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EDITORIAL

Expanding Frontiers of Biomedical Research: The Contributions of Basic Scientific Research

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Introduction

As always, the scientific cause aims at improving human life at all levels through the use of time-tested scientific knowledge and practices. At the root of this lies scientific enquiry which fuels translational research efforts. Generation of scientific knowledge and its dissemination is critical to the scientific cause. In the light of this the Integrated Health Research Journal (IHRJ) was established to serve as the official research conduit of the College of Health and Allied Sciences (CoHAS), University of Cape Coast. Thus, the IHRJ provides a platform for researchers and scientists in the medical and biomedical fields to advance dissemination of quality research outcomes capable of stimulating translational research and generation of health policies to improve human health and wellbeing. In the first call for articles, a total of twenty-one submissions were received out of which seven were accepted for publication after rigorous editorial and review processes.

The focus of all the accepted articles were within that of the IHRJ. For instance, one of the articles highlighted the relationship between indiscriminate use of tetracaine hydrochloride ophthalmic solutions and development of multi-drug antibiotic resistance (Kyei, Boadi-Kusi, Effram-Menyah, Dua, 2023). Telehealth has emerged as one of the approaches to overcome barriers to healthcare coverage. Interestingly, one study assessed barriers to telehealth during the Covid-19 pandemic in rural North America and observed that few studies investigated barriers to telehealth in rural communities and those studies overly focused on short term health outcomes instead of long term health outcomes. Exposure to xenobiotics through matrices such as food, water, air and the soil put humans at high risk for certain diseases. Vowotor and colleagues determined hazard quotient of micronutrients in breastmilk and observed that manganese, sodium, magnesium, calcium, and copper were in levels above the upper limit of the WHO recommended dietary allowance possibly exposing breast feeding infants to risk of metal/metalloid-related toxicity (Vowotor, Sackey, Amuah, Huzortey, Aboh, and Druye, 2023).

Another study (Boachie, Piiga, Dadzie, Essuman, and Boye, 2023) reported transfusion-related adverse reactions from a district hospital in Kumasi detailing the incidence and the factors that contribute to transfusion-related adverse reactions. Non-communicable diseases such as chronic kidney disease (CKD) has been on the increase and it was refreshing to note from a study (Ewua-Gyan, Abdul-Wahab, Donkor, Awuku, Okyere, Botchway et al, 2023) which assessed predictability and accuracy of kidney failure risk equation. Finally, a study detailed the pattern of patient referrals in Northern Ghana.

Summarily, the first issue of IHRJ captured important topics in the core areas of medical and biomedical research and it is hoped that researchers will double their basic research efforts to inform translational research, policy and practice.

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Kyei, S., Boadi-Kusi, S. B., Effriam-Menyah, M. N., Duah, P. (2023) Effect of the Clinical Usage of Tetracaine Hydrochloride Ophthalmic Solution on Multiple Antibiotic Resistant *Staphylococcus Aureus*. Integrated Health Research Journal 1(1), 1-6.

Vowotor, M. K., Sackey, S. S., Amuah, C. L. Y., Huzortey, A., Aboh, I. K., Druye, A. A. (2023) Analysis of Seven Micronutrients in Breast Milk of Lactating Mothers from the Central Region of Ghana Using Epithermal Neutron Activation. Integrated Health Research Journal 1(1), 41-49.

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Integrated Health Research Journal (IHRJ)

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RESEARCH ARTICLE

Effect of the Clinical Usage of Tetracaine Hydrochloride Ophthalmic Solution on Multiple Antibiotic Resistant *Staphylococcus Aureus*

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Abstract

Background: The emergence of resistant strain bacteria is rendering many antibiotics ineffective in the management of infectious diseases.

Objective: The purpose was to investigate the effect of Tetracaine hydrochloride usage on the emergence of a resistant strain of bacteria.

Materials and methods: A total of fifteen New Zealand White rabbits of either sex weighing between 1400-2700 grams were used for this study. Infectious agents of Ophthalmia neonatorum were cultured, isolated and identified. Their susceptibility to various antibiotics was assessed. A resistant strain was picked up and inoculated on the conjunctiva of the rabbits to induce bacterial conjunctivitis. Rabbits were divided into three groups of five rabbits each. Group A received Tetracaine as treatment, group B received 0.3% Ciprofloxacin as treatment and group C received normal saline as a treatment for 14 days. Outcome measures included bacterial colony count, clinical signs and post-antibiotic susceptibility test.

Results: The tetracaine significantly reduced clinical signs (P=0.012) compared to normal saline (control) and 0.3% Ciprofloxacin reduced clinical signs (P =0.003) compared to normal saline (control). This means there was a significant decrease in clinical scores with the interventions as compared to the normal saline which showed minimal change in clinical score. Tetracaine hydrochloride significantly reduced bacteria load (P≤0.0001). It decreased multiple antibiotic-resistant index by 20%.

Conclusion: Tetracaine has a supplemental antibiotic effect on resistant strain of bacteria and does not worsen antibiotic resistance of bacteria. Clinical usage of tetracaine ophthalmic solution should therefore be applied after conjunctival swaps or corneal scrapping have been taken.

Keywords: Antibiotics, Antimicrobial, *Staphylococcus aureus*, Tetracaine hydrochloride.

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Introduction

Some studies have shown that anesthetics possess a supplemental antibiotic effect (Johnson, Saint John, & Dine, 2008). Several topical anesthetic agents have demonstrated distinct antimicrobial activity against specific bacterial strains and Candida (Pelosini, Treffene, & Hollick, 2009). Tetracaine hydrochloride ophthalmic solution is a local anesthetic indicated for processes requiring an ophthalmic anesthetic of fast and brief action. Its usage for diagnostic purposes could promote bacterial resistance to antibiotics since they are used momentarily and not formulated for treatment. The possibility of repurposing older drugs in an attempt to deal with unmet medical needs further reinforces the necessity for such evaluation to inform the decision in this line of thought (Takahashi et al., 2017).

Evidence from research indicates the intrinsic antimicrobial characteristics of local anesthetics against

a broad spectrum of human pathogens (Johnson et al., 2008). At levels typically used in the clinical environment, multiple local anesthetics inhibit the development of numerous bacteria and fungi under different circumstances. Early research noted that Tetracaine exerts its bactericidal effect on the bacterial cell by a mechanism of action. The writers discovered that tetracaine harmed *Pseudomonas aeruginosa* cell membrane through lysis, intracellular leakage, dehydrogenase activity, and enhanced permeability of the cell wall and greater temperature correlates with a rise in the inhibition of microbial development. Observation of cell lysis, intracellular leakage, dehydrogenase activity, and greater sensitivity of spheroplasts to Tetracaine than whole cells led to the conclusion that Tetracaine works by damaging the cell membrane(Leung & Rawal, 1977). This study aimed to investigate the antibiotic effect of Tetracaine hydrochloride on a resistant strain of bacteria to ascertain its contribution to the increasing spate of resistance to conventional antibiotics.

Materials and Methods

Drugs and Chemical Used: Tetracaine hydrochloride (Archdiosesan Health Pharmacy, Kumasi, Ghana) was used as an anesthetic and positive control drug was Ciprofloxacin eye drop (Ciron Drugs Ltd., India). Normal saline drops (MSB Pharma., India) was also used as a negative control drug in the study. Ketamine hydrochloride (Pfizer, USA) was used to anesthetize the rabbits before the induction of conjunctivitis.

Animal husbandry: A total of 15 New Zealand White rabbits of either sex weighing between 1.4kg-2.7kg were purchased from the School of Agriculture Rabbitry, University of Cape Coast and kept at the Animal House of the School of Biological Sciences of the University of Cape Coast, Ghana. The animals were housed singly in aluminum cages (34×47 ×18 -cm3) with softwood shavings as bedding, under ambient laboratory conditions (28 ± 2°C, relative humidity 60%-70%, and a normal light-dark cycle) and fed with normal commercial pellet diet (AGRICARE, Kumasi) and water ad libitum.

Culture and isolation of bacteria: Swabs from clinically diagnosed cases of Ophthalmia Neonatorum were cultured, isolated and identified in the microbiology laboratory using standard microbiological procedures in a previous study(Kang & Lee, 1989). The susceptibility to various antibiotics was assessed using an antibiotic disc (Abtek Biologicals. Liverpool, UK). Multiple antibiotic-resistant strains of *Staphylococcus aureus* (*S. aureus*) as determined in a previous study (Kang & Lee, 1989) were picked from the pure culture with a sterile standard loop was inoculated into 10 ml of nutrient broth. The isolated multiple resistant S. aureus was then incubated for 24 hours at 37°C.

Induction of infectious conjunctivitis: The method as described by Al-Waili (Al-Waili, 2004) and adopted by Ilechie (Ilechie, Kwapong, Mate-Kole, Kyei, & Darko-Takyi, 2012) was used. Each rabbit was anesthetized by an intramuscular injection of 10mg/kg Ketamine hydrochloride and a drop of 0.5% topical Tetracaine hydrochloride ophthalmic solution was instilled into the conjunctival cul-de-sac of the right eye of each animal. An abrasion was then made on the right bulbar conjunctiva of each rabbit. A 10uL of the bacterial suspension of multiple resistant *S. aureus* was inoculated into the abraded bulbar conjunctivae of the rabbits.

Experimental design: Rabbits were pre-examined for clinical signs of infectious conjunctivitis and those with no signs of conjunctivitis were selected and inoculated with the bacterial inoculum. Forty-eight hours after inoculation the rabbits that showed clinical signs of infectious conjunctivitis were selected and randomized for treatment (n=5). Swabs were taken to confirm positive cultures in the right eye of the animals before randomization.

They were randomized for treatment with 0.5% Tetracaine hydrochloride, 0.3% w/v of Ciprofloxacin (because it was the antibiotic that the strains were susceptible) and 0.9 w/v of Normal saline drop. All treatments were given twice daily (12 hourly intervals) for 14 days.

The right eyes of the animals were assessed for clinical signs of bacterial conjunctivitis using a handheld slit lamp every other day alongside swabbing for days of positive culture over the experimental period. The signs were scored and scale of 0-3 except for sensitivity to light. The scoring was as shown in **Table 1**.

The maximum possible score was 21. The swabs were used to assess for Bacteria Colony Count (BCC) and Antimicrobial Sensitivity Testing (AST). Plate count agar (PCA) was used for Bacteria Count Colony. The specimen swab was snapped off the swab shaft at the score line and cut shaft to fit into a test tube containing 9ml of sterilized freshly prepared peptone water. It was incubated at 37°C for 10h. Using a sterilized pipette, the culture was transferred into a sterilized tube containing 10ml of sterilized freshly prepared peptone water. Using a serial dilution method, 1ml of the aliquot was transferred into the sterilized tubes until least 10 x 5 dilution factor was reached. 1000µL of the serially diluted aliquot was transferred into an autoclaved media plate. Employing pour plate method, about 20ml of freshly prepared autoclaved media was then poured into the plates, swirled gently in both clockwise and anti-clockwise directions and allowed to solidify. The solidified plates were labelled and incubated (Panasonic MIR-154-PE Cooled incubator) at 37 ^{O}C for 24 hours. Samples in VRBA were allowed a maximum incubation time of 1 week. Two different dilution factors for each sample was used and the mean found. After incubation, single viable colonies were counted and recorded in CFU/ml, using the formula; CFU/mL= CFU x dilution factor x 1/aliquot.

Modified Kirby-Bauer disc diffusion was employed. 8ml of normal saline was inoculated with portions of at least 3 pure colonies with similar appearance using a hot-flamed sterilized straight wire. The turbidity of the suspension was then compared with 0.5 McFarland turbidity standard (1.5x108CFU/ml) and adjusted by either the addition of more colonies or normal saline. Freshly prepared Mueller Hinton (MH) agar in sterilized media plates were streaked with a sterilized swab stick soaked with the inoculums in

Table 1: Clinical and visual scoring of some features associated with bacterial conjunctivitis

Clinical features	0	1 (mild)	2 (moderate)	3 (severe)
Redness	Clear	Redness size of <2mm	Redness size of 2-5mm	Redness of >5mm
Discharge	None	Mild discharge	Moderate discharge	Severe discharge
Crusty eyelids	None	Mild crusty eyelids	Moderate crusty eyelids	Severe crusty eyelids
Wet eye	None	Mild wet eye	Moderate wet eye	Severe wet eyes
Edema	No edema present in the conjunctiva	Slight edema/general or localized conjunctival edema	General diffuse edema of the conjunctiva	Frank edema of chemosis of conjunctiva
Photophobia	No photophobia	slight difficulty with light causing occasional eye	Moderate difficulty with light requiring regular blinking	Severe difficulty with light cannot bear natural light
Blepharospasm	No spasm	Mild spasm at stimulation only	Visible spasm without impairment of daily life	Visible spasm with impairment of daily life
Photophobia	No photophobia	slight difficulty with light causing occasional eye	Moderate difficulty with light requiring regular blinking	Severe difficulty with light cannot bear natural light
Blepharospasm	No spasm	Mild spasm at stimulation only	Visible spasm without impairment of daily life	Visible spasm with impairment of daily life

the normal saline suspension. The whole surfaces of the media were streaked three (3) times at an angle 60^{O}. The plates were rotated each time, and allowed to air dry. Sterilized hot-flame forceps were used to place the gram appropriate antimicrobial-impregnated disk (Axiom) on the agar, and each disc was pressed gently to ensure complete contact with the surface of the agar. The plates were then incubated at 37 ^{O}C for 24 hours. After 24 hours, the diameters of inhibition zones were measured using a rule and recorded in millimeters (mm). Antimicrobial sensitivity pattern was determined as susceptible (S), intermediate (I) or resistant (R), with reference to AST interpretation chart.

Statistical analysis: Data obtained for control, test and reference drug effects were analyzed by one-way analysis of variance followed by Tukey's multiple comparisons test using GraphPad Prism (version 5.03; GraphPad, La Jolla, CA, USA). Values were expressed as the mean ±standard error of the mean. P≤0.05 was considered to be statistically significant.

Results

After 48 hours of inoculation of S. aureus, there were obvious signs of bacterial conjunctivitis in all treatment groups. The rabbits treated with normal saline showed significantly higher clinical signs of bacterial conjunctivitis as compared to the 0.3% Ciprofloxacin and Tetracaine hydrochloride treatment groups **(Table 2)**.

There was a significant reduction in redness, discharge, crusty eyelids and conjunctiva edema relative to the control; seen as significant decrements (P≤0.001-0.004) in clinical scores of bacteria conjunctivitis (Table 2, Figure 1). However, tetracaine significantly reduced clinical signs (P=0.012) compared to normal saline (control) and 0.3% Ciprofloxacin reduced clinical signs (P =0.003) compared to normal saline (control). This means there was a significant decrease in clinical scores with the interventions as compared to the normal saline which showed minimal change in clinical score **(Figure 1, Table 2)**.

Table 2: The effect of Normal saline (control), Ciprofloxacin and Tetracaine on clinical scores per treatment schedule

Day	Clinical Scores		
	Normal Saline	Ciprofloxacin	Tetracaine
1	13.00±2.12	10.8±0.530	11.4±2.088
3	9.200±2.332	4.4±1.030	6.8±0.860
5	8.400±0.812	5.4±0.40	7.8±0.735
7	8.400±0.510	4.8±0.374*	3.8±0.735*
9	7.600±0.872	4.8±0.374	3.8±0.490*
11	8.600±0.927	3.8±0.735***	4.8±0.970
13	8.400±0.600	4.6±0.675**	3.6±0.400***
15	6.800±0.860*	4.2±0.490***	2.8±0.490***

Significant clinical score on treatment days established using a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. * P≤0.05;**P≤0.01, P≤0.001.

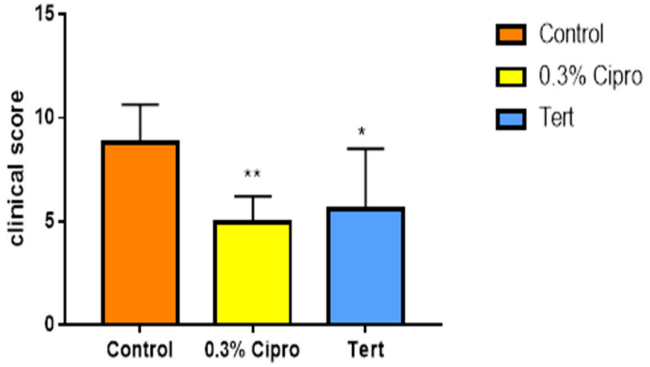

Figure 1: The effect of normal saline (control), 0.3% ciprofloxacin and tetracaine on clinical scores. Significant clinical score per treatment established using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. * P=0.012, **P=0.003.

Bacteria colony count: There was a significant decrease (P=0.002) in the bacteria colony count of rabbits treated with the Ciprofloxacin as compared to the control group (treated with normal saline) **(Figure 2)**. Tetracaine hydrochloride exhibited a significant (P=0.004) antibiotic effect on the multiple antibiotic-resistant S. aureus **(Table 3)**.

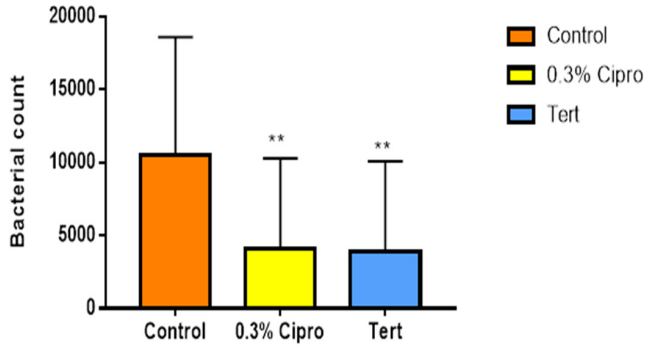

Figure 2: The effect of Normal saline (control), 0.3% Ciprofloxacin and Tetracaine on bacteria count after treatment. Significant reductions in bacteria count per treatment established using a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. **implies P≤0.002-0.004.

Table 3: The effect of Normal saline (control), 0.3% Ciprofloxacin and Tetracaine on bacteria count per treatment schedule.

Day	Bacteria Count		
	Normal Saline	Ciprofloxacin	Tetracaine
1	22348±8749.50	19074.0±6279.15	18945.80±4411.30
3	23632±11391.15	4532.00±1441.023	3262.80±484.85
5	10406±3989.39	2766.00±688.56*	2718.00±199.16*
7	8944±3542.020	2542.20±694.61*	2177.00±302.29*
9	6694±29739.86	1415.00±950.65*	2087.20±387.39*
11	4828±100.10	1058.60±824.00*	1276.40±379.13*
13	4208±900.80	920.00±676.246*	617.40±283.05*
15	3168±463.41	337.80±173.10**	375.60±153.93**
Significant reductions in bacteria count per treatment days established using a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. *P=0.002; **P=0.004			

Multiple antibiotic resistant index: The antibiotic susceptibility test did not show any significant multiple antibiotic-resistant in bacteria isolates treated with Tetracaine hydrochloride and normal saline (control). However, there was a significant increase in multiple antibiotic-resistance in isolates treated with Ciprofloxacin **(Figure3; Table 4)**.

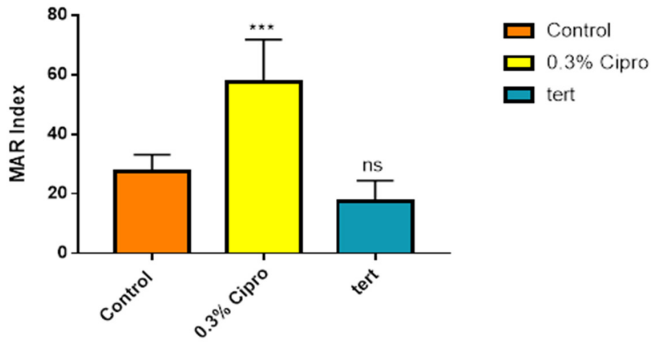

Figure 3: The MAR Indexes for all treatment groups. Significant reduction in MAR Index of treatment groups established using a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. **implies P≤0.01.

Table 4: The MAR Indexes for Normal saline, Ciprofloxacin, and Tetracaine treatment groups

Day	MAR Index values (%)		
	Normal Saline	Ciprofloxacin	Tetracaine
1	25	62.5	12.5
3	37.5	50	25
5	25	62.5	25
7	25	37.5	12.5
9	25	75	12.5
Average	27.500±2.500	57.500±6.374 **	17.500±3.062
One-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. **implies P≤0.01. MAR, Multiple antibiotic resistance define MAR here			

Discussion

Bacterial conjunctivitis can be contracted directly from infected individuals or can result from abnormal proliferation of the native conjunctival flora (Azari & Barney, 2013). Contaminated fingers (Høvding, 2008), oculogenital spread (Varu et al., 2019) and contaminated fomites (Sattar, Dimock, Ansari, & Springthorpe, 1988) are common routes of transmission. Besides, certain conditions such as compromised tear production, disruption of the natural epithelial barrier, abnormality of adnexal structures, trauma, and immune-suppressed status predispose individuals to bacterial conjunctivitis (Varu et al., 2019). The most common pathogens for bacterial conjunctivitis in adults are Staphylococcal species, followed by *Streptococcus pneumoniae* and *Haemophilus Influenza* (Fishovitz, Hermoso, Chang, & Mobashery, n.d.). In children, the disease is often caused by Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis (Fishovitz et al., n.d.). The course of the disease usually lasts 7 to 10 days the reason for the decline in the clinical scores of conjunctivitis in the rabbits in the control group (Boadi-Kusi et al., 2021). Signs and symptoms include red eye, purulent or mucopurulent discharge, and chemosis (Fishovitz et al., n.d.). The period of incubation and communicability is estimated to be 1 to 7 days and 2 to 7 days, respectively (Leung & Rawal, 1977). Bilateral mattering of the eyelids and adherence of the eyelids, lack of itching, and no history of conjunctivitis were strong positive predictors of bacterial conjunctivitis (Sharma, 2011). This study aimed to investigate the antibiotic effect of Tetracaine hydrochloride on a resistant strain of bacteria to ascertain its contribution to the increasing spate of resistance to conventional antibiotics.

In this study resistant strain of Staphylococcus aureus was the causative agent of bacterial conjunctivitis. There was a significant reduction in clinical signs of bacterial conjunctivitis in the rabbits that were treated with Tetracaine hydrochloride ophthalmic solution. An earlier study (Reynolds, Greenwood-Quaintance, Patel, & Pulido, 2016) reported on the mechanism of action by which Tetracaine damaged the cell wall of bacteria through lysis, leakage of intracellular components, dehydrogenase activity and increased cell wall permeability.

A study on the effects of topical anesthetics on bacteria using a disk diffusion technique studied proparacaine and tetracaine at 0.5, 0.25, and 0.125% concentrations

found that tetracaine inhibited S. aureus growth at 5000 µg/mL and Pseudomonas aeruginosa at 2500 to 5000 µg/mL (Chiang, Penadés, & Chen, 2019). Also, a study using broth microdilution demonstrated that tetracaine inhibited strains of S. epidermidis at a concentration of 625µg/mL (Mullin & Rubinfeld, 1997). Tetracaine has demonstrated its antibiotic effects against coagulase-negative staphylococci and S. aureus (Johnson et al., 2008).

In the present study, bacterial colonies were counted from bacterial-induced conjunctivitis in rabbit eye treated with tetracaine and there was a significant reduction in bacteria count. This particular solution contained 0.5% Tetracaine hydrochloride as an active ingredient, a preservative which is Chlorobutanol and Boric Acid, Edetate Disodium, Potassium Chloride as inactive ingredients.

Bacteria may have innate resistance or acquired resistance to antimicrobial agents. This involves; mutations in cell genes (chromosomal mutation) leading to resistance, transformational gene transfer from one microorganism to another, conjugation which needs independent genetic elements including transposons (Tns) and plasmids and also transduction which involves independently replicating bacterial viruses, known as bacteriophages (Kaewjiaranai, Srisatjaluk, Sakdajeyont, Pairuchvej, & Wongsirichat, 2018). The current class of antimicrobial agents targets certain major bacterial processes such as metabolic pathways, cell wall, functions of the cell membrane, protein and nucleic acid synthesis (Rietveld, van Weert, ter Riet, & Bindels, 2003). After the bacteria have gained resistance genes against various antimicrobial agents, the bacteria can, therefore, use several biochemical types of resistance mechanisms including drug inactivation or enzymatic degradation involving enzymes that destroy the antibiotic. These enzymes include B-lactamases that cleave the amide bond in the B-lactam ring (Loka, Sumadja, & Resmi, 2017). Another mechanism is by extrusion of the antibiotic before it reaches the target by the efflux pump. This mechanism extrudes the antibiotic before it reaches the bacteria target-site (Kaewjiaranai et al., 2018). Target modification occurs by an altered bacteria cell wall which modifies the target region. An example is MRSA which involves a modified Penicillin Binding Protein (PBP2a) that confers methicillin resistance to certain S. aureus strains (Loka et al., 2017).

In this study, the antibiotic susceptibility test on bacteria isolates treated with 0.3% Ciprofloxacin showed multiple antibiotic-resistant which was not the case before treatment was commenced. There was no increase in multiple antibiotics resistant in groups treated with Tetracaine hydrochloride and normal saline. A study by Sharma (Sharma, 2011), among 2408 eyes in South Florida revealed an increase resistance of gram-positive by 2-fold and 3-fold to erythromycin and ciprofloxacin respectively. The primary disadvantage associated with treatment with an antibiotic is the probable future resistance. The findings of this study support the assertion that there exists a link between the consumption of antibiotics and subsequent resistance (Leibovici et al., 2001). This was not the case Tetracaine hydrochloride treatment given credence to the fact that the short to medium term diagnostic does not contribute to the growing spate of antibiotic resistance. The limitation to this study was that there were no genetic studies to confirm this finding.

Conclusion

Despite Tetracaine possessing supplemental antibiotic effect as a diagnostic agent, it has no consequential effect on the development of antibiotic-resistant strains of bacteria. It is recommended that further studies involving molecular methods be adopted to confirm this finding.

Declarations

Ethical considerations: The study protocol was approved by the University of Cape Coast Institutional Review Board, UCCIRB, Ghana with reference number: UCCIRB/CHAS/2018/57. All activities performed during the studies conformed to the Association for Research in Vision and Ophthalmology Statement for Use of Animals in Ophthalmic and Vision Research. Biosafety guidelines for the protection of personnel in the laboratory were observed.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Authors' contributions: Author SK conceived the idea, designed the study and wrote the protocol. SBB-K managed the analyses and the interpretation of data. ME-M managed the literature searches, collected data, and wrote the first draft of the manuscript. All authors read, critically revised the content and approved the final manuscript.

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Conflict of Interest: The authors declare no conflict of interest.

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