

Short-chain cyanoacrylates and long-chain cyanoacrylates (Dermabond) have different antimicrobial effects

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ABSTRACT

Objective To compare the antimicrobial effect in vitro of a short-chain cyanoacrylate with a long-chain cyanoacrylate (Dermabond, Ethicon, Johnson and Johnson, USA) against bacterial strains.

Methods and analysis The following bacterial strains were analysed: *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. For each microorganism, standardised sterile discs (6 mm) containing 10 µL of ethyl-cyanoacrylate and 2-octyl cyanoacrylate were applied to the plate. All plates received a blank filter-paper disc with no adhesive (control). All plates were incubated for 24 hours, after which the bacterial inhibitory halos, if present, were measured in millimetres in its greater length.

Results Inhibitory halos were observed for both adhesives for *S. aureus*. Inhibition halos were observed only for ethyl-cyanoacrylate for *K. pneumoniae* and *E. coli*. No inhibition halo was observed for *P. aeruginosa* in any sample. The relationship between the total size of the inhibition halos and the diameter of the paper filter for *S. aureus* was statistically significant compared with 2-octyl cyanoacrylate.

Conclusion Data shown conclude that ethyl-cyanoacrylate showed in vitro bacteriostatic activity for *S. aureus*, *E. coli* and *K. pneumoniae*. 2-Octyl cyanoacrylate showed in vitro lower bacteriostatic activity only against *S. aureus* when compared with ethyl-cyanoacrylate. No in vitro bactericidal activity of ethyl-cyanoacrylate or 2-octyl cyanoacrylate was observed.

INTRODUCTION

Cyanoacrylate is a well-known organic adhesive polymer used in the medical area.^{1–7} The cyanoacrylate monomer is synthesised by the condensation of formaldehyde and cyanoacetate molecules resulting in a polymer called polycyanoacrylate. Since this reaction is reversible, it will be degraded, once again forming formaldehyde monomers and cyanoacetate. It is believed that this degradation mechanism is probably responsible for the toxic effect in human tissues. The greater the amount of adhesive used, the greater

Key messages

What is already known about this subject?

- ▶ First generation cyanoacrylate used to seal corneal injuries has already known for higher antimicrobial effect. Antimicrobial effect of the new generation cyanoacrylate is still unknown against microorganism related to eye infections.

What are the new findings?

- ▶ New generation cyanoacrylate (Dermabond) has shown minimal antimicrobial effect when compared to first generation cyanoacrylate.

How might these results change the focus of research or clinical practice?

- ▶ Considering that studies have shown that old generation cyanoacrylate (short-chain) have higher toxicity (induces vascularisation) against human tissue, the results of our study, suggest the application of short-chain cyanoacrylate to be used in cases of infected corneal thinning/perforations located away from the limbus due to its higher antimicrobial activity and toxicity (induces vascularisation). New generation cyanoacrylate is preferred to be used in cases of sterile and/or infected corneal thinning or perforations located near the limbus due to its lower antimicrobial activity and lower toxicity (induces less vascularisation).

the inflammatory response. Short-chain compounds such as ethyl-cyanoacrylate (EC) are more toxic and have faster degradation. Long-chain compounds such as 2-octyl cyanoacrylate (OC) have low toxicity and slow degradation.^{8–12}

Antimicrobial activity of n-butyl-2-cyanoacrylate and EC was already studied against gram-positive and gram-negative microorganisms by several authors.^{13–16} Previous studies performed by our group have shown in vitro antibacterial benefits of cyanoacrylate that varies in a dose-dependent fashion with its volume.¹⁶ These studies can support the fact that cyanoacrylate can successfully help in the wound healing process in cases associated

with infection. As for the OC, its antimicrobial benefits and mechanisms are still unknown. There are reports showing the importance of the degradation process on the antimicrobial effect of OC without analysing the effects of the polymerisation process.^{17,18}

The cyanoacrylate polymerisation process plays an important role on the antimicrobial effect of all cyanoacrylates.¹⁵ The antimicrobial effect of polymerisation with degradation process of OC has never been analysed together as a whole (search protocol source: Pubmed; keywords: octyl-cyanoacrylate, Dermabond, antimicrobial; year: all).

The purpose of this study is to compare the antimicrobial effect in vitro of a shortest chain cyanoacrylate (EC) with a long-chain cyanoacrylate (OC) (Dermabond, Ethicon, Johnson and Johnson, USA) against bacterial strains.

MATERIAL AND METHOD

The study was conducted at the Microbiology Laboratory of the Department of Microbiology of the Serviço de Controle de Infecção Hospitalar of the Medical School of Santa Casa de Misericórdia de São Paulo.

The following bacterial strains from the American Type Culture Collection (ATCC) were analysed: *Staphylococcus aureus* (ATCC25923), *Escherichia coli* (ATCC25922), *Klebsiella pneumoniae* (ATCC13883) and *Pseudomonas aeruginosa* (ATCC27853). They were primarily incubated in a nutrient broth (tryptic soy broth) at 35°C until reaching 0.5 on the McFarland turbidity scale (represents turbidity of bacterial suspension at approximate population of 1.5×10^8 microorganisms per cubic centimetre).¹⁹ The bacteria were then transferred as monolayer cultures to Müller-Hinton media following modified Kirby-Bauer technique^{20,21} according to standards of the National Committee for Clinical Laboratory Standards.

For each organism, 10 standardised sterile filter-paper blank discs measuring 6 mm in diameter containing 10 µL of EC (Superbonder, Loctite, Brazil) were applied to the plate and 10 other discs with 10 µL of OC (Dermabond, Ethicon, Johnson and Johnson, USA) were also applied to the plates. Both adhesives were applied directly onto the filter-paper disc using micropipette and disposable tips (Eppendorf, Hamburg, Germany). All plates received a blank filter-paper disc with no adhesive in the centre (control). All plates were incubated at 35°C±2°C for 24 hours, after which the inhibitory halos, if present, were measured in millimetres in its greater length (figure 1). All standardised tests were duplicated.

OC is presented by the manufacturer in a glass ampoule, surrounded by a plastic ampoule with a sponge applicator, at one end of the vial, which contains a catalyst (benzalkonium chloride). For this study, the vial was carefully withdrawn and OC was manipulated with sterile micropipette.

For statistical analysis, the relationship between inhibition halo and the filter paper was calculated as the ratio of the diameter of the disc (6 mm) and the total size of the inhibition halo (at its greatest length) (figure 1).

In order to evaluate if the bacterial inhibitory halos were the result of actual bactericidal effects, samples from the clear area within the inhibitory halo were collected after 48 hours and re-cultured on new bacterial culture plates. The new plates were then re-incubated at 35°C±2°C and analysed after 48 hours.

All measurements of inhibitory halos were performed by one individual and confirmed by another individual. The results the ratio were statistically analysed with Student's t-test and significance was defined as $p < 0.05$.

RESULTS

Table 1 shows the average and SD of the inhibition halo (mm) representing the antimicrobial activity of EC, OC and control group for the microorganisms studied.

Data show the presence of antimicrobial activity for both adhesives against *S. aureus*. Data also show the presence of antimicrobial activity for EC against *K. pneumoniae* and *E. coli*.

No inhibition halo was observed for *P. aeruginosa* in any samples. No inhibition halo was observed in any control samples.

Table 2 shows the average and SD of the ratio of the disk diameter (6 mm) and the total size of the inhibition halo, when present, of EC, OC and control representing the quantification of antimicrobial activity of the adhesives against microorganisms studied.

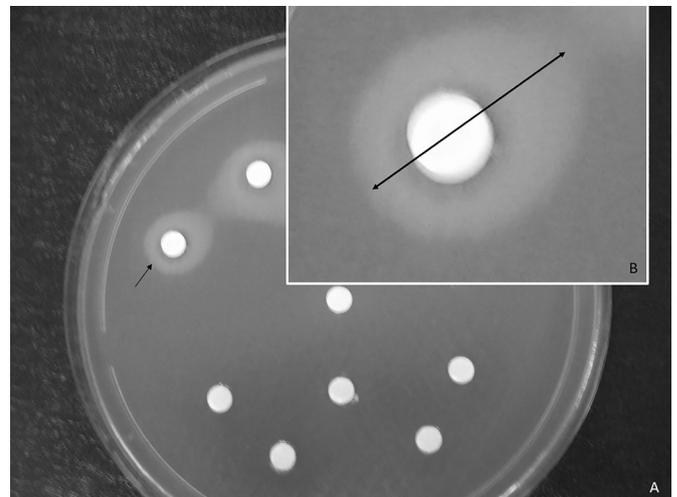


Figure 1 (A) Muller-Hinton media plate showing inhibitory halos around sterile filter paper with cyanoacrylate adhesive 24 hours after application showing white inhibitory halo around the filter paper (black arrow). (B) Measurement of total size of inhibitory halo at its greatest length (black arrow).

Table 1 Average and SD of the inhibition halo and paper filter disc size (6mm) in millimetres, showing the antimicrobial activity of ethyl-cyanoacrylate and 2-octyl cyanoacrylate for different microorganisms

	EC	OC	C	P value
<i>Staphylococcus aureus</i>	18.1±2.55	12.5±1.24	6.00	<0.0001
<i>Pseudomonas aeruginosa</i>	6.00	6.00	6.00	NA
<i>Klebsiella pneumoniae</i>	11.05±0.50	6.00	6.00	NA
<i>Escherichia coli</i>	14.25±0.83	6.00	6.00	NA

C, control; EC, ethyl-cyanoacrylate; OC, 2-octyl-cyanoacrylate.

Our data show that EC has higher antimicrobial activity against *S. aureus* ($p<0.0001$) when compared with OC. EC also showed higher and important antimicrobial activity against *K. pneumoniae* ($p<0.0001$) and *E. coli* ($p<0.0001$) when compared with OC.

No microorganisms were observed on the re-cultured plates of samples collected from the clear area within the inhibitory halo, showing no bactericidal activity.

DISCUSSION

The present study shows that bacteriostatic activity of EC is statistically higher than OC for some microorganisms. This fact reinforces the hypothesis that adhesive toxicity may be directly proportional to its antimicrobial activity; however, different degradation rates of EC and OC may possibly be another factor to influence in the sizes of inhibition halo.

Previous studies, using EC directly to the bacterial strain, have reported bacteriostatic and bactericidal activity against some microorganisms.¹³ Our study has also showed bacteriostatic activity of EC against *S. aureus* and *E. coli*, supporting these reports. However, no bactericidal activity was observed in our study.^{15 16} Direct contact of EC to the bacterial plates, in previous studies, might explain higher bactericidal activity than using discs. We also believe that the EC is not potent enough to cause any structural damage to destroy bacteria.

It is known that cyanoacrylates easily connect to free amine groups and hydroxyl groups found in the cell wall of gram-positive microorganisms. This would explain the bacteriostatic activity exerted by the adhesive against such bacteria. Structural differences of the outer capsule of *E. coli* can explain its heterogeneous

behaviour in relation to other gram-negative bacteria; however, other studies must be performed to clarify such fact.^{22 23}

Our data observed that none of the adhesives studied showed antimicrobial activity against *P. aeruginosa*, confirming previous reports analysing EC.^{13 15 16} Since long-chain compounds such as OC have shown in other studies, lower toxicity and slower degradation, it is expected that OC has the same or lower antimicrobial activity than EC. EC antimicrobial activity also supports previous data shown by our group.^{13 15 16}

Considering the results of our study, EC is preferred to be used in cases of infected corneal thinning or perforations located away from the limbus due to its higher antimicrobial activity and toxicity (can induce vascularisation).^{13 15 16 24 25} And OC is preferred to be used in cases of sterile and/or infected corneal thinning or perforations located near the limbus due to its lower antimicrobial activity and lower toxicity (induces less vascularisation). The cyanoacrylate's toxicity may be related to the cyanoacrylate's degradation products as the adhesive polymerisation process, which varies with the type of cyanoacrylate.¹⁵ The potential of all different cyanoacrylates against bacteria interacting with corneal epithelial cells in vitro may clarify the best indication for each human eye diseases.

Data shown in this study conclude that EC showed in vitro bacteriostatic activity for *S. aureus* (ATCC25923), *E. coli* (ATCC25922) and *K. pneumoniae* (ATCC13883). OC showed in vitro lower bacteriostatic activity only against *S. aureus* (ATCC25923) when compared with EC. No in vitro bactericidal activity of EC or OC was observed.

Table 2 Average and SD of the ratio of the diameter of the disc (6mm) and the inhibition halo, when present, of EC, OC and control

	EC	OC	C	P value
<i>Staphylococcus aureus</i>	3.02±0.43	2.08±0.21	1.00	<0.0001
<i>Pseudomonas aeruginosa</i>	1.00	1.00	1.00	NA
<i>Klebsiella pneumoniae</i>	1.84±0.08	1.00	1.00	<0.0001
<i>Escherichia coli</i>	2.38±0.14	1.00	1.00	NA

C, control; EC, ethyl-cyanoacrylate; OC, 2-octyl-cyanoacrylate.

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