional unit which comprises the main and accessory lacrimal gland of the ocular surface (cornea, conjunctival and Meibomian gland), the eyelids and the interconnecting sensory and motor nerves.[10] The lacrimal gland is supplied by sensory, sympathetic and parasympathetic nerves which branch along the vessels and from sphenopalatine ganglion and facial nerves. Afferent fibres go along the trigeminal nerves and efferent fibres leave via the sympathetic and parasympathetic nerves. The sympathetic nerve controls the normal tear and the parasympathetic controls the reflex tear or excessive lacrimation. Reflex tearing occurs in response to challenges resulting from stimulation of the free nerve endings in the densely innervated cornea and to some degrees from stimulation of the conjunctiva. Stimulation of the individual tear secretion glands is also influenced by a range of hormones and cytokines.[10] The alteration of any component of the lacrimal functional unit or of the hormonal or cytokine balance might result in compromised tears secretion leading to an imbalance in tear dynamics.

2. *Tears Drainage*

The lacrimal glands secrete tears, which flows through the main excretory ducts into the space between the eyeball and lids. When the eyes blink, the tears are spread across the surface of the eye. Tear gathers in the lacrimal lake, and is drawn into the Puncta by capillary action, then flows through the lacrimal canaliculi at the inner corner of the eyelids entering the lacrimal sac. Then into the nasolacrimal duct, and finally into the nasal cavity. An excess of tears, as with strong emotion, can thus cause the nose to run.

3. *Tear Production*

Tear production of an inadequate quantity or of an inadequate quality leads to a condition known as "Dry eye syndrome".[11,12] Dry eye is one of the most common ophthalmic medical problems. Complaints of dry eye are an1ong the most common reasons patients seek help from eye doctors. Dry eyes are common disorders of the tear film that results from inadequate tear production and excessive tear evaporation.[13] Dry eye disease is divided into two major categories: Aqueous deficient dry eye known as keratoconjunctivitis sicca and evaporative dry eye. Aqueous deficient dry eye is mainly due to the failure of the lacrimal gland to produce the aqueous components of the tears while evaporation dry eye is due to the excessive evaporation of the aqueous layer of the tear film and is mainly caused by meibomian.[10] Patients with keratoconjunctivitis sicca typically experience ocular discomfort. The most common irritation symptoms include scratchiness, grittiness, foreign body sensation, burning, and itching; these symptoms are exacerbated by prolonged visual activity (e.g., viewing a video display terminal) and environmental stresses, such as low humidity and air drafts.[14] They often complain of blurred and fluctuating vision that stimulates them to blink more frequently to clear their vision. Together, these symptoms are a considerable source of ocular fatigue; many patients report that they are unable to read or concentrate for more than a few minutes at a time. Clinically, dry eyes appear as a decreased tear meniscus with debris and strands of mucus in the tear film. It can also lead to the formation of filaments (filamentary keratitis) in advanced cases. Additional clinical signs include reduced wetting on schirmer's testing, reduced tear breakup time as well as ocular surface staining.

4. *Causes and risk factors of dry eye*

Dry eyes can be a temporary or chronic condition.

- It can be the side effect of some medications including antihistamines, nasal decongestants, tranquillizers, certain blood pressure medications, Parkinson's medications, birth control pills and antidepressants.
- Skin disease on and around the eyelids can result in dry eye.
- Diseases of the glands in the eyelids such as meibomian gland dysfunction can cause dry eye
- Dry eye can occur in women who are pregnant
- Women who are on hormone replacement therapy, women taking oestrogen.
- Dry eyes can also develop after refractive surgery known as LASIK. The symptoms generally last three to six months, but may last longer in some cases.
- Dry eye can result from chemical and thermal burn that scars the membrane lining the eyelids and covering the eye.
- Allergies can be associated with dry eye.
- Infrequent blink, associated with staring at computer or video screens may also cause dry eyes.
- Loss of sensation in the cornea from long term contact lens wears.
- Dry eyes can be associated with immune system disorders such as Sjogren's syndrome, lupus and rheumatoid arthritis.
- Dry eye may also occur from exposure keratitis, in which the eyelids do not close completely during sleep.
- Ophthalmic preparations with benzalkonium chloride as preservative

B. Anaesthetic

Anaesthetic comes from the Greek word "anaesthesia" which means loss of sensation. Anaesthetics are drugs that cause anaesthesia. Anaesthesia is a reversible loss of sensation. Anaesthetics are categorised into two glasses: General and local anaesthetics. General anaesthetics cause reversible loss of sensation and loss of consciousness. Local anaesthetics cause reversible loss of sensation for a particular part of the body while maintaining consciousness.[1] Local anaesthetics have the suffix "-caine" in their names. Examples include tetracaine, lidocaine, proparacaine, oxybuprocaine, benzocaine etc.

Topical anaesthetic is a local anaesthetic Anaesthetic that is used to numb the surface of a body part. They can be used to numb any area of the skin as well as the eyeball, the inside of the nose, ear or throat, the anus and the genital area. Topical anaesthetics are available in creams, ointments, aerosols, sprays, lotions, drops and jellies. Examples include lidocaine,proparacaine

and tetracaine (also named amethocaine) all derived from the natural chemical cocaine from the coca plant.

1. *Roles of topical Anaesthetic*

- Topical anaesthetics are used in ophthalmology and optometry to numb the surface of the eye (the outermost layers of the cornea and conjunctiva) for the following procedures:To perform a contact/ applanation tonometry.
- To perform a Schirmer's test. The Schirmer's test is sometimes used with a topical anaesthetic and sometimes performed without it. The use of a topical anaesthetic might impede the reliability of the Schirmer's test and should be avoided if possible.
- Removal of small foreign objects from the uppermost layer of the cornea or conjunctiva. The deeper and the larger foreign object lies within the cornea, the more complicated it is to be removed. Drops of topical anaesthetic are necessary prior to the removal of the foreign object to numb the surface of the eye with enough intensity and duration.
- When performing eye surgeries or during pterygium excision, topical anaesthetics are used to numb the eye.

2. *Classification of topical anaesthetics*

Local anaesthetics are made mostly from amino esters and an1ino-amides. Proparacaine and Tetracaine are the most common forms of amino esters. Ester local anaesthetics are generally unstable in solution and fast-acting and allergic reactions are common. They produce an almost instantaneous and significant anaesthetic effect when applied to the pain sensitive cornea, but they are relatively "short lived". This is because plasma cholinesterase agents in the blood rapidly metabolise esters. Lidocaine is a prototype of amide-linked agents, which are metabolised by the liver and are long acting. Amide local anaesthetics are generally heat-stable, with a long shelf life (around 2 years). They have a slower onset and longer half-life than ester anaesthetics

3. *Mechanism of action of topical anaesthetics.*

Anaesthetics act on any part of the nervous system and on every type of nerve and fibre. Different sensations are lost according to the size of the axon serving them. Topical anaesthetic use in ophthalmology and optometry function by blocking nerve conduction in the superficial cornea and conjunctiva. The ocular surface is innervated by the multiple branches of the trigeminal nerve. The cornea is supplied by the long and short ciliary nerves, the nasociliary nerve and the lacrimal nerve. Anaesthetics prevent the temporary increase in sodium permeability that occurs during nerve-impulse conduction. Without the ability of the nerve cell to generate action potentials, the nerve impulse is blocked and sensation is eliminated. There are several hypotheses as to why this may occur. Anaesthetics may interfere directly with channel activation by decreasing the number of available channels, they may inhibit the conformational change that the channels undergo when opening or they may reduce the ion flow through the open channels.[15]

The length of the anaesthetic effect is defined by the time it takes for the anaesthetic molecules to diffuse out of the nerve and be removed by the circulatory system. The duration of topical anaesthesia might depend on the type and amount applied, but is usually about half an hour. When used excessively, topical anaesthetics can cause severe and irreversible damage to corneal tissues and even loss of the eye.[15,16,17]

The abuse of topical anaesthetics often creates challenges for correct diagnosis in that it is a relatively uncommon entity that may initially present as a chronic keratitis masquerading as acanthamoeba keratitis or other infectious keratitis. When a keratitis is unresponsive to treatment and associated with strong ocular pain, topical anaesthetic abuse should be considered. Because of the potential for abuse, clinicians have been warned about the possibility of theft and advised against prescribing topical anaesthetics for therapeutic purposes. Some patients who suffer from eye pain, which is often considerably strong neuropathic pain caused by the irritation of the nerves within the cornea and/or conjunctiva, unfortunately try to illegally obtain eye anaesthetics (for example by stealing them at their ophthalmologist or optometrist, by forging medical prescriptions or by trying to order it via an online pharmacy) and secretly use the substance to numb their eye pain, often ending up with irreversible corneal damage or even destruction.[18]

C. An overview on Proparacaine, Lidocaine and Tetracaine Hydrochloride.

1. *Proparacaine Hydrochloride*

Proparacaine is a topical anaesthetic drug of the amino ester group. It is available as its hydrochloride salt in ophthalmic solutions at a concentration of 0.5%. The IUPAC name for proparacaine hydrochloride is: 2-(diethyl amino) ethyl 3-amino-4-propoxybenzoate.

Chemical Formula: C16H26N203 and 330.85g/mol molecular weight.

1.1 *Pharmacodynamics of proparacaine hydrochloride*

Proparacaine stabilises the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby affecting local anaesthetic action. More specifically, proparacaine appears to bind or antagonise the function of voltage gated sodium channels.

1.2 Pharmacokinetics and metabolism of proparacaine hydrochloride

Proparacaine is rapidly absorbed by conjunctiva capillaries and it is hydrolyzed by plasma esterase. Anaesthetic action begins within 20 seconds after applying the product and its duration is 15 minutes or longer.

2. *Lidocaine Hydrocloride*

Lidocaine is a common local anaesthetic. It is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anaesthetic or as a local anaesthetic for minor surgery. The efficacy profile of lidocaine as a local anaesthetic is characterised by a rapid onset of action and intermediate duration of efficacy. Therefore, lidocaine is suitable for infiltration, block and surface anaesthesia. Longer-acting substances. Lidocaine, on the other hand, has the advantage of a rapid onset of action. Lidocaine drops can be used on the eyes for short ophthalmic procedures.The IUPAC name of Lidocaine is: 2-(diethyl amino)-N-(2, 6-dimethylphenyl) acetamide. Its chemical formula is: C14 H22 N20 with a molecular weight of 234.34 g/mol.

2.1 *Pharmacodynamics of lidocaine hydrochloride*

Lidocaine alters signal conduction in neurons by blocking the fast voltage gated sodium (Na+) channels in the neuronal cell membrane that are responsible for signal propagation. With sufficient blockage the membrane of the postsynaptic neuron will not depolarize and will thus fail to transmit an action potential. This creates the anaesthetic effect by not merely preventing pain signals from propagating to the brain but by stopping them before they begin. Careful titration allows for a high degree of selectivity in the blockage of sensory neurons, whereas higher concentrations will also affect other modalities of neuron signalling.

2.2 *Pharmacokinetics and metabolism of lidocaine hydrochloride*

The onset of action of lidocaine is about 45 to 90 seconds and its duration is 10 to 20 minutes. It is approximately 95% metabolized (dealkylated) in the liver mainly by cytochrome P450 3A4(CYP3A4) to the pharmacologically-active metabolites mono ethyl glycine xylidide (MEGX) and then subsequently to the inactive glycine xylidide. MEGX has a longer half life than Lidocaine but also is a less potent sodium channel blocker. The volume of distribution is 1.1-2.1 L/kg but congestive heart failure can decrease it. 60-80% circulates bound to the protein alpha 1 acid ·glycoprotein. The oral bioavailability is 35% and the topical bioavailability is 3%. The elimination half-life of lidocaine is biphasic and approximately 90-120 minutes in most patients. This may be prolonged in patients with hepatic impairment (average 343 minutes) or congestive heart failure (average 136 minutes). Lidocaine is excreted in the urine (90% as metabolites and 10% as unchanged drug).

3. *Tetracaine Hydrochloride*

Tetracaine (Amethocaine) is a potent local anaesthetic of the ester group. It is available as its hydrochloride salt in ophthalmic solutions at a concentration of 0.5%.

Formular: C15 H24 N2 O2

Molecular mass: 264.363g/mol

3.1 *Pharmacodynamics of tetracaine hydrochloride*

Tetracaine hydrochloride is used as a local anaesthetic which acts by reversibly blocking the propagation and conduction of nerve impulses along nerve axons. Tetracaine stabilises the nerve membrane, preventing the increase in sodium permeability necessary for the production of an action potential.

3.2 *Pharmacokinetics and metabolism of tetracaine hydrochloride*

Tetracaine is a weak base (pKa8.5), therefore, significant changes in the rate of ionised lipid soluble drug uptake may occur with changes in the acid base balance. The onset of action of tetracaine is approximately 15 seconds and its duration is 10 to 20

minutes. In vitro studies have shown that tetracaine has a high affinity for melanin, therefore, differences in duration of action may be expected between deeply pigmented eyes and less pigmented eyes. The primary site of metabolism for tetracaine is the plasma. Pseudocholinesterases in the plasma hydrolyse tetracaine to 4-aminobenzoic acid. Unmetabolized drugs are excreted in the urine.

D. Statement of problem

The incidence of dry eye is estimated to be high especially in the older population and dry eye is one of the most common reasons why people visit their optometrists.[19] Some researchers have reported alteration in the tear film with the use of topical anaesthetic.[20,21] This research seek to investigate the effect of three anaesthetic agents (0.5% proparacaine, 0.5% tetracaine and 2% lidocaine) on tear production

II. LITERATURE REVIEW

Dry eye was defined by the National Eye Institute (NEl)/industry workshop in 1993 as a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the inter palpebral ocular surface and is associated with symptoms of discomfort.[13] TFOS DEWS defined dry eye as a multifactorial disease of the tears and the ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage of the ocular surface. It is mostly accompanied by an increased osmolarity of the tear film and inflammation of the ocular surface. Dry eye is the most frequently encountered ocular disorder, a growing public health problem and one of the most common ocular conditions seen by eye care practitioner.[22] Patients with dry eye syndrome typically experience ocular discomfort. The most common irritation symptoms include scratchiness, excessive tearing, grittiness, foreign body sensation, burning, and itching; these symptoms are exacerbated by prolonged visual activity (e.g., viewing a video display terminal) and environmental stresses, such as low humidity and air draft.[14] Dry eye patients often complain of blurred and fluctuating vision that stimulates them to blink more frequently to clear their vision. Together, these symptoms are a considerable source of ocular fatigue. Many dry eye patients report that they are unable to read or concentrate for more than a few minutes at a time. Both eyes are usually affected.[14]

Dry eye disease is seen with increased prevalence in patient with autoimmune diseases.[10] which affect approximately 8% of the population of whom 78% are women.[23] Dry eye disease affects postmenopausal women and the elderly population.[24,25] The prevalence of dry eye disease is estimated to be 7.4% to 33.7%, depending on which study is cited, how the disease is diagnosed and which population is surveyed.[27,28] The Beaver Dam population based study found the dry eye prevalence rate to be 14% in adults between 48 to 49 years of age.[28] The study also found that dry eye disease affects more women than men with a percentage of 16.7% versus 11.4% respectively. Reliable epidemiological studies from the large Women's Health Study and Physician Health Study indicates that the prevalence of symptomatic dry eye in United states is about 7% in women and 4% in men over the age of 50 years.[29] These numbers translate into approximately 3.2 million women 1.05 million men with dry eye disease in the united state.[27] In the United states alone, estimate of those affected by dry eye disease amount to approximately 20 million or more.30 International epidemiological studies reported similar findings around the world. The prevalence of dry eye disease is approximately 7.4% in Australia with significant increase of prevalence in older patients and a significant decrease of tear production in women 50 to 59 years of age.[31] In Indonesia, dry eye prevalence is approximately 27.5%, with increased prevalence associated with age, cigarette smoking and pterygium.[32] In Taiwan, the prevalence of dry eye disease is 33.7% in a tested elderly population With significantly more women reporting dry eye symptoms than men.[33] The incident of dry eye is also estimated to be 25% in Canada,[34] and 33% in Japan.[35] It is worth noting that the prevalence and incidence of dry eye disease in clinical setting may also be under reported, as patients may fail to recognize the symptoms of dry eye disease or do not report the problem to their optometrists. Several risk factors for the development of dry eye disease have been identified repeatedly in epidemiological studies. These factors include:

- Age: Tear production usually decreases with an increasing age.[32]

- Sex: Dry eye disease has been reported to be more common in women than in men most especially in post menopausal women.[36]
- Low humid environment.[14]
- Dry eye disease is seen with increased prevalence in patient with autoimmune diseases such as diabetes.[37]
- Extended visual tasks during computer use, television watching and prolong reading provoke symptoms of dry eye.[38]
- Contact lens wear can sometimes cause dry eye syndrome because an adequate tear film is required to tolerate a contact lens comfortably on the eye.[39]
- Systemic medications such as antihistamines, nasal decongestant and anti depressants have a drying effect which can exacerbate or lead to dry eye.[40]
- After LASIK due to severing of the cornea nerve endings during the surgery.[41,42]

Although topical anaesthetics are generally safe, complications may rarely occur from their use. Balanced prescription for specific diagnosis in addition to careful clinical monitoring of the effects of treatment can minimise their risks. However, the arbitrary use of these medications is likely to do more harm than good. Topical anaesthetics restrain the corneal epithelium cell migration rate by damaging the superficial corneal epithelium microvilli,[43] they may also have a direct toxic effect on the stromal keratocytes. Ring infiltrates have been described to be associated with topical anaesthetics abuse.[44] Pathological mechanism such as immunologic, irritation, toxic, cumulative deposition, phototoxic and microbial imbalance may occur. The ocular and adnexal tissues can respond to these insults by manifesting cutaneous changes including papillary, follicular, keratinizing or cicatrizing conjunctivitis and keratitis, hyper or hypo pigmentation and infectious complications.[45,46,47,48]

Topical anaesthetic abuse resulting in sight threatening keratitis may be seen as a masquerading syndrome in many cases. Because of the often poor outcome, we must be aware of this entity, prevent abuse and be vigilant in our prohibition of topical anaesthetic for any therapeutic use.[49] Topical anaesthetic can cause severe and irreversible damage to the corneal tissues, and even loss of the eye.[15] The abuse of topical anaesthetics often creates challenges for correct diagnosis in that it is a relatively uncommon entity that may initially present as a chronic keratitis masquerading as acanthamoeba keratitis or infectious keratitis.[17,18] When a keratitis is unresponsive to treatment and associated with strong ocular pain, topical anaesthetic abuse should be considered. Previous study reported a significant increase in the thickness of the corneal after the instillation of topical anaesthetic[50]. This study was in agreement with that of Asensio *et al* (2003) who also reported a significant increase in corneal thickness after the instillation of topical anaesthetic.

Although topical anaesthetic has a lesser risk than retrobulbar or peribulbar anaesthesia, adverse effects can occur with its use. One such adverse effect is alteration of lacrimation and tear-film stability. Topical anaesthetics disrupt surface microvilli of the epithelial cells, causing decreased stability in the tear film.[16] Anaesthetic also lessens mucous adherence, shortens tear breakup time, decreases the blink rate and blocks the reflex-tearing pathway, resulting in inadequate tear production in response to noxious stimuli. Combined, these effects contribute to the deterioration of the ocular surface by increasing dry-eye symptoms, staining and vulnerability.[45]

Tear production using Schirmer's technique was measured on 30 subjects following the instillation of 0.5% tetracaine, 0.5% proparacaine and 2% lidocaine hydrochloride, it was found that Schirmer's test value was significantly reduced with 0.5% proparacaine hydrochloride ($P<0.05$) when compared to the baseline. There was no significant reduction with 0.5% tetracaine and 2% lidocaine hydrochloride.[52] Research on the effect of 2% Lignocaine hydrochloride on tear quantity carried out in population between the age range of 18-35years, showed that Lignocaine hydrochloride caused a significant reduction in normal tear production and sex has no significant relationship with normal tear production in younger population.[53] Non invasive tear break up time (NIBUT) test following the instillation of 0.5% proparacaine, 0.5% tetracaine and 2% xylocaine revealed a significant reduction in tear film stability with 0.5% proparacaine, no significant effect on tear film stability with 2% xylocaine hydrochloride on tear and a significant

increase in tear film stability with 0.5% tetracaine hydrochloride.[53] Experiment conducted by Cho P (1995)[54] to examine the effect of 0.4% Benoxinate hydrochloride on tear stability using the Non invasive tear break up time (NIBUT) and Tear break up time (TBUT) showed a significant increase of NIBUT while TBUT was unaffected 30 seconds after instillation. The effect of unpreserved 0.4% Oxybuprocaine hydrochloride on tear film stability, using a non invasive tear film break up technique (NIBUT) was investigated, it was found that the topical anaesthetic did not reduce the pre-corneal tear film stability.[55]

Ophthalmic preservatives help to prevent bacterial contamination and prolong shelf life limiting biodegradation and maintaining a non hazardous level of contamination. When used chronically, preservatives can disrupt the precorneal tear film and lead to the epithelial surface, cornea, conjunctiva and worsening of the ocular surface disorders.[56]

Benzalkonium chloride is a quarternary ammonium that acts as a detergent to interrupt the lipid membrane of cells, thus killing microorganisms. Originally developed as a germicide in the 1910s, it was first used in the ophthalmic industrynin the 1940s as apreservative in hard contact lens solutions. Since then, it has been used nearly in all ophthalmic solutions., from from articial tears to glaucoma medications. Benzalkonium chloride is a highly effective antimicrobial with broad activity against Gram-positive bacteria, Gram-negative bacteria and fungi. However, it has also been associated with multiple adverse effects. Cytotoxicity to the ocular surface was documented as early as the 1970s.[57] This leds to attempts to develop other, less toxic preservatives to replace it including others detergents like polyquaternium-1 (P0lyquads; Alcon laboratories, Inc.,Forth Worth, TX, USA), as well as newer classes of preservatives, like stabilized oxidizing agents and inic beffered preservatives.[58] Although significantly less toxic than Benzalconium chloride, these new formulations still exhibit some adverse effects.[59]

The toxicity of Benzalkonium chloride have been well documented, most notably its effect on the ocular surface. Common side effects include conjunctiva hyperaemia, decreased tear production, tear film instability, and superficial punctate keratitis. This can result in ocular discomfort due to dry eye and inflammatory irritation.[60] BAC's inherent detergent properties disrupt the lipid layer of the tear film, resulting in increased aqueous tear evaporation and decreased tear film break-up time.[61] Benzalkonium chloride has also been associated with a decrease in density of goblet cells, which are particularly susceptible to toxic insults. This deficiency in goblet cells results in decreased mucin production and decreased tear film stability.[62] Together, these effects on tear film contribute to dry eye symptoms and ocular discomfort in glaucoma patients, who already experience a decreased rate of basal tear turn over.[63] Even in patients who do not experience discomfort, signs of tear film instability and corneal epithelial damage can be found.[64] Not only does benzalkonium chloride's effect on the tear film indirectly damage the cornea, it also exerts a direct cytotoxic effect on the cornea. In animal models, benzalkonium chloride has been shown to have a dose-dependent cytotoxic effect on the corneal epithelium, with which it is in direct contact. At concentrations of 0.0025%, it results in loss of micro villi at the epithelial cell edges. At 0.005% it causes cell wrinkling, and at 0.01% it causes peeling and exposure of the underlying cell layers (Burstein, 1980). Even at concentrations as low as 0.001%, epithelial dysfunction and damage to the corneal epithelial barrier have been documented.[65] The concentration of benzalkonium chloride in ophthalmic preparations typically ranges from 0.004%-0.02%, well within the range of producing toxic effects. Corneal epithelial toxicity is much more pronounced with benzalkonium chloride when compared to other newer preservatives, such as Polyquad or sofZia.[58] Benzalkonium chloride is also cytotoxic to corneal endothelial cells in vitro. The clinical relevance of this is still under investigation, as benzalkonium chloride tends to become diluted as it is absorbed through the layers of the cornea. However, certain patients may be at higher risk for endothelial toxicity if their epithelium is already damaged and exacerbated by benzalkonium chloride or if repeated instillations of drops preserved with benzalkonium chloride results in accumulation in the ocular tissue.[65] In fact, keractonized corneas receiving benzalkonium chloride showed changes to the endothelium involving pale and swollen mitochondria as well as membranous

aggregates within the mitochondria.[66] Benzalkonium chloride effects on the conjunctiva tend to be related to inflammatory reactions, with symptoms such as congestion, tearing, photophobia, and burning sensations. Because detergents like BAC cannot be neutralized by mammalian cells, they act as an irritant or even a hapten to induce an allergic response in the eye. Numerous biomarkers of inflammation have been associated with application of BAC to conjunctiva cells. These include interleukins,[59,64] tumour necrosis factor-alpha, and even C-reactive protein.[67] Additionally, BAC has been associated with increased expression of the CCR4 chemokine receptor, a marker for the T-helper 2 pathway, which is involved in immunoglobulin E secretion and allergic responses in the body. Benzalkonium chloride is also associated with increased CCR5, a T-helper 1 marker, which is involved in type IV delayed hypersensitivity. Although benzalkonium chloride seems to induce primarily allergic and inflammatory responses in the conjunctiva, there still may be a direct toxic effect, as evidenced by enhanced desquamation of superficial layers of the conjunctiva. BAC has been shown to deeply penetrate the conjunctiva tissues and accumulate for up to one week after a single drop.[57] The increase in inflammatory cells induced by BAC has resulted in increased fibroblasts and subsequent sub conjunctiva fibrosis after long-term use. Conjunctiva fibrosis and shrinkage have been associated with pseudo pemphigoid.[57]

III. METHODOLOGY

This is a prospective cross sectional study designed to compare the effects of 0.5% tetracaine hydrochloride, 2% lidocaine hydrochloride and 0.5 proparacaine hydrochloride on tear quantity and tear quality.

A. Study Population

The population of the study comprise of 51 staff and students of the university of Benin City, Nigeria comprises 25 males and 26 females, between the ages of 18-35 years who willingly agreed to partake in the study after their informed consent was obtained.

B. Sampling Technique

The convenient sampling technique was used and subjects that satisfied all the inclusion criteria were included in the study.

C. Inclusion criteria:

Subjects with Schirmer's test value greater than 10mm and NIBUT values ranging from 10-45 seconds with no systemic conditions and ocular pathologies and between 18-35 years of age.

D. Exclusion criteria

- Subjects with schirmer's test values less than l 0mm
- Subjects with NIBUT values less than 10 seconds
- Subjects with systemic or ocular conditions.
- Persons outside 18-35 years of age.
- Contact lens users
- Subjects that have performed refractive surgery
- smokers
- Pregnant women

E. Material and instruments used

- Bausch and Lomb Keratometer
- Visual acuity chart
- Opthalmoscope
- Penlight
- Topical anaesthetic drugs (2% Lidocaine hydrochloride, 0.5% tetracaine hydrochloride and 0.5% proparacaine hydrochloride)
- Schirmer's strip
- Cotton wool
- Stop watch
- Notebook
- Pen

F. General Procedure

Each of the subjects was properly examined in the clinic with a good case history, VA and ophthalmoscopy. Those that were free from ocular and visual problems were added to the study after examination of the anterior and posterior segments. In the first week of visit, the tear quantity and tear quality were measured using the Schirmer's technique and the Non invasive tear break up time respectively. The values before the instillation of the topical anaesthetic serve as the control for each of the subjects. Subjects with Schirmer's test value less than 10mm and NIBUT value of less than 10 seconds were considered not qualified for the study as they may have compromised tear film. After the baseline values were taken for each of the subjects, 0.5% tetracaine hydrochloride was instilled into the eyes of each of the subjects. In the

second week of clinic visit, 2% lidocaine hydrochloride was instilled and in the third week of clinic visit, 0.5% proparacaine hydrochloride was instilled in the eyes of each subject. Two minutes after the instillation of the drug at every clinic visit, tear quantity was assessed in the right eye and the tear quality was assessed on the left eye.

1. *Schirmer's test*

After explaining to the subjects that the procedure may be uncomfortable but not painful, they were made to comfortably sit on the chair. The Schirmer's strip was removed from the sterile paper, bent at a notch to a 90 degree angle. The patients were asked to look up and with the index finger, the lower lid of the right eye was pulled down gently and the bent strips were hooked over the centre of the lower eyelid and allowed it to sit inside. The subjects were asked not to squeeze the eye but to gently close them. After 5 minutes, they were asked to open their eyes and look upward. The schirmer 's strips were carefully removed and the length of the moistened area on the strips was measured as the tear quantity of each of the subjects. Wetting values of 10 mm and above wetting after 5 minutes were considered normal and any subject with a schirmer's strip wetting less than 10mm was not included in this study

2. *Non-Invasive Tear Break-up Time*

Non-invasive tear break up time (NIBUT) was done with the Bausch and Lomb keratometer. The procedure was explained to the subjects. The subjects were comfortably positioned with the forehead on the instrument headrest and the chin on the chinrest. The room's illumination was dimmed. With the instrument positioned on the subject's left eye, the keratometer mires (the reflected image of the keratometer grid) were adjusted until they became sharp. The subjects were instructed to blink once and then keep their eyes open for the rest of the examination period. The crisp mires were carefully focused and the time it took for the central mire to double was recorded as the Non invasive tear break up time (NIBUT).Values of 10 seconds and above were considered normal values while values less than 10 seconds were not included in this study.

G. Statistical Package

The result of this research was analysed using the window software SPSS Version 21.0 with the one way analysis of variance (ANOVA).

H. Limitation of study

This study was limited by the reflex tearing that occurred as a result of irritation that was caused on the cornea by the Schirmer's strip

IV. RESULTS

A total of fifty one (n=51) subjects with mean age of 22.02±1.82 years (range 18 to 35 years) comprising 25 males and 26 females were used for this study. It was found that the mean baseline tear quantity was 22.39±8.085; that of 0.5% tetracaine was 18.84±7.862; that of 0.5% proparacaine was 16.04±7.430 while that of 2% lidocaine was 21.41±7.494.

See table 4.1.

Table 1 showing the mean tear quantity of the control and the anaesthetics

Treatment	Tear quantity	Tear quality
Baseline	22.39±8.085	20.59±7.089
0.5% tetracaine	18.84±7.862	19.19±7.989
0.5% Proparacaine	16.04±7.430	15.65±6.479
2%Lidocaine	21.41±7.494	16.92±6.471

Post Hoc was done using the Scheffe's method for tear volume it was revealed that 0.5% tetracaine was not significantly different from 0.5% proparacaine (p=0.342), however it was significantly different from 2% lidocaine and the control. There was no significant difference between 0.5% tetracaine, 2% lidocaine and the control (p=0.149). See table 2.

Table 2 showing post Hoc comparison table for tear volume using Scheffe's method

Treatment	N	Subset for alpha = 0.05	
		1	2
0.5% Proparacaine	51	16.04	
0.5% Tetracaine	51	18.84	18.84
2% Lidocaine	51		21.41
Baseline			22.39
Sig.		0.342	0.149

For the tear quality result, it was found that the mean baseline tear quality was 20.59±8.089; that of 0.5% tetracaine was 19.18±7.989; that of 0.5% proparacaine was 15.65±6.474 while that of 2% lidocaine was 16.92±6.471.

Post Hoc was done using Scheffe's method and 0.5% proparacaine was found not to be significantly different from 2% lidocaine and 0.5% tetracaine ($p=0.096$) however, it was significantly different from baseline ($p<0.05$). There was no significant difference between 2% lidocaine, 0.5% tetracaine and the control ($p=0.078$). See table 3.

Table 3 showing post Hoc comparison table for tear quality using Scheffe's method

Treatment	N	Subset for alpha = 0.05	
		1	2
0.5% Proparacaine	51	15.65	
2% Lidocaine	51	16.92	16.92
0.5% Tetracaine	51	19.18	19.98
Baseline	51		20.59
Sig.		0.096	0.078

V. DISCUSSION

The aim of this study was to compare the effect of three different anaesthetic agents on tear quantity and tear quality (tear stability). The Schirmer's tear test results for tear quantity revealed that there was no significant reduction in tear quantity with 0.5% tetracaine and 2% lidocaine when compared with the baseline value. With 0.5% proparacaine, there was a statistically significant reduction in tear quantity following its instillation when compared to the baseline value. This indicates that proparacaine can reduce tear quantity significantly. This study is in agreement with the previous study by George *et al* (2010)[52], who reported a statistically significant reduction in mean tear quantity after the instillation of 0.5% proparacaine hydrochloride on human subjects.
Basal tear secretion increases in response to a variety of irritants applied to the ocular surface or the nasal and oral mucosa. This reflex tear secretion can be prevented by damage to the sensory root of the trigeminal nerve or by topical application of cocaine and other local anaesthetic drugs into the eye. This suggests that the afferent branch of the tearing response to ocular surface irritation is formed by sensory axons of trigeminal ganglion neurons supplying the eye. The efferent pathway of this reflex is formed by parasympathetic fibres of the superior cervical nerve that act on the main accessory lacrimal glands and meibomian glands to regulate the production of proteins, electrolytes, water and mucin of the tear film. These major findings go a long way to confirm that topical anaesthetic measure only basic secretion thus reducing normal tear production/ secretion, which is both reflex and basic.[68] This could be attributed to the fact that anaesthetics have an adrenergic potentiating effects and because lachrymal fluids receive a preganglionic parasympathetic supply from the lacrimal muscles and leave the facial nerve to synapse in the sphenopalatine ganglion before running into the lacrimal gland, its secretion produces secretion of tears (reflex secretion).[69]

The results for tear quality revealed that with 0.5% tetracaine hydrochloride, there was no significant reduction in mean tear quality when compared with the control; 2% lidocaine hydrochloride had no significant reduction in mean tear quality while 0.5% proparacaine hydrochloride showed a statistically

significant reduction in mean tear quality after its instillation when compared with the control. From the research result, it can be reported that these three anaesthetic had a reducing effect on tear quality but 0.5% proparacaine gave a significant reduction in tear quality.0.5% tetracaine hydrochloride had a least reducing effect in tear stability time as compared with the control. This study is in agreement with George *et., al* (2010)[52] who reported a significant reduction in tear quality following the instillation of 0.5% proparacaine hydrochloride. It has been previously reported by Pharmakakis *et al (2002)*[16] that topical anaesthetics disrupt microvilli epithelial cells, causing decreased stability in the tear film. Anaesthetics also lessens mucous adherence, shortens tear breakup time, decreases the blink rate and blocks the reflex-tearing pathway, resulting in inadequate tear production in response to noxious stimuli. from these, it can be inferred that proparacaine hydrochloride has more effect in disrupting the surface microvilli of the epithelial cells, causes more decrease in blink rate and lessen mucous adherence more than the other anaesthetic.

CONCLUSION

The Schirmer's tear test and the NITBUT test results for tear quantity and quality respectively revealed that there was no statistically significant reduction in tear quantity and tear quality with the instillation of 0.5% tetracaine and 2% lidocaine when compared with the baseline value. However, with 0.5% proparacaine, there was a statistically significant reduction in tear quantity and quality following its instillation when compared to the baseline value. This indicates that0.5% proparacaine can reduce tear quantity and quality significantly when used compared to the other two.

RECOMMENDATION

In this comparative analysis of the three topical anaesthetic agents, 2% lidocaine hydrochloride is recommended as topical anaesthetic agent of choice for optometric practice paticularly in patients with aqueous deficient dry eye. For tear film stability, 0.5 % Tetracaine hydrochloride gave the least reduction in mean tear quality therefore, it is recommended as the anaesthetic of choice for patients with evaporative dry eye because its complication will be lesser when compared to other anaesthetic agents. For both tear quantity and tear quality, 0.5% Proparacaine hydrochloride gave a statistical significant reduction and this can be attributed that Proparacaine has more effect on the destruction of the surface microvilli epithelial cells, shortening mucous adherence, decreasing the blink rate and blocking the reflex-tearing pathway which result to inadequate tear productionin response to noxious stimuli. Eye care practitioners are discouraged from using Proparacaine as a topical anaesthetic of choice in patients with dry eye syndrome or in person at risk of having dry eye because this may worsen their dry eye symptoms of grittiness and burning sensation.

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