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David Lockington, Elisabeth Ca Macdonald, David Young, Philip Stewart, Muriel Caslake, et al..
Presence of free radicals in intracameral agents commonly used during cataract surgery. British
Journal of Ophthalmology, 2010, 94 (12), pp.1674. 10.1136/bjo.2009.171009 . hal-00557343

HAL Id: hal-00557343

<https://hal.science/hal-00557343>

Submitted on 19 Jan 2011

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Presence of free radicals in intracameral agents commonly used during cataract surgery

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Keywords:

Free radicals, intracameral, cataract surgery, TASS

Word Count: 1767

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Competing Interest: None declared. No author has any commercial interest in any product/equipment mentioned in this article.

Presence of free radicals in intracameral agents commonly used during cataract surgery

Abstract/Summary:

Background:

Free radicals are known to cause cellular damage and are present in ophthalmic preparations. Corneal defence mechanisms are bypassed in intra-ocular surgery. We evaluated commonly used intracameral agents to ascertain the presence of free radicals and investigate the possibility of anterior segment and endothelial toxicity.

Methods:

Samples of 19 commonly used intracameral preparations were analysed for total free radical presence on an Instrument Laboratory IL600 using a Randox Kit for Total Antioxidant Status (RANDOX Laboratories Ltd, Crumlin, UK).

Results:

Free radical concentrations for these 19 intracameral agents ranged from 0 – 3.59 mmol/l, with median value of 0.34 mmol/l (mean value of 0.933 mmol/l, S.D. 1.19). Phenylephrine had the highest presence of free radicals, which were considerably higher than those for 0.5% hydrogen peroxide at all tested dilutions. Other notable results included Cefuroxime (0.61 mmol/l), 2% undiluted Lidocaine (0.34 mmol/l) and Bevacizumab (0.59 mmol/l).

Conclusion:

The results indicate that free radicals are present in intracameral surgical agents and some are in the order of 0.5% hydrogen peroxide. The risks of endothelial damage must be considered when using multiple intracameral preparations in complicated cataract surgery. Free radicals in intracameral preparations may be a contributing cause in cases of Toxic Anterior Segment Syndrome.

Presence of free radicals in intracameral agents commonly used during cataract surgery

Introduction:

Preservatives in ophthalmic medications have been implicated in oxidative stress that contributes to ocular surface disorders, demonstrated in glaucoma patients on long-term topical medication.¹ Cytotoxicity to the conjunctiva, corneal epithelium and endothelium decreases in the absence of preservatives, leading to the development of less cytotoxic, preservative-free preparations.² However, preservatives are not the sole contributing factor to ocular surface damage. Free radicals have been shown to be present in similar quantities in both preservative and preservative-free topical ophthalmic preparations.³ These free radicals have the potential to be toxic to the corneal and conjunctival epithelium.⁴ The ocular surface is normally protected by the healthy tear film, containing components such as lactoferrin, aldehyde dehydrogenase, superoxide dismutase and glutathione.^{5,6}

This combined protective barrier is breached by intra-ocular surgery during which the intracameral route is increasingly used for a variety of agents. To investigate the possibility of anterior segment and endothelial toxicity from these agents we evaluated the intracameral agents commonly used in cataract surgery for the presence of free radicals.

Methods:

Samples of commonly used intracameral preparations were analysed for total free radical presence on an Instrument Laboratory IL600 using a Randox Kit for Total Antioxidant Status(TAS) Cat No NX2332 with its own calibrator (RANDOX Laboratories Ltd, Crumlin, UK, <http://www.randox.com>). This provides an indirect measurement of free radicals.

Incubation of ABTS (ferrylmyoglobin) with a peroxidase (metmyoglobin) results in production of the radical cation ABTS⁺. This species is blue-green in colour, and can be detected at 600nm. Presence of antioxidants in the added sample cause inhibition of this colour production to a degree that is proportional to their concentration in this two reagent assay. The results are linear up to a concentration of 5mmol/l. [See manufacturer's website and supplementary figure for further details]

Samples were stored as per the manufacturers' instructions, including in the dark as required. The analyser used a 4ul sample, and 200ul Buffer/Chromogen plus 40ul diluted substrate. Analysis occurred at 37°C.

The agents evaluated were Miochol-E (20mg acetylcholine chloride), Betnesol (5.3mg betamethasone sodium phosphate), Cefuroxime (1mg/0.1ml solution), Cidomycin (80mg/2ml Gentamicin Sulphate), dilutions of Minims Phenylephrine Hydrochloride (2.5% and 10%), dilutions of Lidocaine Hydrochloride (1% and 2%), Balanced Salt Solution (BSS), Avastin (bevacizumab), Lucentis (ranibizumab) and Kenalog (triamcinolone acetonide 40mg per ml of sterile suspension). See Figure 1 for formal product information and trademarks. Various concentrations of hydrogen peroxide were also assessed to provide an appropriate reference result. Data were tested for normality using the Anderson-Darling test in Minitab (version 15). As anticipated, the data was found not to be normally distributed ($p < 0.005$). A Mann-Whitney test was performed to investigate differences in the median values between the intracameral group and our previous study³ of non-preserved Minims topical preparations.

Results:

Free radical concentrations for these 19 intracameral agents ranged from 0 – 3.59 mmol/l, with median value of 0.34 mmol/l (mean value of 0.933 mmol/l, S.D. 1.19).

Phenylephrine had the highest concentration of free radicals, which reduced with 1:1 and 1:3 dilutions. These levels were considerably higher than those for 0.5% hydrogen peroxide (1.39mmol/l) at all tested dilutions. Other notable results included Cefuroxime (0.61 mmol/l), 2% undiluted Lidocaine (0.34 mmol/l) and Bevacizumab (0.59 mmol/l). [See Figures 1 and 2]

Comparison with our previous survey of topical Minims (preservative-free) ophthalmic preparations³ revealed no statistically significant difference between the median values of the two groups (0.34 mmol/l Intracameral vs 0.145 mmol/l Minims; Mann-Whitney $p = 0.574$).

[See Figure 2 and box plot in Figure 3]

Discussion:

The intracameral route is increasingly utilised in cataract surgery for drug delivery. Anaesthetic agents are routinely used to supplement topical anaesthesia and reduce the discomfort from iris movement during phaco-emulsification.⁷ The routine use of an intracameral antibiotic such as cefuroxime for endophthalmitis prophylaxis is becoming more common across Europe following the publication of the ESCRS study.⁸ The intracameral route is also used to improve surgical conditions in more technically difficult cases. This includes enhancing pupillary dilation with phenylephrine, visualisation of the

capsule with stains such as trypan blue, or triamcinolone for identifying vitreous strands, and Miochol to cause pupil constriction at the end of surgery. Some of these products are diluted by the theatre staff at the time of cataract surgery, and concerns have been raised regarding the methods used and the resultant accuracy of concentration.^{9,10}

There is a reasonable body of evidence regarding the impact of these agents on the corneal endothelium. Borazan et al investigated the effect of local anaesthetic agents such as preservative-free lidocaine hydrochloride 2%, ropivacaine 1%, and levobupivacaine 0.75% in the rabbit cornea, and found significant apoptotic endothelial cell loss and degenerative changes.¹¹ Although the induced apoptosis was temporary and recovered in 7 days, they raised concerns regarding permanent cell loss in the human corneal endothelium. Yoneruek et al investigated the in vitro effects of vancomycin and cefuroxime on human endothelial cells and found a reduction in cell viability in a dose dependent manner, leading to cell death at the higher concentrations.¹²

The endothelium is protected during cataract surgery by the use of viscoelastic devices (OVD), cohesive or dispersive substances mainly derived from sodium hyaluronate.¹³ They have been shown to act as free radical scavengers.^{14,15} Free radicals are known to be generated throughout phaco-emulsification.¹⁶⁻¹⁸ Reductions in the irrigation/aspiration settings have been shown to alter free radical production.¹⁵ Total ultrasound energy has been shown to contribute to endothelial cell loss in cataract surgery, and free radicals induced by ultrasound oscillation can cause corneal endothelial damage.^{18,19} The OVD should act to protect the endothelium during these stages, but their effectiveness in suppressing free radicals is dependent on their retention in the anterior chamber.¹⁶ It should be noted that the intracameral agents we studied are often used before insertion or after removal of such protective OVDs.

To our knowledge this is the first study to measure the levels of free radicals present in the intracameral products commonly used during cataract surgery. Our overall results were not dependent on whether the product contained preservatives or not. The excipients detailed in our results table probably contribute to these measurements, and are necessary for effective drug delivery.

A surgeon performing complicated cataract surgery could be expected to utilise many of these agents during a single operation. The accumulative total of free radicals from using intracameral 2.5% Phenylephrine (1:1 dilution), 2% Lidocaine (1:1 dilution), Miochol, and Cefuroxime is 2.88mmol/l, which is more than twice the result for 0.5% hydrogen peroxide. All the agents used in this example would be introduced into the anterior segment without OVD protecting the endothelium.

It has been our clinical observation that the use of an intracameral agent during routine cataract surgery can instantly affect the corneal clarity and intraocular view. This is often temporary, consistent with a transient dysfunction of the endothelial pump mechanism. It is possible the endothelial function is being partially compromised by the intracameral surgical agents. This is unlikely to be of long term significance in the healthy cornea, but warrants consideration in patients with endothelial disease, such as Fuchs' Endothelial Dystrophy. There is also increasing evidence that the endothelium of diabetic patients is compromised compared to normal controls, which is significant as diabetics have a higher rate of cataracts than the normal population.²⁰

Agents can be introduced in a more diluted form by addition to the irrigation fluid, for example adrenaline to improve pupillary dilatation.²¹ Some surgeons may believe this route to be a safer alternative. The use of intracameral epinephrine has been reported to be toxic to the endothelium, especially during procedures when minimal irrigating solution is used, such as IOL repositioning.²² The irrigating fluid may also be used for antibiotic delivery by surgeons who have concerns regarding the accuracy and safety of an intracameral antibiotic bolus.^{9,10,23} Studies have evaluated the benefit of adding free radical scavengers to the irrigation solutions. Addition of ascorbic acid was shown to reduce the amount of endothelial cell loss during phaco-emulsification by 70% in rabbit eyes.²⁴

In essence, the literature indicates that 2 main factors correlate to the extent of potential damage to endothelial cells of the cornea. These are the exposure amount and the exposure time of intracameral agents which contain or generate oxidising stress from free radicals. By reducing these 2 variables, the accumulative amount of free radical assault to the tissue should be minimised. The presence of free radicals identified in this study warrants consideration by surgeons to minimise endothelium damage by having a minimalistic

approach to intracameral adjuncts. This is particularly relevant for patients with compromised and vulnerable corneas.

The presence of accumulative levels of free radicals derived from multiple intracameral agents in the setting of prolonged complicated cataract surgery could play a role in the increasingly recognised Toxic Anterior Segment Syndrome. The increasing awareness of Toxic Anterior Segment Syndrome has been paralleled by the widespread use of topical anaesthesia in cataract surgery, supplemented with intracameral agents. A recent review of the literature by Mamalis et al ²⁵ indicated causes including “intraocular solutions with inappropriate chemical composition, concentration, pH, or osmolality, preservatives, denatured ophthalmic viscosurgical devices, enzymatic detergents, bacterial endotoxin, oxidized metal deposits and residues, and factors related to intraocular lenses such as residues from polishing or sterilizing compounds.” We wonder if high levels of free radicals from accumulative intracameral agents and the interaction of these intraocular solutions may be a contributing factor.

Limitations

The Radox TAS kit indirectly measures the presence of free radicals by addition or inhibition of antioxidant, generation of a 2 reagent assay and analysis by colorimetry. The specific free radical responsible for depletion is not identifiable from this method. Our study was also limited by the method of assay as we were unable to evaluate coloured products such as capsular stains (Trypan Blue) or vitreal stains such as the opaque Triamcinolone suspension. We acknowledge that this is a cell free study, and so may not provide direct correlation to physiological conditions in human corneal endothelial cells. The excipients in the products may influence the measurements, however, these same excipients are still being used intracamerally, and so the magnitude of their results warrants consideration.

Conclusion:

We have shown that free radicals are present in commonly used intracameral ophthalmic preparations and some are in the order of 0.5% hydrogen peroxide. The potential for endothelial damage from free radicals should lead the surgeon to consider the need for these additional surgical agents carefully, particularly in patients with already compromised corneas.⁴ More research is required to further investigate this interesting field, which would

benefit from in vivo studies correlating endothelial cell tissue culture observations with free radical concentrations from intracameral agents.

The accumulative presence of free radicals also warrants consideration as a contributing cause to cases of Toxic Anterior Segment Syndrome.²⁵

Funding/Competing Interests: Nothing to declare.

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Legend:

Figure 1: Table showing total results for presence of free radicals in commonly used intracameral agents for cataract surgery and formal product information/trademarks.

Figure 2: Descriptive statistics comparing presence of free radicals for intracameral agents with preservative-free topical preparations.

Figure 3: Boxplot comparing presence of free radicals for intracameral agents with preservative-free topical preparations.

Figure 1: Table illustrating total results and formal product information/trademarks. Excipients obtained where available from electronic Medicines Compendium. <http://emc.medicines.org.uk/>

Product	Dilution?	Manufacturer	Excipients	TAS (mmol/l)
Miochol-E (20mg acetylcholine chloride)	neat	Novartis	Mannitol, Sodium acetate trihydrate, Magnesium chloride hexahydrate, Potassium chloride, Calcium chloride dehydrate, Water for injection	0.03
Betnesol (5.3mg betamethasone sodium phosphate BP)	neat	UCB Pharma Limited	Disodium edentate, Sodium metabisulphite, Sodium chloride, Sodium hydroxide, Hydrochloric acid, Water for injection	0.01
Cefuroxime 1mg/0.1ml	neat	Preston Pharmaceuticals	None stated	0.61
Cidomycin (80mg/2ml Gentamicin Sulphate Ph Eur)	neat	sanofi-aventis	Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216), Disodium Edetate, Water for Injection, 2M Sodium Hydroxide, 1M Sulphuric Acid	0.00
Minims Phenylephrine Hydrochloride 2.5%	neat	Bausch & Lomb	Sodium metabisulphite, Disodium edentate, Purified water	3.22
Minims Phenylephrine Hydrochloride 2.5%	1+1 BSS	Bausch & Lomb	Sodium metabisulphite, Disodium edentate, Purified water	2.08
Minims Phenylephrine Hydrochloride 2.5%	1+3 BSS	Bausch & Lomb	Sodium metabisulphite, Disodium edentate, Purified water	1.70
Minims Phenylephrine Hydrochloride 10%	neat	Bausch & Lomb	Sodium metabisulphite, Disodium edentate, Purified water	3.59
Minims Phenylephrine Hydrochloride 10%	1+1 BSS	Bausch & Lomb	Sodium metabisulphite, Disodium edentate, Purified water	2.47
Minims Phenylephrine Hydrochloride 10%	1+3 BSS	Bausch & Lomb	Sodium metabisulphite, Disodium edentate, Purified water	2.09
Lidocaine Hydrochloride Injection BP 1% w/v	neat	hameln pharmaceuticals	Hydrochloric acid, Sodium hydroxide, Water for injection	0.14
Lidocaine Hydrochloride Injection BP 1% w/v	1+1 BSS	hameln pharmaceuticals	Hydrochloric acid, Sodium hydroxide, Water for injection	0.14
Lidocaine Hydrochloride Injection BP 1% w/v	1+3 BSS	hameln pharmaceuticals	Hydrochloric acid, Sodium hydroxide, Water for injection	0.06
Lidocaine Hydrochloride Injection BP 2% w/v	neat	hameln pharmaceuticals	Hydrochloric acid, Sodium hydroxide, Water for injection	0.34

Lidocaine Hydrochloride Injection BP 2% w/v	1+1 BSS	hameln pharmaceuticals	Hydrochloric acid, Sodium hydroxide, Water for injection	0.16
Lidocaine Hydrochloride Injection BP 2% w/v	1+3 BSS	hameln pharmaceuticals	Hydrochloric acid, Sodium hydroxide, Water for injection	0.08
BSS (sterile irrigating solution)	neat	Alcon	None stated	0.00
Avastin (bevacizumab)	neat	Roche	Trehalose dehydrate, Sodium phosphate, Polysorbate 20, Water for injections	0.59
Lucentis (ranibizumab)	neat	Novartis	α,α -trehalose dehydrate, Histidine hydrochloride, monohydrate, Histidine, Polysorbate 20, Water for injection	0.41
Kenalog (triamcinolone acetonide 40mg per ml of sterile suspension)		E.R.Squibb & Sons Limited	Benzyl alcohol, Polysorbate 80, Sodium carboxymethylcellulose, Sodium chloride, Water	Not suitable for analysis
Trypan blue 0.06%		D.O.R.C.	Sodium mono-hydrogen orthophosphate, Sodium di-hydrogen orthophosphate, Sodium chloride, water for injection	Not suitable for analysis
0.05% peroxide	neat		0.05% hydrogen peroxide	0
0.1% peroxide	neat		0.1% hydrogen peroxide	0.04
0.5% peroxide	neat		0.5% hydrogen peroxide	1.39

Figure 2: Descriptive statistics comparing presence of free radicals for intracameral agents with preservative-free topical preparations.

	Number	Mean (mmol/l)	Standard Deviation	Minimum	Median	Maximum
Intracameral Agents	19	0.933	1.190	0	0.340	3.590
Comparative Minims Group	18	0.844	1.217	0	0.145	3.940

Figure 3: Boxplot comparing presence of free radicals for intracameral agents with preservative-free topical preparations. Scale is mmol/l.