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COMPARATIVE EVALUATION OF THE ANTIMICROBIAL EFFECT OF N-BUTYL AND ISO-AMYL CYANOACRYLATE TISSUE ADHESIVE

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ABSTARCT

Introduction

Conventional suture materials tend to accumulate microorganisms which be the possible cause of surgical wound infection. This led to the use of tissue adhesives like cyanoacrylate. The aim of this study is to assess if iso-amyl cyanoacrylate tissue adhesive had an inherent antimicrobial effect.

Material and Methods

Pure cultures *Staphylococcus Aureus*, *Lactobacillus*, *Pseudomonas Aeruginosa* and *Candida Albicans* were seeded on agar plates with different volumes of iso-amyl cyanoacrylate or n-butyl cyanoacrylate were prepared. Ampicillin and amphotericin B were used as positive controls. The plates were incubated overnight at 37 °C and the zone of inhibition was measured.

Results

Cyanoacrylate exhibited an inhibitory activity against the gram positive organisms and candida but did not show any effect on the gram negative organism. The n-butyl cyanoacrylates exhibited stronger antimicrobial properties when compared to iso-amyl cyanoacrylate

Keywords: Cyanoacrylate, tissue adhesive, antimicrobial, antibacterial

INTRODUCTION

Surgical wound infection is one of the most common complications of any surgery **[1]**. The cause of wound infection could be due to patient related as well surgical technique related **[2]**. Patient-related factors are: diabetes, cigarette smoking, use of systemic steroid, obesity, extremes of age and poor nutritional status. Surgical technique related factors are: improper skin asepsis, prolonged surgical time, inadequate and/or improper sterilization of operating theatre environment and surgical instruments **[3]**.

Suturing is an integral part of any surgical procedure. Multiple techniques and different material are available, the choice of which is made based on the type of procedure performed. When using conventional sutures, the materials requires for the passage of the suture thread, a foreign material, through the tissue, which evokes an inflammatory response. Wicking is a phenomenon associated with silk suture material and other multifilament suture materials. The multifilamentous nature of these materials makes the surgical site retentive to bacteria and allows for the entrance of bacteria into the tissues, acting as a reservoir for secondary infection **[4]**. The pathogen most commonly associated with the surgical site infections *is Staphylococcus aureus*. The other implicated organisms are: Enterobacteriaceae (18.8%), Enterococcus spp. (8.0%), *Pseudomonas aeruginosa, Pseudomonas spp., Streptococcus spp., Acinetobacter spp*., other anaerobic bacteria and fungi like *candida* **[5, 6]**.

In order to overcome these limitations alternatives to suture material were introduced, tissue adhesive is one such alternative. An ideal tissue adhesive has the following pre-requisites: high binding strength, ease of application, tissue biocompatibility, biodegradability and cost effectivity. Cyanoacrylates demonstrate most of these properties, giving them an leverage over the conventional suture materials.

Coover *et al* first synthesized cyanoacrylate in 1959. The chemical structure of cyanoacrylate is H 2C = C (CN) COOR, where R- is any alkyl group ranging from methyl to decyl **[7]**. Due to cytotoxicity the lower homologs were discontinued for medical use, however, higher homologs, were considered safe **[8, 9]**. Cyanoacrylate preparations have been used for more than five decades in surgical practice. Their application is a diverse, the surgical specialties utilizing cyanoacrylate tissue adhesives are ophthalmic, orthopedic, gastrointestinal, microvascular to plastic surgeries **[10]**.

Cyanoacrylates consist of liquid monomers that polymerize on contact with wound moisture to form a solid bond. These solidified adhesives unite and hold the incised tissues stably, avoiding penetration of foreign bodies, thus promoting wound healing and vascularization **[11, 12]**. The use of 2-octyl cyanoacrylate tissue adhesive is a commonplace in plastic and cardiac surgery; investigations prove that it was associated with a decrease in rates of post-surgical infection **[13]**. Another advantage of cyanoacrylate tissue adhesive is that might act as a physical barrier restricting the ingress of micro-organisms into the tissues **[14]**. The aim of this invitro study was to compare the antimicrobial activity iso-amyl cyanoacrylate and n-butyl cyanoacrylate tissue adhesive. The organisms used were the ones that were commonly associated with wound infections.

MATERIAL AND METHODS

A supply of cotton wool swabs on wooden applicator sticks was prepared. They were sterilized in tins, culture tubes, or on paper, either in the autoclave or by dry heat. The Assay was performed by agar disc diffusion method. 5 plates each with different concentration (50, 75 and 100µL) of unpolymerized n-butyl cyanoacrylate ((Ruseal® 0.25 ml) or iso-amyl cyanoacrylate (Amcrylate® 0.25 ml) were used.

For Bacteria: Muller Hinton Agar (MHA) medium is poured in to the petriplate. After the medium was solidified, the inoculums were spread on the MHA plates with sterile swab moistened with the bacterial suspension. Sterile sample containing discs and 20µl of standard antibiotic (Ampicillin) disc were placed in MHA plate. The plates were incubated at 37ºC for 24 hrs. The antimicrobial activity was determined by measuring the diameter of zone of inhibition.

For Fungi: Sabouraud Dextrose Agar (SDA) medium is poured in to the petriplate. After the medium was solidified, the inoculums were spread on the SDA plates with sterile swab moistened with the bacterial suspension. Sterile sample containing discs and 20µl of standard antibiotic (Amphotericin B) disc were placed in SDA plates. The plates were incubated at 37ºC for 24 hrs.

After the completion of the incubation period, the agar plates were observed carefully to rule out any form of contamination by organisms other than the species which were standardized and inoculated for the purpose of the study. These plates were then analysed to observe the bacterial inhibitory halos or zone of inhibition (if any). These bacterial inhibitory halos or zone of inhibition were then measured in millimeters and compared with the positive control.

Microorganism Used in this Study:

Bacteria: *Staphylococcus aureus; Pseudomonas aeruginosa; Lactobacillus sp.*

Fungi: *Candida albicans*

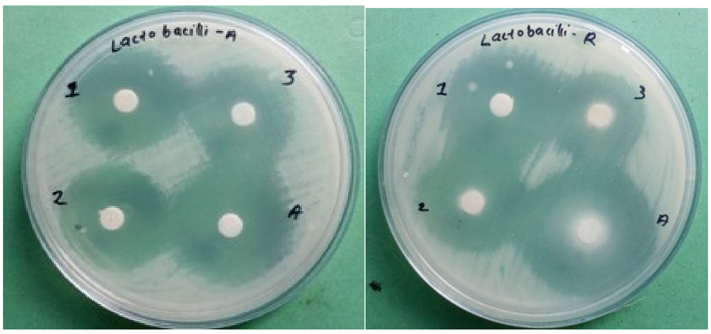
RESULTS

Table 1 shows the measure of the mean zone of inhibition in millimeters for isoamyl cyanoacrylate and n-butyl cyanoacrylate at different concentrations for different microorganisms after an incubation period of 24 hours. The gram positive aerobic organisms namely: *Staphylococcus aureus* and *lactobacilli* a positive zone of inhibition for both cyanoacrylate adhesives **(Figure 1)**. For all the three microorganisms n-butyl cyanoacrylate showed a larger zone of inhibition (p< 0.05) when compared to isoamyl cyanoacrylate, however the largest zone of inhibition was expressed by the control group. Both the cyanoacrylates were ineffective against *Pseudomonas aeruginosa.*

Table 1: mean zone of inhibition for isoamyl cyanoacrylate (A) and n-butyl cyanoacrylate (B) in millimeters

Concentration (µg/ml)	50		75		100		Antibiotic
Organism	**A**	**B**	**A**	**B**	**A**	**B**	
Staphylococcus aureus	8.6 ± 0.4	14.6 ± 0.4	10 ± 0.6	15.6 ± 0.4	11.8 ± 0.4	16.6 ± 0.4	18
P value	0.001*		0.001*		0.001*		
Lactobacillus sp	9.6 ± 0.4	9.8 ± 0,4	11 ± 0.6	11 ± 0.6	15.8 ± 0.4	11.8 ± 0.4	19
P value	0.452		1.000		0.001*		
Candida. albicans	8.8 ± 0.4	9.8 ± 0.4	9.7 ± 0.4	11.8 ± 0.6	14.5 ± 0.5	19.4 ± 0.5	22
P value	0.004*		0.001*		0.001*		

*** = p < 0.05**



A **B**

Figure 1: zone of inhibition for isoamyl cyanoacrylate (A) and n-butyl cyanoacrylate (B) for *lactobacillus*

DISCUSSION

Post-surgical wound closure is usually performed with the intention of wound approximation by primary intension. The different materials to achieve wound closure are suture materials, tissue adhesives and surgical staples. The tissue adhesives commonly employed in surgical practice include cyanoacrylate tissue adhesives with varying chain lengths such as methyl, butyl, amyl up to octyl. Fibrin based tissue adhesives is another innovative advancement in the field of surgery. Clinical studies have proven that there are fewer wound infections associated with cyanoacrylate tissue adhesives **[14]**. In a previous study done by us we proved that isoamyl cyanoacrylate had an inherent antimicrobial effect **[15]**.

The organism used the study i.e. *Staphylococcus aureus; E. coli; Lactobacillus sp.*and *Candida albicans* are the organisms that are commonly associated with nosocomial infections **[16-18]**. This study show that both iso-amyl cyanoacrylate and n-butyl cyanoacrylate have an inherent inhibitory effect on aerobic, gram positive organisms namely: *Staphylococcus aureus* and *Lactobacillus* and on fungi *Candida albicans,* however there was no such effect on *pseudomonas aeruginosa* which is an aerobic, gram negative organism, these results are confluent with those obtained by a similar study **[19]**. We observed that the antimicrobial activity increases with the increase in the volume of adhesive. The cyanoacrylate adhesive as well as ampicillin did not have any inhibitory effect on *Pseudomonas aeruginosa,* a common opportunistic pathogen associated with nosocomial infections, also known for its multi drug resistance **[20]**.

The lack antibacterial effects of cyanoacrylate on gram-negative organisms are possibly because they are protected by an outer capsule **[21-23]**. The possible explanation for the inhibitory effect of the gram positive organisms could be the strong electronegative charge of the cyanoacrylate polymer that could reacts with the positively charged cell wall of gram-positive organisms **[24]**.

Cyanoacrylates are applied to the tissue margins in an unpolymerized form, following which polymerization occurs by anionic or zwitter-ionic interactions with hydroxide or amine groups presented in the body **[25, 26]**. The breakdown products of cyanoacrylate polymer decomposition could also play a role in its antibacterial activity, cyanoacrylate decomposes to form cyanoacetate and formaldehyde which diffused out producing inhibition halos even in a polymerized state **[26, 27]**. As n-butyl cyanoacrylate is of a lower molecular weight then isoamyl cyanoacrylate it decomposes faster, which could be the reason for the greater zone of inhibition for n-butyl cyanoacrylate.

This study compared the inhibitory effect of n-butyl cyanoacrylate to iso-amyl cyanoacrylate. This antibacterial activity could either be bacteriostatic or bactericidal; this aspect was not assessed by this study, which is a limitation of the study. Another limitation of the study is that only the unpolymerized form of the adhesive was tested, the role of heat of polymerization, if any, needs to be assessed. Further tests using both the polymerized as well as the unpolymerized forms of the adhesives need to be tested; this would establish if the polymercaptan reaction has a role to play in the antimicrobial effect.

CONCLUSION

Iso-amyl and n-butyl cyanoacrylate tissue adhesives have an antimicrobial effect on gram positive organisms and fungi commonly associated with surgical wound infections. The n-butyl cyanoacrylates exhibited stronger antimicrobial properties. This when translated to clinical practice could result in lesser postoperative infections. This would be an added benefit these tissue adhesives have over conventional suture materials.

Conflict of interest: None

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