The Safety Profile of Long-Term Intraocular Ophthalmic Viscoelastic Devices

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The Current Market

Cohesive viscoelastic agents

Trade name	Manufacturer	Content
Healon Pro®	Johnson & Johnson Vision, Irvine, CA	1% HA
Healon GV Pro®	Johnson & Johnson Vision, Irvine, CA	1.8% HA
Amvisc®	Bausch + Lomb, Rochester, NY	1.2% HA
Eyefill-C®	Bausch + Lomb, Rochester, NY	1.4% HA
Eyefill-SC®	Bausch + Lomb, Rochester, NY	2% HA
Amvisc Plus®	Bausch + Lomb, Rochester, NY	1.6% HA
Provisc®	Alcon, Ft Worth, TX	1% HA

Dispersive viscoelastic agents

Trade name	Manufacturer	Content
OcuCoat®	Bausch + Lomb, Rochester, NY	2% HPMC
Viscoat®	Alcon, Ft Worth, TX	3% HA + 4% CS
DisCoVisc®	Alcon, Ft Worth, TX	1.65% HA + 4% CS
Healon Endocoat®	Johnson & Johnson Vision, Irvine, CA	3% HA
Eyefill-HD®	Bausch + Lomb, Rochester, NY	2% HPMC

Cohesive-dispersive viscoelastic agents

Trade name	Manufacturer	Content
Eyefill-DC®	Bausch + Lomb, Rochester, NY	1.37% HA + 0.57% HPMC
Eyefill-MB®	Bausch + Lomb, Rochester, NY	1.8% HA + 1.4% HPMC
Healon5 Pro®	Johnson & Johnson Vision, Irvine, CA	2.3% HA

Background

- Complications: TASS, secondary glaucoma, corneal decompensation
- Different retention times depending on rheologic properties & molecular weight: 12 hours – 2 years
- Remnant degradation products detected in liver
- Absence of adequate long-term vitreous substitutes
- -> Recent interest in the development of long-lasting, non-toxic, biocompatible OVDs

Methods

- EMBASE & MEDLINE literature review: HA, HPMC, CS
- 38 studies included in review
  - 21 Animal studies
  - 3 In vitro studies
  - 10 Posterior segment human studies
  - 4 Anterior segment human studies

Results

CS-BASED OVDS

- Natural GAG in human stroma
- Shark cartilage
- Oral supplement in osteoarthritis, up to 1200mg/day
- No formal studies describing the safety profile of intraocular CS

HPMC-BASED OVDS

	Location	Duration	Adverse effects
In vitro	Cultured RPE cells	n/a	Normal morphology and function
Animal	Anterior segment	Up to 4 weeks	• No AC toxicity • Self-limiting post-operative IOP spike and inflammatory reaction
	Posterior segment	Up to 4 weeks	Self-limiting post-operative IOP spike
Human	Anterior segment	Up to 4 weeks	• No AC toxicity (endothelial cell morphology, corneal thickness, IOP, cells/flare, BCVA) • IOP spike may last several days; may need AC washout or Diamox / vitamin C
	Posterior segment	No data	No data

- Modified plant cellulose
- Cosmetic/skincare industry up to 10% w/v, safe
- Prebiotic; passes unchanged through gut
- Oral non-toxicity and non-teratogenicity

HA-BASED OVDS

	Location	Duration	Adverse effects
In vitro	No data	No data	No data
Animal	Anterior segment	Up to 4 weeks	• Non-toxic (endothelial cell density & morphology, corneal thickness) • Moderate AC flare settling within few days • Maximal IOP rise within 4 hrs, return to baseline by 24 hrs
	Posterior segment	Up to 9 years	Self-limiting post-operative IOP spike
Human	Anterior segment	Up to 3 months	• No safety concerns (corneal assessment) • Maximal IOP rise within 24 hours • Self-limiting mild AC reaction
	Posterior segment	Up to 5.5 years	No electrophysiology changes

Non-cross-linked cohesive HA eg Healon®, Healon GV®

	Location	Duration	Adverse effects
In vitro	Human fibroblasts, human embryonic stem cell-derived RPE cells and photoreceptors	n/a	• Bio- and cyto-compatibility • Preserved metabolic activity and cell-cell interactions
Animal	Anterior segment	Up to 4 weeks	• Moderate AC flare settling within few days • 4-fold rise in IOP settling within a week
	Posterior segment	Up to 6 months	• No effect on in vivo electrophysiology • No effect on cell viability of retinal explants
Human	Anterior segment	No data	n/a
	Posterior segment	Up to 12 months	• Sustained IOP rise (less enzymatic degradation; good for hypotony) • Biocompatible on OCT

Cross-linked cohesive HA eg gellan/HA, UVHA, ADH-cross linked, Healaflow®

	Location	Duration	Adverse effects
In vitro	No data	No data	No data
Animal	Anterior segment	No data	No data
	Posterior segment	No data	No data
Human	Anterior segment	24 hours	• If retained, greater 24-hour postop IOP rise (vs removed) which settles • No difference in endothelial density loss removed vs retained
	Posterior segment	No data	No data

Dispersive HA eg OcuCoat®, Viscoat®, DisCoVisc®, Endocoat®

- Swelling factor 10,000x its weight – IOP spike
- Human umbilical cord, rooster comb or streptococcal culture
- Natural HA short intravitreal half-life (<2 weeks)
- Difficult to inject through a small-bore cannula

CONCLUSIONS

- Lack of high quality evidence; animal studies majority
- Direct comparisons NOT possible
- **HPMC-based** -> most associated with IOP spikes and inflammatory reaction
- **HA-based** -> most well described; good biological stability and biocompatibility in vitreous for ≥3/52 in animal & ≥8/52 in human studies, with up to 4ml injected
- **CS-based** -> no long-term intraocular safety data