

Compounded Medications and Injections in OSD Treatment | Ahmad M. Fahmy, OD

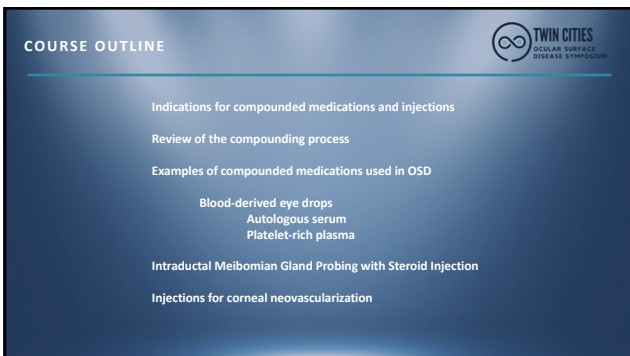
TWIN CITIES
OCULAR SURFACE
DISEASE SYMPOSIUM



Disclosures

- Allergan
- NovaBay
- Alcon

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DISEASE SYMPOSIUM



COURSE OUTLINE

Indications for compounded medications and injections

Review of the compounding process


Examples of compounded medications used in OSD

- Blood-derived eye drops
 - Autologous serum
 - Platelet-rich plasma

Intraductal Meibomian Gland Probing with Steroid Injection

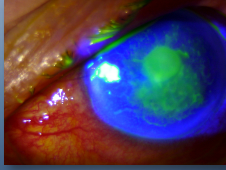
Injections for corneal neovascularization

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WHEN ONLY COMPOUNDED MEDICATIONS WILL DO 

- Fortified antibiotics, antifungals, antiseptic medications in urgent care

Hi Ahmed, 17 year old -
DOB: [redacted] Athlete
- football and baseball. Has been using his contact lenses more and sleeping in them once in a while. Significant pain, light sensitivity. We seen yesterday by another provider in my group. Began Lotemax four time a day. Did this for one day. Pain didn't resolve. On my exam: central corneal ulcer. 201400. Thanks so much for taking care of him on a Saturday. Let me know if there's anything you need from me.

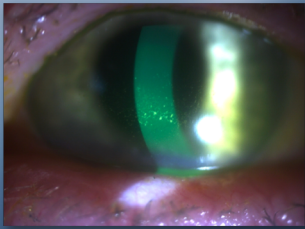


Vancomycin / Tobramycin
Amphotericin B
Fluconazole

COMPOUNDED MEDICATIONS AND INJECTIONS 

More chronic conditions

- Blepharospasm
- Ocular Surface Disease
- Corneal neovascularization
- Macular degeneration
- Cystoid macular edema
- Glaucoma




COMPOUNDED MEDICATIONS AND INJECTIONS 

- Autologous Serum
- Platelet-Rich Plasma
- Decadron Injections - MGP's
- 0.5% CsA
- Healon
- Pred-Healon
- Risk of glaucoma and cataract
- Tacrolimus
- Adrogens
- Anti-VEGF injection
- Corneal neovascularization
- Botulinum Toxin Type A injection
- Impact on MMP-9 and cytokines
- Bupivacaine and Dexamethasone injection

LOW DOSE BOTULINUM TOXIN FOR OSD WITH SECONDARY BLEPHAROSPAM





BLEPHAROSPASM



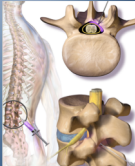
Past Ocular History					Past Ocular History						
Ocular Disease	Eye	Year	Procedure	Eye	Date	Ocular Disease	Eye	Year	Procedure	Eye	Date
Blepharospasm	OU	2018	INJECTION-BOTOX	OU	11/14/2018	Strabismus	OU	2018	INJECTION-BOTOX	OU	02/09/2017
Blepharospasm	OU	2017	INJECTION-BOTOX	OU	10/21/2017	Strabismus	OU	2017	INJECTION-BOTOX	OU	04/10/2017
Blepharospasm	BLKLL	2015	INJECTION-BOTOX	BLKLL	08/14/2015				INJECTION-BOTOX		10/11/2016
Blepharospasm	OU	2014	INJECTION-BOTOX	OU	09/12/2014				INJECTION-BOTOX		01/04/2013
Blepharospasm	BLKLL	2013	INJECTION-BOTOX	BLKLL	06/08/2013				INJECTION-BOTOX		05/06/2012
Blepharospasm	OU	2013	INJECTION-BOTOX	OU	05/13/2013				INJECTION-BOTOX		07/30/2012
Blepharospasm	OU	2014	Injection-lexivan	OU	04/11/2014				INJECTION-BOTOX		04/03/2012
Blepharospasm	OU	2017	INJECTION-BOTOX	OU	03/20/2017				INJECTION-BOTOX		10/18/2012
Blepharospasm	OU	2013	INJECTION-BOTOX	OU	03/02/2013				INJECTION-BOTOX		10/18/2012
Blepharospasm	OU	2018	INJECTION-BOTOX	OU	01/29/2018				INJECTION-BOTOX		06/17/2011
Blepharospasm	OU	2018	Injection-lexivan	OU	01/04/2018				INJECTION-BOTOX		01/14/2011
	OU		LASIK - Cornea	OU	05/05/1999				INJECTION-BOTOX		08/21/2010
	OU		cataract	OU					INJECTION-BOTOX		05/20/2010
	OU		Dry Eye	OU					INJECTION-BOTOX		01/22/2010
	OU		Function Plug	OU					INJECTION-BOTOX		10/13/2009
	OU		cataract	OU					INJECTION-BOTOX		10/13/2009
	OU		Compaction/Chalasis	OU					INJECTION-BOTOX		07/13/2009
	OU		Mediastinal Swell	OU					INJECTION-BOTOX		04/07/2009
	OU		Dysfunction	OU							
	OU		Subconjunctival hemorrhage	OU							

COMPOUNDING PHARMACIES



A New England Compounding Center meningitis outbreak that began in September 2012 sickened over 800 individuals and resulted in the deaths of 76

The CDC traced the outbreak to fungal contamination in three lots of methylprednisolone used for epidural injections



COMPOUNDING EYEDROPS

The image shows two boxes of ophthalmic solutions. The left box is for 0.1% (mometasone furoate) ophthalmic solution, containing 3 mL. The right box is for 0.5% Proparacaine Hydrochloride Ophthalmic Solution, USP, containing 15 mL. Both are sterile and for topical use only.

WHAT TO LOOK FOR IN A COMPOUNDING PHARMACY

Strict adherence to manufacturing guidelines

Clearly written procedures and protocols for each ophthalmic product:

- Defines each step, including aseptic methods
- Microbiologic filtration
- Terminal sterilization - autoclaving

The image shows a person wearing a white lab coat and a hairnet, working in a cleanroom environment. They are using a pipette to dispense liquid into a vial.

WHAT TO LOOK FOR IN A COMPOUNDING PHARMACY

- Mathematical calculations – MUST be reviewed by another staff member
- Ophthalmologic preparations
- Intraocular injections
- Small doses = more dilutions
- Decimal errors may have serious consequences

The image shows a person wearing a white lab coat and a hairnet, working in a cleanroom environment. They are standing at a workstation with a computer monitor and various pieces of laboratory equipment.


WHAT'S SO HARD ABOUT COMPOUNDING MEDICATIONS



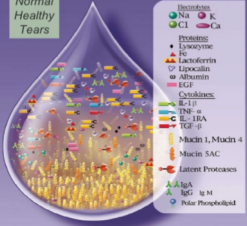

Factors:

- Sterility
- Tonicity
- pH, buffering
- Inherent toxicity of the drug
- Need for preservative
- Solubility
- Stability in the vehicle
- Viscosity
- Packaging and storage of the finished product

COMPLEX MIXTURE

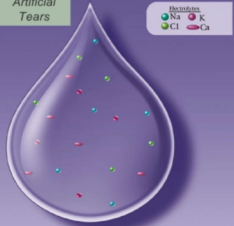


Normal Healthy Tears




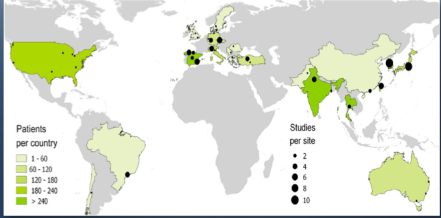
- Electrolytes: Na⁺, K⁺, Cl⁻, Ca²⁺
- Proteins: Lysozyme, IgA, Lactoferrin, Albumin, IgG, Complement
- ECF: TGF- α , EGF, IGF-1
- Mucin 1, Mucin 4, Mucin 5AC
- Latent Proteases
- Algae
- Auto-antibodies
- Polar Phospholipid

Artificial Tears



- Electrolytes: Na⁺, K⁺, Cl⁻, Ca²⁺

BLOOD DERIVED DROPS FOR OCULAR SURFACE DISEASE

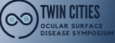
Patients per country

- 1-60
- 60-120
- 120-180
- 180-240
- > 240

Studies per site

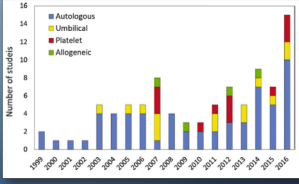
- 2
- 4
- 6
- 8
- 10

G. Giannaccare et al. / Transfusion and Apheresis Science 56 (2017) 595–604


BLOOD DERIVED DROPS FOR OCULAR SURFACE DISEASE 

STIMULATION of cellular proliferation and migration by supplying an active mixture of **growth factors and cytokines** at the ocular surface, mimicking the function of the lacking natural tears.

Dry Eye Disease
Persistent Corneal Epithelial Defects
Neurotrophic Keratitis
Corneal Ulcer
Ocular Surface Burns
Recurrent Corneal Erosions
Limbal Stem Cell Deficiency



G. Gianmaccare et al. / Transfusion and Apheresis Science 56 (2017) 593–604

PREPARATION OF AUTOLOGOUS SERUM EYEDROPS 

50-100mL of whole blood is collected and left for 2 hours at room temperature without anticoagulant, reaching complete clotting

Blood is centrifuged – separating serum from solid components.

Diluted with balanced salt solution (BSS)

Should be kept away from light to avoid Vitamin A degradation

Blood collection from patient

↓ Centrifugation for 10 min at 2,000 xg

Autologous serum

↓ Sterilization by filtration

↓ Dilution with 0.9% Saline

Eye Drops: 20% Diluted-autologous serum

Expiration: 3 months at -20°C, 2 weeks at 4°C

Invest Ophthalmol Vis Sci. 2018;59:DES121–DES129. <https://doi.org/10.1167/iov.17.23760>

AUTOLOGOUS SERUM EYE DROPS 

DM
 Neurotrophic keratitis
 21 days QID



Matsumoto. AS Application in the Treatment of Neurotrophic Keratopathy. Ophthalmology 2004;111:1115-1120

AUTOLOGOUS SERUM EYEDROPS

DM
Neurotrophic keratitis
Central Ulcer with infiltration and NV
17 days QID

Matsumoto. AS Application in the Treatment of Neurotrophic Keratopathy. Ophthalmology 2004;111:1215-1220

AUTOLOGOUS SERUM AND TEAR FILM COMPONENTS

Lysozyme, lactoferrin, albumin = major components in tears
Albumin, IgG = major components in serum

Infection via serum can occur
Serum itself is unstable and probably degraded by internal enzymes

Use of serum components – can minimize these challenges

Components	Concentration	
	Tear, Basal	Serum ¹
Proteins		
Total protein	7.51 mg/mL	66-81 mg/mL
Lysozyme	2.56 mg/mL	5.0-10.2 µg/mL
Lactoferrin	1.84 mg/mL	0.17-20.26 mg/mL
Albumin	1.5 mg/mL	41-51 mg/mL
IgG	0.50 mg/mL	0.93-5.93 mg/mL
IgG	ND	0.03 mg/mL
IgA	0.1 µg/mL	0.1 µg/mL
IgE	0.126 mg/L	8.61-17.47 mg/mL
IgM	0.86 µg/mL	0.35-1.85 mg/mL
Ca/Zn-SOD	103 ng/mg protein	202
Growth factors		
EGF	1.66 ng/mL	0.72 ng/mL
TGF- α , male	247 pg/mL	147 pg/mL
TGF- α , female	186 pg/mL	147 pg/mL
TGF- β	Not detected	140.3 ng/mL
TGF- β 1	2.53 ng/mL	-
TGF- β 2	55 pg/mL	-
Vitamins		
Vitamin A	16 ng/mL	200-500 ng/mL
Vitamin C	117 µg/mL	5-9 µg/mL
Ascorbic acid		
Tyrosine	45 µM	77 µM
Glucuronic	107 µM	202
Carbohydrate		
Glucose	26 mg/L	0.6-1.2 g/L

Invest Ophthalmol Vis Sci. 2018;59:DES121-DES129. https://doi.org/10.1167/iov.17-23760

TEAR FILM COMPONENTS

Side View of an Eye

Evaporation

Rotate 90° anticlockwise

40-90nm

Up to 4000nm

Air

Nonpolar Lipid Sublayer
CE (4.8), WE (35.2), TAG (2.8), DAG (0.3), Free Cho (5.9)

Amphiphilic Lipid Sublayer
OAHFA (2.5), CS (0.1), lysoPL (2.4), PL (4.1), SPL (1.8)

Aqueous-Mucin Gel Layer
water, salts, proteins, carbohydrates etc

Glycocalyx Layer

Corneal Epithelial Cells

Molecular Structure of Cholesteryl Sulfate

J. Lipid Res. 2014. 55: 289-298

TEAR FERNING PATTERNS

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INTERFEROMETRY

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PLATELET – RICH PLASMA

Platelets are **FUNDAMENTAL** for wound healing
Most widely used in maxillo-facial surgery and orthopedics
in order to stimulate and accelerate tissue healing

Platelet rich in growth factors, Platelet lysate: treatment of OSD

Major effects are mediated from **PDGF** – the first growth factor
involved in wound healing

PDGF – increase in the number of repaired cells, stimulation of
angiogenesis, support of activated macrophages

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PREPARATION OF PLATELET-DERIVED EYE DROPS

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The patient's blood is extracted using 3.2% sodium citrate as an **anticoagulant** and centrifuged for 10min at 1600rpm.

Three layers: Platelet poor plasma on top, PRP below this layer, and at the bottom separated white and red cells.

PRP is aspirated and 3-4mL aliquots are transferred into 10mL new sterilized amber glass bottles with eye drop applicators.

The bottle in use should be kept in the refrigerator at +4C for one week, the rest in the freezer at -20C.

PRP INJECTION FOR SEVERE DRY EYE

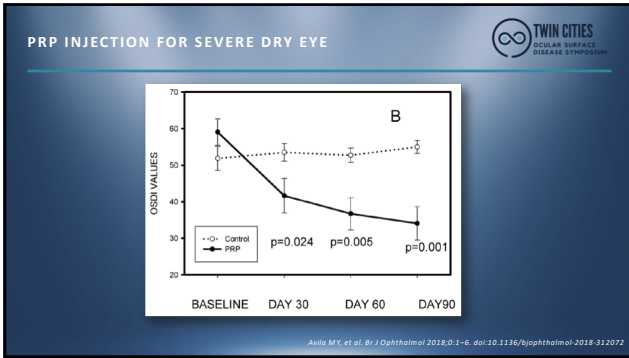
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DISEASE SYMPOSIUM

Avila MY, et al. Br J Ophthalmol 2018;0:1-6. doi:10.1136/bjophthalmol-2018-312072

PRP INJECTION FOR SEVERE DRY EYE

TWIN CITIES
OCULAR SURFACE
DISEASE SYMPOSIUM

Avila MY, et al. Br J Ophthalmol 2018;0:1-6. doi:10.1136/bjophthalmol-2018-312072



Abstract

Purpose: To retrospectively review results of intracanalicular meibomian gland probing with adjunctive intracanalicular microtube steroid injection for patients with Meibomian Gland Dysfunction manifested by more severe symptoms and/or signs including lid tenderness (LT) and excluding lid tenderness (DLT).

Methods: Charts were reviewed of patients status post MGP for MGD as previously described in Cornea 2010;29:1145-1152. Indications for probing include LT in 11 patients and DLT in 5 patients. Due to severity of signs/symptoms, an intracanalicular injection of steroid through sterile microtubes was performed immediately after probing. Severity of symptoms were evaluated pre and post procedure using VAS. Inclusion criteria required pre probing VAS greater than 25mm.

Results: For MGPs for LT, average age was 58.5 with range from 23-82. Sixteen lids of 9 patients had pre probe VAS of 44.2 ± 13.3 and had immediate reduction of 49% with further reduction of 67% at less than one month, 79% at one month, 94% at one to three months and 81% at 3-6 months. The average post VAS was reduced 66% at average follow up of 2.3 ± 3.1 months. For MGPs for DLT, average age was 67 with range from 59-74. Thirteen lids of 5 patients had pre probe VAS of 72.9 ± 14.4 with immediate reduction of 41% with further reduction of 53% at less than one month, 88% at one month, 69% at 2-3 months, and 40% at 3-6 months. The average post VAS was reduced 36.5% at average follow up of 4.23 ± 2.68 months. Symptoms which improved included lid pressure, burning and stinging and photophobia.

Conclusions: Meibomian gland probing with adjunctive intracanalicular microtube steroid injection has been successfully performed and tolerated without adverse sequelae. The addition of intracanalicular steroid to probing for these severe cases of MGD may have enabled clinical improvement to a peak of 94% relief from LT and 88% relief from DLT.

INTRACANALICULAR MGP WITH ADJUNCTIVE MICRO-TUBE STEROID INJECTION (MGPs) FOR MGD. ARVO 2011

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MGP DOCUMENTATION

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Lid: RU LU
Probe: 3mm 2mm 4mm

MG	Form	Soft	None	N.F	N.V	N.N	None	RP	EG	N.P	N.TG
1											
2											
3											
4											
5											
6											
7											
8											
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Lid: RL LU
Probe: 3mm 2mm 4mm

TSP: Total Glands Probed
 MR: Mechanical Resistance = Firm = Soft
 Form: (S) Good shows MR (S) Firm, Good, (S) Soft, (S) Unyielding (resistant)
 Soft: (S) Good shows non-Firm, non-Firm, easily yielding, with resistance
 None: (N) No resistance
 None: (N) Good present at the end of probe
 Firm: (F) (S) Good shows firm from probe
 None: (N) (S) Multiple pops from probe

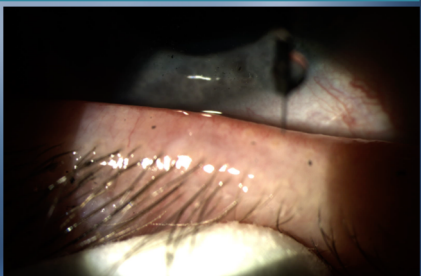
INTRADUCTAL MGP WITH ADJUNCTIVE MICROTUBE STEROID INJECTION (MGPs) FOR MGD

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8% Lidocaine gel
Contact lens
20 minutes of gel application
5mg Valium 15-20 minutes

Use the globe as a backstop

Focal symptoms:
Lid Tenderness
Lid Pressure
Lid Thickening
Lid Heaviness




CORNEAL NEOVASCULARIZATION

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Severe Visual Impairment

- Trauma
- Trachoma
- Pterygium-related
- Chemical Injury
- Microbial Keratitis
- HSV, HZO



CORNEAL NEOVASCULARIZATION

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- 1.4M patients in the US every year
- 12% of these cases are associated with decreased visual acuity

An important cause of severe visual impairment, associated with Corneal Blindness

Leading causes of Corneal Neovascularization:

- Infection
- Inflammation
 - Untreated Severe Ocular Rosacea
- Ischemia
 - Associated with Contact Lens Use
- Loss of limbal stem cell barrier
 - S/P Chemical Injury

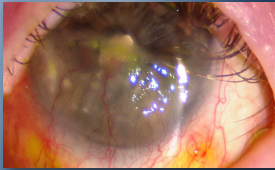
UNWANTED CONSEQUENCES

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Corneal Neovascularization leads to:

- Corneal Scar
- Corneal Edema
- Lipid deposition
- Persistent inflammation
- Circulating immune cells
- Reduces immune privilege

Graft survival of subsequent keratoplasty

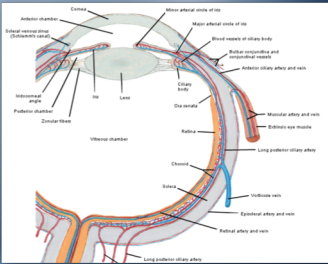


THE NORMAL CORNEA

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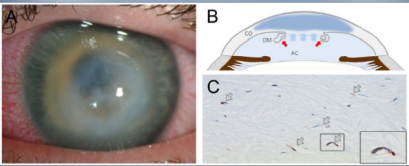
Avascular
Physiologically devoid of blood and lymphatic vessels
Ciliary arteries – branch of the ophthalmic
End in the pre-corneal plexus near the limbus

Transparent
Corneal clarity is a result of intricate balance between its cellular components



DISRUPTION OF HOMEOSTASIS


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Evidence of isolated corneal lymphangiogenesis in a patient with acute hydrops

After transplantation LYVE-1 positive lymphatic vessels without evidence of blood vessels.
Support egress of macrophages from the inflamed cornea

SHIFT OF BALANCE




Corneal Neovascularization occurs when:

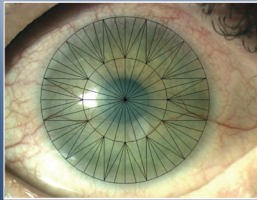
Balance between angiogenic and anti-angiogenic factors is tipped toward angiogenic molecules

Upregulation of Vascular Endothelial Growth Factor (VEGF)


- Neovascular AMD
- Diabetic retinopathy
- Macular edema
- Neovascular Glaucoma

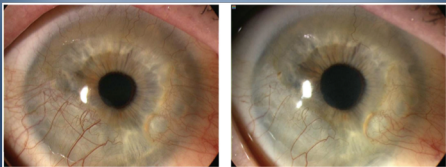
Treatment of CN with Anti-VEGF



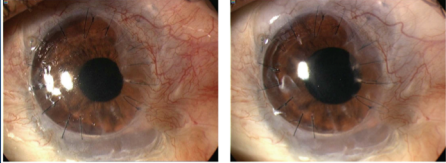


Treatment of CN with Anti-VEGF





Treatment of CN with Anti-VEGF



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CONCLUSIONS

- ✓ Important to review pertinent clinical studies
- ✓ Develop excellent relationship with local pharmacist
- ✓ Think of compounded medications early in treatment algorithm if no improvement with traditional options
- ✓ Be well-prepared to communicate indication and clinical benefit to patient
- ✓ Consider positive and negative impact of injections

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