The ESCRS Endophthalmitis Study

Prophylaxis of Endophthalmitis following Cataract Surgery with Phacoemulsification

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The ESCRS funded the study and has no financial interest in the materials or products used.

Santen GmbH provided the Levofloxacin, placebo drops and an unrestricted educational grant.

The Questions

- Do perioperative antibiotics prevent endophthalmitis?
- If so, how administered?
  - Intracameral injection
  - Intensive topical
  - Both
- What are the true rates of endophthalmitis?
- What are the risk factors?

The Design

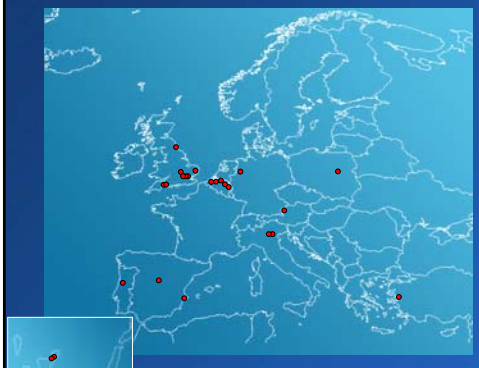
Group A - - Placebo vehicle drops x 5 No injection	Group B - + Placebo vehicle drops x 5 Intracameral injection of cefuroxime 1mg
Group C + - Levofloxacin drops 0.5% x 5 No injection	Group D + + Levofloxacin drops 0.5% x 5 Intracameral injection of cefuroxime 1mg

- All groups received povidone iodine preoperatively.
- All groups received topical levofloxacin postoperatively for six days.
- Note that Group A was a **minimum** treatment group not a **control** group.

The Design – Half Factorial

Group A - - Placebo vehicle drops x 5 No injection	Group B - + Placebo vehicle drops x 5 Intracameral injection of cefuroxime 1mg
Group C + - Levofloxacin drops 0.5% x 5 No injection	Group D + + Levofloxacin drops 0.5% x 5 Intracameral injection of cefuroxime 1mg

The Centres



Austria
Belgium
Germany
Italy
Poland
Portugal
Spain
Turkey
United Kingdom

The End Point

- **Infective Endophthalmitis**
  - Presumed (Clinical)
  - Proven (Vitreous / Anterior Chamber sample)
    - Positive Gram Stain
    - Positive Culture
    - Positive PCR (Polymerase Chain Reaction)

The Patients and Lenses

Optic Material	Number	Percentage
Acrylic	11 749	73.6%
Silicone	4 083	25.6%
Other	101	0.6%
None	38	0.2%
Total	**15 971**	**100.0%**

* All results based on Per Protocol dataset.

The Results

Group A - -	Group B - +
Placebo vehicle drops x 5	Placebo vehicle drops x 5
No injection	Intracameral injection of cefuroxime 1mg
13 presumed	3 presumed
9 proven 4 not proven	2 proven 1 not proven
Group C + -	**Group D + +**
Levofloxacin drops 0.5% x 5	Levofloxacin drops 0.5% x 5
No injection	Intracameral injection of cefuroxime 1mg
10 presumed	2 presumed
7 proven 3 not proven	1 proven 1 not proven

16 proven

3 proven

Observed Rates of Endophthalmitis

- **Minimum treatment - Group A**
  - Presumed 33 per 10 000 (95% confidence limits 15 to 50 per 10 000)
  - Proven 23 per 10 000 (95% confidence limits 8 to 37 per 10 000)
- **Cefuroxime treatment - Groups B & D**
  - Presumed 6 per 10 000 (95% confidence limits 1 to 12 per 10 000)
  - Proven 4 per 10 000 (95% confidence limits 0 to 8 per 10 000)

The Organisms

- **11** ***Staphylococcus***
- **8** ***Streptococcus***
- **2** ***Propionibacterium acnes***
- **1** ***Gemella haemolysans***
- **1** ***E. coli* / *Salmonella* / *Shigella* complex**

Principal Organism Distributions

Group A - -	Group B - +
Placebo vehicle drops x 5	Placebo vehicle drops x 5
No injection	Intracameral injection of cefuroxime 1mg
4 *Staphylococcus*	2 *Staphylococcus*
5 *Streptococcus*	0 *Streptococcus*
Group C + -	**Group D + +**
Levofloxacin drops 0.5% x 5	Levofloxacin drops 0.5% x 5
No injection	Intracameral injection of cefuroxime 1mg
4 *Staphylococcus*	1 *Staphylococcus*
3 *Streptococcus*	0 *Streptococcus*

8 Staph
8 Strep

3 Staph
0 Strep

Principal Organisms and Visual Outcomes

Staphylococcal Infections

- Final visual acuity range of 11 cases 20/20 - 20/80
- **No** study cases legally blind i.e. 20/200 or less

Streptococcal Infections

- Final visual acuity range of 8 cases 20/20 - No Light Perception
- 5 study cases legally blind
- **All** 5 due to *Streptococci*
- None of these 5 received Cefuroxime

Potential Risk Factors

Time Factors
Date of operation
Time operation started
Operation duration

Patient Data
Patient age
Patient gender
Diabetic

Clinician Data
Surgeon experience level
Surgeon age range
Surgeon gender

Surgical Procedure
Shared operation
Day case / overnight case
Left or right eye
First or second cataract
Anaesthesia procedure
Number of viscoelastic fluids
Size of incision
Position of incision
Site of incision
Position of IOL
Type of insertion
Wound closure type
Conjunctival closure type
Occlusion
No additional intraocular drugs
Any surgical complications

Environmental Factors
Theatre air change rate
Hospital ID
Country

Disease Data
Cataract causation
Cataract type

Prophylaxis Data
Treatment group
Cefuroxime injection vs none
Periop levofloxacin vs none

Surgical Materials
Viscoelastic fluid
Tubing system
Irrigation fluid
IOL lens type
IOL construction
IOL optic material
IOL optic hydro property
IOL haptic material
Power of IOL

Significant Risk Factors Presumed Endophthalmitis

Key Risk Factor	*p*-value	Odds Ratio *	95% confidence limits for Odds Ratio	
			Lower limit	Upper limit
# Cefuroxime Injection (present, absent)	0.002	4.8	1.8	12.5
IOL Optic Material (other, silicone)	0.002	3.3	1.2	7.1
Site of Incision (scleral tunnel, clear corneal)	0.021	5.8	1.3	25.4
# Levofloxacin peri-op drops (present, absent)	0.462	1.3	0.6	2.8

Study objective factor
* Odds ratios after adjustment for age, gender and other factors within regression model

Clear Corneal Incision

- **Centre effect? Possible, but unlikely**
- **Temporal / oblique / superior - no significant difference**
- **Injector / forceps - no significant difference**

Lens Material

Optic Material	Number	Endophthalmitis Cases	
		Non-Cefuroxime	Cefuroxime
Acrylic	11 749	12	3
Silicone	4 083	11	2

- Hydrophobic / hydrophilic – no significant difference
- One-piece / three-piece – no significant difference

The Paradox

- The antithesis of a clinical trial
- Result, but no drug
  - Cefuroxime not licensed for intra-ocular use
  - Cefuroxime not commercially available for intra-ocular use
- The risks of "kitchen" pharmacy
  - Dilution errors
  - Diluent errors
  - TASS induction
  - Contamination e.g. *Pseudomonas*
- Appeal to industry
  - A single sterile unit dose

The Implications

- If Cefuroxime was a new drug….?
- Preparing your own Cefuroxime:
  - Hospital Pharmacy - Sterile
  - Kitchen Pharmacy - Not ideal, better than denial
- If Cefuroxime is good:
  - Is vancomycin, moxifloxacin or gatifloxacin better?
  - Safety studies, clinical trials
  - Topical versus Intracameral
  - Ethics and Futility

The Evidence Base

- Over 400 000 Swedish patients show efficacy and safety of Intracameral Cefuroxime
- The ESCRS Study has proven it