The *in vitro* antimicrobial activity of silicone oils used in ophthalmic surgery

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Background. The aim of the study was *in vitro* assessment and comparison of the antimicrobial activity of three types of silicone oils used in ophthalmic surgery.
Methods. The silicone oils (Arciolane 1300 centistokes, Arciolane 5500 centistokes and Oxane Hd, heavy silicone oil) were inoculated with microbes common in endophthalmitis and their growth was observed continuously. Control tests of microbial growth were performed on silicone oil-free media, i.e. saline and standard enrichment media. In both tested oils and control media, the microbes were cultured aerobically for 21 days, bacteria at 37 °C and yeasts and fungi at 30 °C. Prior to and during incubation at given intervals (days 0, 2, 4, 7, 9, 11, 14, 16, 18 and 21), 10 µl samples were taken from all test tubes. These were diluted in saline in a series of test tubes, with the minimum concentration reaching 10^{-8}. From each dilution, 25 µl were inoculated onto agar media. After 24 h of aerobic incubation at 37 °C (bacteria) and 48 h at 30 °C (yeasts and fungi), the grown colonies were counted and the numbers of colony-forming units in 1 ml (CFU/ml) were determined.
Results. *In vitro*, the highest antimicrobial effect was observed for the Oxane Hd silicone oil.
Conclusions. If endophthalmitis is treated by pars plana vitrectomy, the application of Oxane Hd silicone oil into the vitreous cavity at the end of surgery may contribute to the elimination of microorganisms from the intraocular space but clinical trials are needed to assess its safety.

Key words: antimicrobial activity, endophthalmitis, silicone oil

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INTRODUCTION

Silicone oil is used in vitreoretinal surgery for internal tamponade. It is used especially in complex cases of rhegmatogenous retinal detachment if the condition is complicated by proliferative vitreoretinopathy and giant retinal tears[1-3]. In cases where the proliferative vitreoretinopathy and retinal breaks are found in the lower periphery of the retina, the use of heavy silicone oil is also considered[4,5].

It may be indicated too, in patients with proliferative diabetic retinopathy for conditions connected to repeated intravitreal hemorrhage, tractional retinal detachment, traction-rhegmatogenous retinal detachment and tractional retinal detachment with neovascular glaucoma[6,7]. The literature also mentions the antimicrobial activity of silicone oil which may improve the surgical treatment of endophthalmitis[8-10]. At present, a large number of silicone oil variants which differ in viscosity and specific gravity, are available for use in vitreoretinal surgery. These differences may affect their antimicrobial activity and thus the treatment of endophthalmitis which is a very serious condition caused by common pathogens. This study aimed at *in vitro* assessment and comparison of the antimicrobial effects of silicone oils with viscosities of 1,300 centistokes (cSt) and 5,500 cSt and heavy silicone oil.

MATERIAL AND METHODS

The antimicrobial activity was tested for the following types of silicone oils: Arciolane 1300 cSt (Arcadophta, France), Arciolane 5500 cSt (Arcadophta, France) and Oxane® Hd (Bausch & Lomb Inc., Ireland). The oil was inoculated with microbes etiologically most common in endophthalmitis, i.e. *Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Bacillus* sp., *Pseudomonas aeruginosa, Candida albicans* and *Aspergillus fumigatus*. The growth capability of the inoculated agents was then observed continuously. The strains were obtained during routine microbiological analyses from patients at the University Hospital Olomouc. Control tests for microbial growth were performed on silicone oil-free media, i.e. saline and standard enrichment media BHI (HiMedia, India) in the case of bacteria, or GPB (Trios, Czech Republic) in the case of yeasts and fungi. 0.1 ml of 1 McFarland standard microbial suspension was pipetted into 0.9 ml of silicone oil, saline and enrichment medium. In both the tested oils and control media, the microbes were cultured aerobically for 21 days, bacteria at 37 °C and yeasts and fungi at 30 °C. After careful mixing in a vortex, 10 µl samples were taken from all test tubes (with both inoculated oils and control media)

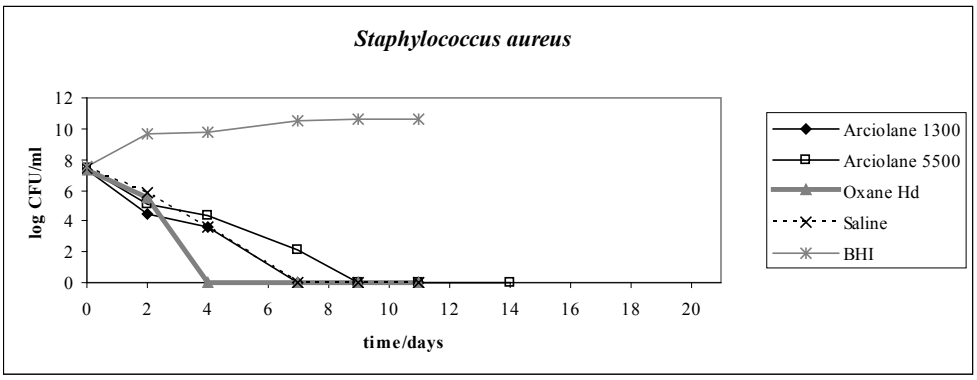

Fig. 1. The effects of silicone oils, saline and BHI on the survival of *Staphylococcus aureus.*

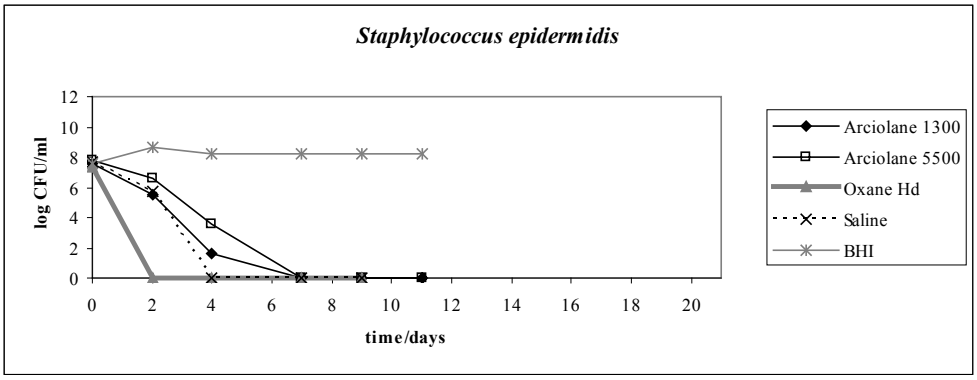

Fig. 2. The effects of silicone oils, saline and BHI on the survival of *Staphylococcus epidermidis.*

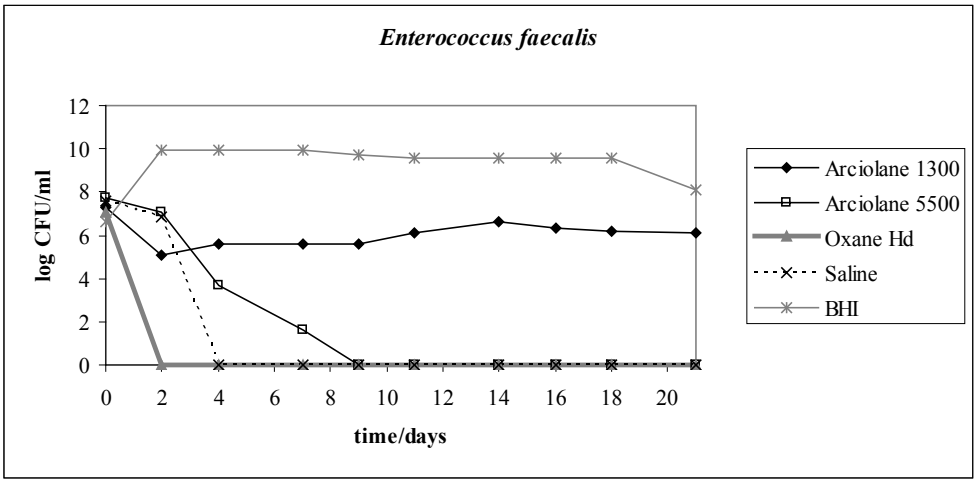

Fig. 3. The effects of silicone oils, saline and BHI on the survival of *Enterococcus faecalis.*

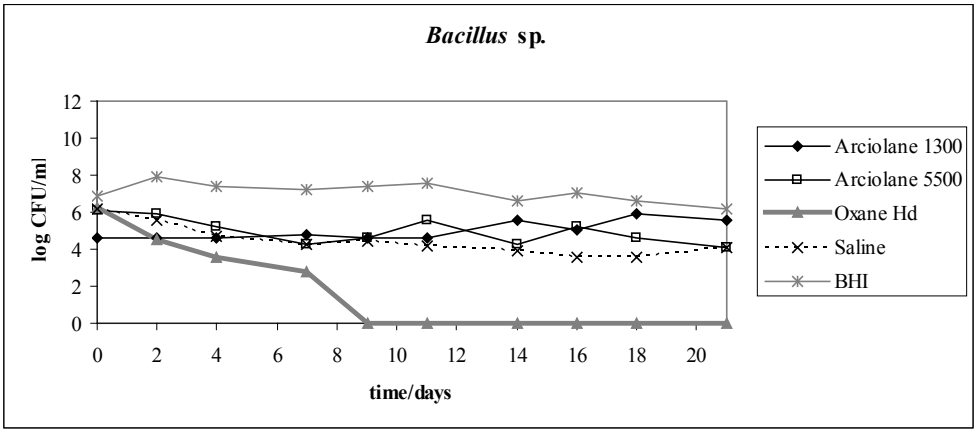

Fig. 4. The effects of silicone oils, saline and BHI on the survival of *Bacillus* sp.

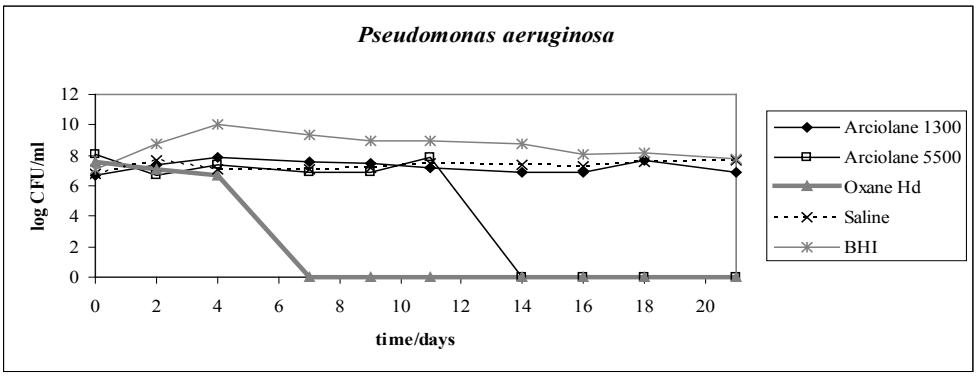

Fig. 5. The effects of silicone oils, saline and BHI on the survival of *Pseudomonas aeruginosa.*

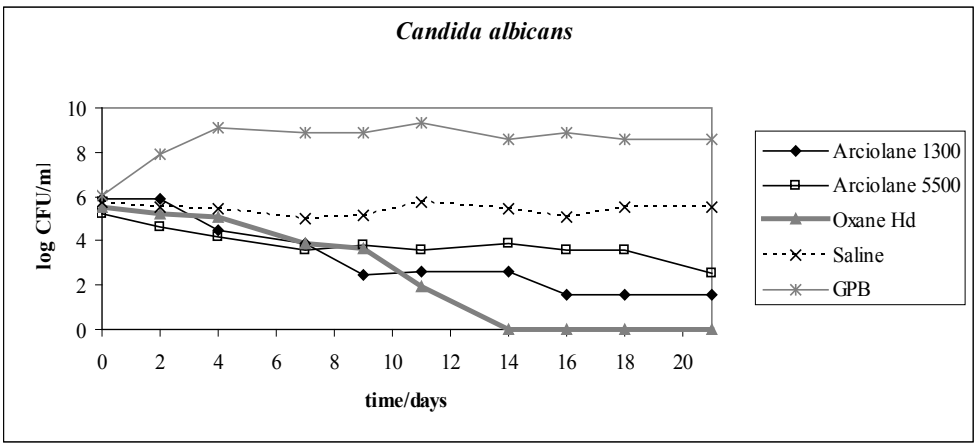

Fig. 6. The effects of silicone oils, saline and GPB on the survival of *Candida albicans.*

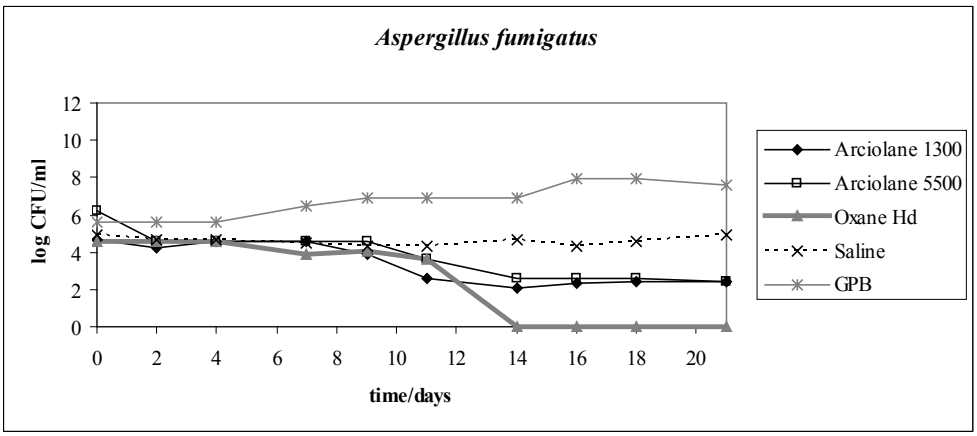

Fig. 7. The effects of silicone oils, saline and GPB on the survival of *Aspergillus fumigates.*

prior to and during incubation at given intervals (days 0, 2, 4, 7, 9, 11, 14, 16, 18 and 21). These were diluted in saline in a series of test tubes, with the minimum concentration reaching 10^{-8}. From each dilution, 25 µl were inoculated onto agar media (Trios, Czech Republic) – Mueller-Hinton (for *S. aureus, S. epidermidis, P. aeruginosa*), blood (*E. faecalis, Bacillus* sp.*)* or glucose-peptone (*C. albicans, A. fumigatus*). After 24 h of aerobic incubation at 37 °C (bacteria) and 48 h at 30 °C (yeasts and fungi), the colonies growing on solid media were counted and the numbers of colony-forming units in 1 ml (CFU/ml) were determined[11].

RESULTS

For *S. aureus*, growth inhibition was detected in the Oxane Hd silicone oil after 4 days, in Arciolane 1300 as well as in saline after 7 days, but in Arciolane 5500 after as many as 9 days. In the BHI enrichment medium, staphylococci were observed to survive for the whole 21 day period of testing (Fig. 1).

S. epidermidis was inhibited by the Oxane Hd oil as early as after 2 days of culture, by saline after 4 days, and by both Arciolane 1300 and Arciolane 5500 after 7 days. For the whole tested period, it was detectable in BHI (Fig. 2).

E. faecalis was not observed in the Oxane Hd silicone oil after 2 days, in saline after 4 days and in Arciolane 5500 after 9 days. Neither Arciolane 1300 nor BHI inhibited the growth capability of the enterococcus (Fig. 3).

The growth of *Bacillus* sp. was inhibited by the Oxane Hd oil after 9 days culture. In Arciolane 1300, Arciolane 5500, saline and BHI, it survived for the whole period of testing (Fig. 4).

The *P. aeruginosa* gram-negative rod was not observed in the Oxane Hd oil after 7 days, and in Arciolane 5500 after as many as 14 days. In the other media, i.e. Arciolane 1300, saline and BHI, it could be detected for the entire 21 day period (Fig. 5).

C. albicans was inhibited by the Oxane Hd silicone oil only after 14 days. It survived till the end of the test in Arciolane 1300, Arciolane 5500, saline and the GPB culture medium (Fig. 6).

Similarly, *A. fumigatus* was only inhibited by the Oxane Hd oil after 14 days incubation. The other tested and control media did not affect its ability to grow (Fig. 7).

In conclusion, the highest antimicrobial effect was observed for the Oxane Hd silicone oil in which the growth of the *S. epidermidis* and *E. faecalis* strains was not seen after only 2 days of culture, *S. aureus* after 4 days, *P. aeruginosa* after 7 days, *Bacillus sp.* after 9 days and *C. albicans* and *A. fumigatus* after 14 days. The remaining oils, Arciolane 1300 and Arciolane 5500, had only weak antibacterial and no antifungal effects. Survival of the individual microbes (in CFU/ml) in the tested types of silicone oil including control media is documented in Table 1. Rates of elimination of the microbes (in days) from the oils and control media are listed in Table 2.

DISCUSSION

Endophthalmitis always represents an extremely serious ophthalmologic finding, with the potential risk of loss of visual function. Patients may be also threatened by loss of the entire eye or even, if the infection penetrates the intracranial space, by death. Most commonly, exogenous endophthalmitis develops after intraocular surgery or penetrating eye injury.

The incidence after cataract surgery is reported to be between 0.07% and 0.58% (ref.[12-15]). Sandvig et al.[16] evaluated 111 cases of postoperative endophthalmitis, of which 80 (72%) were culture-positive. The detected etiologic agents were mostly (in 75 cases) gram-positive bacteria (coagulase-positive and -negative staphylococci, streptococci, enterococci, anaerobic propionibacteria); the rare gram-negative isolates included enterobacteria, *Haemophilus influenzae, Moraxella* sp.; fungal agents were represented by *C. albicans*. Similarly, Ernest et al.[17] described 34 cases of endophthalmitis after cataract surgery, of which 25 (73%) had positive culture findings. The etiology of the infection was almost identical with the list of agents in the former article, plus a representative of the *Bacillus* genus. The results of microbiological examinations documented both in the literature and in common clinical practice suggest that the inflammation is commonly caused by agents naturally present in the microflora of the skin and mucosae, i.e. the eyelids and conjunctiva[14,18-22]. The incidence of posttraumatic endophthalmitis ranges from 3.3% to 17% (ref.[23]). Thus, the likelihood of intraocular infection after penetrating eye injury is approximately 100 fold that after intraocular surgery. Posttraumatic infections are more frequently due to streptococci and gram-negative bacteria; those caused by *Bacillus* sp. strains are generally considered to be among the most serious[13,24].

Endogenous endophthalmitis is intraocular inflammation, with microorganisms entering the intraocular space via the bloodstream as a result of bacteremia. Two to ten percent of all cases of endophthalmitis are estimated to be of endogenous etiology[25,26]. Zhang et al.[27] stated that the most frequent predisposing risk factors were tumor surgery, intravenous administration in a rural setting for minor ailments, liver disease, and oral cavity disease, and that the most common agents causing endophthalmitis were fungi (62%), in particular *C. albicans*. This finding is identical to that of Schiedler et al.[28] who showed that 62% of cases were positive for fungi, and *C. albicans* was found in 33% of all cases. Okada et al.[25], Wong et al.[29] and Jackson et al.[30] stressed the main risk of diabetes contributing to the infection. Chen et al.[31] and Yoon et al[10] reported liver abscess as the most frequent source of endogenous endophthalmitis, with *Klebsiella pneumoniae* as the most common pathogen.

In the treatment of endophthalmitis, intravitreal administration of antibiotics or PPV are often considered. Both the EVS (ref.[13]) and Aaaberg et al.[12] concluded that there were no differences in results achieved by the two approaches. PPV is significantly more effective only in findings with uncertain light projection. Kaynak et al.[9] in their retrospective study compared 24 eyes with postoperative endophthalmitis after cataract surgery that had vitrectomy as an initial procedure according to EVS criteria (core vitrectomy) with 28 eyes with postoperative endophthalmitis after cataract surgery that had total PPV, encircling band, silicone tamponade, and endolaser. They claimed that total PPV with buckling surgery, silicone tamponade and endolaser, increases the chance of surgical success and decreases the number of additional procedures in eyes with severe postoperative endophthalmitis. Yoon et al. reviewed the records of seven patients (10 eyes) with endogenous endophthalmitis who were followed for 6 months or longer. The patients were identified as having *Klebsiella pneumoniaea* endogenous endophthalmitis. In most cases, the inflammation progressed within days and resulted in decreased vision worse than hand motions and a total vitreous abscess, despite systemic and intravitreal antibiotic injections. Yoon et al.[10] observed better results in patients with early PPV with subretinal abscess drainage and silicone oil tamponade.

Ernest et al.[17] recommended PPV for developing endophthalmitis, without previous intravitreal administration of antibiotics. They stated that early PPV prevented toxic damage of the retina and raised hope of maintaining favorable visual acuity of the affected eye. Immediate vitrectomy for endophthalmitis offers several advantages including removal of the infectious organisms and the toxins they produce, clearing of vitreous opacities, collection of abundant material for culture, removal of traction caused by condensed vitreous on the retina, and removal of inflammatory debris and bands over the ciliary body.

Table 1. Number of CFU/ml over time (days).

		Number of CFU/ml over time (days)									
		0	2	4	7	9	11	14	16	18	21
Arciolane 1300	S. aureus	$2.2x10^7$	$3.2x10^4$	$4x10^3$	0	0	0	0	0	0	0
	S. epidermidis	$3.2x10^7$	$3.2x10^5$	$4x10^1$	0	0	0	0	0	0	0
	E. faecalis	$2x10^7$	$1.2x10^5$	$4x10^5$	$4x10^5$	$4x10^5$	$1.2x10^6$	$4x10^6$	$2x10^6$	$1.5x10^6$	$1.2x10^6$
	***Bacillus* sp.**	$4x10^4$	$4x10^4$	$4x10^4$	$5.6x10^4$	$4x10^4$	$4x10^4$	$4x10^5$	$1.2x10^5$	$8x10^5$	$4x10^5$
	P. aeruginosa	$4.8x10^6$	$2.4x10^7$	$8x10^7$	$4x10^7$	$2.8x10^7$	$1.6x10^7$	$8x10^6$	$8x10^6$	$5.2x10^7$	$8x10^6$
	C. albicans	$8x10^5$	$8x10^5$	$3.2x10^4$	$8x10^3$	$2.8x10^2$	$4x10^2$	$4x10^1$	$4x10^1$	$4x10^1$	$4x10^1$
	A. fumigatus	$4.8x10^4$	$1.6x10^4$	$4x10^4$	$4x10^4$	$8x10^3$	$4x10^2$	$1.2x10^2$	$2.4x10^2$	$2.4x10^2$	$2.4x10^2$
Arciolane 5500	S. aureus	$2.8x10^7$	$1.4x10^5$	$2x10^4$	$1.2x10^2$	0	0	0	0	0	0
	S. epidermidis	$6.1x10^7$	$4x10^6$	$1x10^3$	0	0	0	0	0	0	0
	E. faecalis	$5.6x10^7$	$1.2x10^7$	$5x10^3$	$4x10^1$	0	0	0	0	0	0
	***Bacillus* sp.**	$1.2x10^6$	$8x10^5$	$1.6x10^5$	$2x10^5$	$4x10^4$	$4x10^5$	$2x10^4$	$1.6x10^5$	$4x10^4$	$1.2x10^4$
	P. aeruginosa	$1.2x10^8$	$4.8x10^6$	$2.4x10^7$	$8x10^6$	$8x10^6$	$7.6x10^7$	0	0	0	0
	C. albicans	$1.6x10^5$	$4.4x10^4$	$1.6x10^4$	$3.6x10^3$	$6.4x10^3$	$4x10^3$	$8x10^3$	$4x10^3$	$4x10^3$	$3.6x10^2$
	A. fumigatus	$1.6x10^6$	$4x10^4$	$4x10^4$	$4x10^4$	$4x10^4$	$4x10^3$	$4x10^3$	$4x10^2$	$4x10^2$	$2.4x10^2$
Oxane Hd	S. aureus	$2.1x10^7$	$3x10^5$	0	0	0	0	0	0	0	0
	S. epidermidis	$2.4x10^7$	0	0	0	0	0	0	0	0	0
	E. faecalis	$1.2x10^7$	0	0	0	0	0	0	0	0	0
	***Bacillus* sp.**	$2x10^6$	$3.6x10^4$	$4x10^3$	$6.2x10^2$	0	0	0	0	0	0
	P. aeruginosa	$3.4x10^7$	$1.2x10^7$	$5.2x10^6$	0	0	0	0	0	0	0
	C. albicans	$3.2x10^5$	$1.6x10^5$	$1.1x10^5$	$8x10^3$	$4.8x10^3$	$8x10^1$	0	0	0	0
	A. fumigatus	$3.6x10^4$	$4x10^4$	$4x10^4$	$8x10^3$	$1.2x10^4$	$4x10^3$	0	0	0	0
Saline	S. aureus	$2.8x10^7$	$6.5x10^5$	$4x10^3$	0	0	0	0	0	0	0
	S. epidermidis	$5.2x10^7$	$5.2x10^5$	0	0	0	0	0	0	0	0
	E. faecalis	$4x10^7$	$8x10^6$	0	0	0	0	0	0	0	0
	***Bacillus* sp.**	$1.6x10^6$	$4x10^5$	$5.2x10^4$	$2x10^4$	$2.8x10^4$	$1.6x10^4$	$8x10^3$	$4x10^3$	$4x10^3$	$1.2x10^4$
	P. aeruginosa	$6x10^6$	$5.2x10^7$	$1.2x10^7$	$1.2x10^7$	$1.6x10^7$	$2.8x10^7$	$2.4x10^7$	$2x10^7$	$4x10^7$	$4.4x10^7$
	C. albicans	$6x10^5$	$3.2x10^5$	$2.6x10^5$	$9.4x10^4$	$1.3x10^5$	$6x10^5$	$2.8x10^5$	$1.2x10^5$	$3.6x10^5$	$3.2x10^5$
	A. fumigatus	$8x10^4$	$4x10^4$	$4x10^4$	$2.8x10^4$	$2x10^4$	$2x10^4$	$4.4x10^4$	$2x10^4$	$4x10^4$	$8x10^4$
BHI	S. aureus	$3.4x10^7$	$4.8x10^9$	$5.8x10^9$	$2.9x10^{10}$	$4x10^{10}$	$4x10^{10}$	*	*	*	*
	S. epidermidis	$3.6x10^7$	$4.8x10^8$	$1.5x10^8$	$1.5x10^8$	$1.5x10^8$	$1.5x10^8$	*	*	*	*
	E. faecalis	$4x10^7$	$8x10^9$	$8x10^9$	$8x10^9$	$4.8x10^9$	$4x10^9$	$4x10^9$	$4x10^9$	$4x10^9$	$1.2x10^8$
	***Bacillus* sp.**	$8x10^6$	$8x10^7$	$2.4x10^7$	$1.6x10^7$	$2.4x10^7$	$4x10^7$	$4x10^6$	$1.2x10^7$	$4x10^6$	$1.6x10^6$
	P. aeruginosa	$1.3x10^7$	$6x10^8$	$1.2x10^{10}$	$2x10^9$	$8x10^8$	$8x10^8$	$6x10^8$	$1.2x10^8$	$1.3x10^8$	$6x10^7$
GPB	C. albicans	$1x10^6$	$8x10^7$	$1.2x10^9$	$8x10^8$	$8x10^8$	$2x10^9$	$4x10^8$	$8x10^8$	$4x10^8$	$4x10^8$
	A. fumigatus	$4x10^5$	$4x10^5$	$4x10^5$	$2.8x10^6$	$8x10^6$	$8x10^6$	$8x10^6$	$8x10^7$	$8x10^7$	$4x10^7$

* Key: 0...growth inhibition *... growth, CFU count undetermined

Table 2. Time to elimination of bacteria in the tested samples (days).

Sample	Elimination of bacteria in the tested samples (days)						
	Staphylococcus aureus	*Staphylococcus epidermidis*	*Enterococcus faecalis*	*Bacillus* sp.	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus fumigatus*
Arciolane 1300	7	7	>21	>21	>21	>21	>21
Arciolane 5500	9	7	9	>21	14	>21	>21
Oxane Hd	4	2	2	9	7	14	14
Saline	7	4	4	>21	>21	>21	>21
BHI/GPB	>21	>21	>21	>21	>21	>21	>21

In the 1980s and 1990s, reports in the literature claimed that low-molecular-weight components, impurities commonly found in silicone oil, may display a certain toxicity. Because of their high volatility, some of these components may diffuse as vaporized molecules into the surrounding tissues, where they are thought to produce toxic effects[32]. Inactivated catalyst remaining in the silicone oil may be toxic[33].

Özdamar et al.[34] were the first to notice and describe, under *in vitro* conditions, the antimicrobial activity of silicone oil with a viscosity of 1,300 cSt. Its antimicrobial effects were tested on agents more commonly responsible for endophthalmitis, namely the strains of *S. aureus, S. epidermidis, P. aeruginosa, C. albicans* and *Aspergillus* sp. The decrease and clearance of all agents was more rapid when cultured in silicone oil than in saline or culture media. The authors hypothesized that the antimicrobial effects of the oil, observed *in vitro*, could be due to either insufficient nutrients necessary for microbial growth, or its toxicity. An insufficient supply of nutrients would be expected to inhibit the growth and multiplication of the bacterial population, and may eventually lead to its death. However, nutrient insufficiency may also be considered in the case of saline, although saline potentially provides microbes not only with the necessary water but also other substances which enrich the solution after the natural disintegration of the inoculated agents. Özdamar et al. observed that microorganisms decreased more significantly in silicone oil than in saline and they assumed that its antimicrobial activity resulted from the toxicity of low-molecular-weight components.

The present study confirms the antimicrobial effects of silicone oils of different viscosity and specific gravity. Of the tested oils, Arciolane 1300, Arciolane 5500 and Oxane Hd, the most pronounced antimicrobial effects observed *in vitro* were those of the Oxane Hd heavy silicone oil. If all silicone oils represent an environment with insufficient nutrients for microbes, and yet there are differences in their antimicrobial effects, these may presumably result from their chemical composition, with potentially negative effects on a broader spectrum of microorganisms.

The question for further clinical examination remains whether Oxane Hd heavy silicone oil could be used in clinical practice to treat acute endophthalmitis. Based on in vitro tests it has the best antimicrobial activity. However, increased risk of inflammatory reaction in eyes with implanted heavy silicone oil has been discussed in the literature. Theelen et al.[35] evaluated 19 eyes of 18 patients who underwent PPV and intraocular tamponade with high-density silicone oil Oxane HD. The indication for this type of intraocular tamponade was limited to cases with complicated retinal detachment of the inferior quadrants. One to eight weeks following PPV with high-density silicone oil, intraocular inflammation was found in 7 of 19 eyes (37%). The intraocular inflammatory signs completely resolved following removal of the high-density silicone oil. In contrast, Rizzo et al.[4] used Oxane Hd heavy silicone oil in 28 patients who were operated on for recurrent retinal detachment with proliferative vitreoretinopathy (stage ≥C2) after vitreoretinal surgery, penetrating trauma and combined rhegmatogenous and choroidal detachment. No patient showed intraocular inflammation with Oxane Hd in situ. Heimann et al.[36] in their review of 21 articles on the clinical use of 9 different heavy tamponades (fluorosilicone, C10F18, F6H8, OL62HV, Oxane Hd, O62, F6H8-silicone oil mixture, Densiron 68, and HWS 46-3000) concluded that the first generation (fluorinated silicone and perfluorocarbon liquids) and second generation (partially fluorinated alkanes) of heavy tamponades were associated with relatively high complication rates, for example, tamponade emulsification, intraocular inflammation, and rise in intraocular pressure. The complication spectrum of the new generation of heavy silicone oils (Oxane Hd, Densiron 68, and HWS 46-3000) seems to be comparable to conventional silicone oil tamponades.

CONCLUSION

The Oxane Hd silicone oil exhibited the highest antimicrobial activity, both antibacterial and antifungal. It inhibited the growth activity of all inoculated bacteria,

albeit after various times; after 14 days, it acted upon candidas and aspergilli as well.

From this, it may be assumed that the various antimicrobial effects of different types of silicone oil are caused by their chemical composition. The results also suggest that, if endophthalmitis is treated by PPV, the application of silicone oil, in particular heavy silicone oil, into the vitreous cavity at the end of the surgery may contribute to the elimination of microorganisms from the intraocular space. However, given the potential risks and complications of inflammatory reactions in eyes with implanted heavy silicone oil discussed in the literature, clinical trials to confirm the safety of implanting heavy silicone oil Oxane Hd in the eye area in eyes with acute endophthalmitis are necessary.

ABBREVIATIONS

BHI, Brain Heart Infusion; CFU/ml, Colony-forming units in 1 ml; cSt, Centistokes; EVS, Endophthalmitis Vitrectomy Study; GPB, Glucose-Peptone Broth; H, Hours; PPV, Pars plana vitrectomy.

CONFLICT OF INTEREST STATEMENT

Author's conflict of interest diclosure: None of the authors has any proprietary interest.

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