

Successful use of intravitreal and systemic colistin in treating multidrug resistant *Pseudomonas aeruginosa* post-operative endophthalmitis

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We report a case series of post-operative endophthalmitis due to *Pseudomonas aeruginosa*. A total of 8 patients operated for cataract, were referred to our facility with acute onset of decreased vision 1-2 days following surgery. All patients had clinical evidence of acute exogenous endophthalmitis with severe anterior chamber exudative reaction. Ocular samples (aqueous aspirate and vitreous tap) for microbiology were taken from

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all eyes. Microbiology from all revealed *P. aeruginosa* which was resistant to all antibiotics except colistin. With prompt and accurate microbiological support it was possible to control the infection in all the eyes with the use of colistin intravitreally and intravenously which to the best of our knowledge, has been never reported. Intravitreal injection of colistin could be an option effective in the management of multi-drug-resistant endophthalmitis caused by Gram-negative bacteria.

Key words: Cataract, colistin, endophthalmitis, *Pseudomonas aeruginosa*

Endophthalmitis is an ocular inflammation resulting from the introduction of an infectious agent into the posterior segment of the eye. Post-operative endophthalmitis has been reported following nearly every type of ocular surgery. Endophthalmitis following cataract surgery is the commonest with incidence of approximately 0.1-0.3% respectively.^[1] We present a case series of multidrug resistant (MDR) post cataract surgery pseudomonas endophthalmitis, treated successfully with intravitreal and intravenous (IV) colistin injection.

Case Report

Eight patients four female and four male, operated for cataract surgery by phacoemulsification, were referred to our facility with acute onset of pain, redness, sticky discharge, decreased vision. At admission, all patients underwent slit-lamp examination, fundus evaluation and B-scan Ultrasonography. There were no ocular risk factors, one patient had diabetes mellitus and was on tablet daonil.

At presentation lid edema, gross corneal edema with severe anterior chamber exudative reaction was seen in three patients and remaining five patients had corneal edema with streak hypopyon and wound integrity was maintained in all patients. Two patients had only perception of light with accurate projection, three had hand movements close to face and two patients had visual acuity (VA) counting finger at one meter distance. Fundus examination was difficult due to severe corneal edema in all patients. Ultrasound demonstrated signs of severe vitreous inflammation and chorioretinal thickening.

Vitrectomy was performed in all patients within first 36 h of presentation. Aqueous and vitreous samples were sent for culture and antibiotic sensitivity. In two patients retinal detachment (RD) was found hence, vitrectomy with intraocular lens removal with silicon oil injection was done and in one patient because of necrotic nature of the peripheral retina vitrectomy with silicon oil injection was used as prophylaxis against RD and possible ocular hypotony. In all patients intravitreal injection vancomycin (1 mg/0.1 ml) + ceftazidime (2.25 mg/0.1 ml) + dexamethasone (4 mg/0.1 ml) were given intra-operatively. All vitreous and aqueous samples revealed Gram-negative bacilli on smear and similar growth on culture and fungal filaments were absent on culture. The organism was identified as *Pseudomonas aeruginosa*. Susceptibility testing by Kirby Bauer Disc diffusion method as per latest Clinical and Laboratory Standards Institute guidelines 2008 revealed sensitivity patterns in all samples. It was resistant to all antibiotics and sensitive to colistin only.

Clinically, following vitrectomy, desired favorable response was lacking and there was worsening of signs and symptoms, so based on antibiotic sensitivity report intravitreal injection

colistin (0.1 mg/0.1 ml) was given in all patients. It was repeated after 48 h depending on clinical response. Topical 10 mg/ml colistin was started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice a day in all eyes. IV injection of colistin was given in all eight patients 1 million IU 12 hourly for 5 days along with IV imipenem 1 g 12 hourly. Duration of hospitalization was 5-15 days depending on the response to treatment. The visual outcome and follow-up of our patients are given in Table 1. At 4 weeks after treatment with colistin one patient was found to have recurrent RD with no perception of light and seven patients regained VA 6/60 or better. We looked for any gross diminution of vision, gross optic atrophy and any signs of macular infarction to rule out any obvious drug related toxicity. Hence, resolution of infection was achieved in all eyes with salvage of the globe in all cases [Fig. 1].

Discussion

P. aeruginosa is commonest Gram-negative organism causing endophthalmitis following cataract surgery. Vitreous tap for smear and culture followed by immediate intravitreal administration of broad spectrum antibiotic and vitrectomy is the current standard of treatment.^[2]

Based on the culture and antibiotic sensitivity reports, we used colistin intravenously and intravitreally for treatment of endophthalmitis due to multidrug-resistant Gram-negative bacteria, which was safe and effective.

Colistin belongs to polymyxins, a group of polypeptide antibiotics which includes five different chemical compounds (polymyxins A, B, C, D and E). Colistin binds to Gram-negative bacterial cell membrane phospholipids, producing a disruptive physiochemical effect, which leads to the cell membrane permeability changes and ultimately cell death.^[3] Most Gram-negative microorganisms are susceptible to colistin, including multidrug-resistant *Acinetobacter baumannii* and *P. aeruginosa* strains.^[4] Two forms of colistin are commercially available, colistin sulfate and colistimethate sodium (also called colistin methanesulfate, pentasodium colistimethanesulfate and colistin sulfonylemethate). The target of antimicrobial activity of colistin is a bacterial cell membrane. The initial association of colistin with bacterial membrane

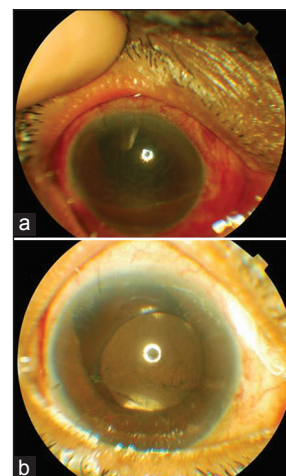


Figure 1: (a) Right eye with redness, corneal oedema, hypopyon. (b) Resolution of infection after vitrectomy and intravitreal colistin injection

Table 1: BCVA on presentation and at 1 month and treatment

Case no.	Age/gender	BCVA on admission	Follow-up period	Final visual outcome	Treatment given			
					Surgery	Intravitreal drugs	Intravenous drugs	Topical drugs
1	60/male	PLPR+	4 month	20/200	Vitreotomy with silicon oil injection on 2nd day of admission	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 2 injections of colistin (0.1 mg/0.1 ml) (1 intra-operative+1 after 48 h)	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily
2	60/female	PLPR+	3 month	No PL	Vitreotomy with IOL removal+silicon oil on day 1	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 2 injections of colistin (0.1 mg/0.1 ml) (1 intra-operative+1 after 48 h)	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulphate 1% twice daily
3	51/female	HMCF	5 month	20/200	Vitreotomy with IOL removal+silicon oil on day 1	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 1 injection of colistin (0.1 mg/0.1 ml) intra-operative	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily
4	55/female	FC 1 mt	2 month	20/30	Vitreotomy on day 2	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 1 injection of colistin (0.1 mg/0.1 ml) intra-operative	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily
5	51/female	20/200	1 month	20/60	Vitreotomy on day 2	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 1 injection of colistin (0.1 mg/0.1 ml) intra-operative	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily
6	48/male	HMCF	2 month	20/200	Vitreotomy on day 1	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 1 injection of colistin (0.1 mg/0.1 ml) intra-operative	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily
7	55/male	20/200	3 month	20/120	Vitreotomy on day 2	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 1 injection of colistin (0.1 mg/0.1 ml) intra-operative	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 hourly with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily
8	45/male	20/200	1 month	20/120	Vitreotomy on day 2	Vancomycin (1 mg/0.1 ml)+cefazidime (2.25 mg/0.1 ml)+dexamethasone (4 mg/0.1 ml) intra-operative 1 injection of colistin (0.1 mg/0.1 ml) intra-operative	Colistin 1 million IU 12 hourly for 5 days+imipenem 1 g 12 hourly	10 mg/ml colistin started 1 h with prednisolone acetate (1%) 1 hourly and atropine sulfate 1% twice daily

PLPR: Perception of light and projection of rays, HMCF: Hand movements close to face, FC: Finger counting, RD: Retinal detachment, IOL: Intraocular lens, BCVA: Best corrected visual acuity, PL: Perception of light

occurs through electrostatic interactions between the cationic polypeptide (colistin) and anionic lipopolysaccharide (LPS) molecules in the outer membrane of the Gram-negative bacteria, leading to derangement of the cell membrane.^[5]

The endotoxin of Gram-negative bacteria is the lipid A portion of LPS molecules and colistin binds and neutralizes LPS.^[6] Polymyxin E (colistin), only polymyxin B has been used in clinical practice in several countries. Polymyxin B has the same mechanism of action and resistance as does colistin. Colistin sulphate has greater activity than polymyxin B against *P. Aeruginosa*.^[7] The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 h and around 80% in 24 h. Because colistimethate sodium is largely excreted in the urine, dose reduction is required in renal impairment to prevent accumulation. After IV administration to healthy adults, the elimination half-life is around 1.5 h. In cystic fibrosis study patients were given a single 30 min IV infusion, the elimination 1/2 life was 3.4 ± 1.4 h.^[8]

Since colistin belongs to polymyxin group of a drug, which includes aminoglycoside group of drug we tried to use recommended molar equivalent dose of this intravitreal drugs. So far there is no reference in animal models. There is no known minimal inhibitory concentration for ocular use, it is known for IV use only.

Reconstitution for parenteral administration

The normal adult dose of colistin 2 million units should be dissolved in 10-50 ml of 0.9% sodium chloride IV infusion or sterile water for injections to form a clear solution. The solution is for single use only and any remaining solution should be discarded.

Intravitreal dose was - 0.1 mg/0.1 ml (1000 IU/0.1 ml) and IV dose was 2.5-5 mg/kg daily in 2-4 doses.^[9]

In our series, we used a combination of colistin with an anti-pseudomonal agent imipenem. Colistin acts by increasing the permeability of the cell membrane and thus could act synergistically with other antimicrobial agents by facilitating their entrance into the bacterial wall.^[10] Toxicity, specifically nephrotoxicity is a major concern when colistin is administered, mainly because of some previous reports. We did not observe any systemic complications secondary to use of colistin in our patients.

We used colistin intravitreally as there is no documented contraindication for ocular use of this drug as the polymyxin group of drug mainly B group is used routinely for eye. At the same time nowhere in the literature it has been used intravitreally in endophthalmitis.

Conclusion

Intravenous and intravitreal colistin constitutes a relatively safe and effective therapeutic intervention in cases of endophthalmitis due to MDR Gram-negative bacteria like *P. aeruginosa*. Gram-negative bacteria pseudomonas are the

most common MDR organism, MDR is new emerging problem.

Because colistin was introduced into clinical practice over 50 years ago, it was never subject to the regulations that modern drugs are subject to and therefore there is no standardized dosing of colistin and no detailed trials on pharmacology or pharmacokinetics, the optimal dosing of colistin for most infection like endophthalmitis is therefore unknown.

In the battle against rapidly emerging bacterial resistance we can no longer rely entirely on the discovery of new antibiotics, we must also pursue rational approaches to the use of older antibiotics such as colistin for which further clinical trials are essential. Use of these new alternative groups of drugs for the management of these isolated cases will further help us to prove their efficacy and safety.

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