• Clinical Research •

Complications of dexamethasone implants: risk factors, prevention, and clinical management

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Abstract

● **AIM:** To evaluate major complications after intravitreal injection of dexamethasone implants (Ozurdex) and their clinical management.

● **METHODS:** In a retrospective observational study between 2014 and 2016 at two university hospitals, we reviewed the clinical records of 1241 consecutive macular edema patients treated with the dexamethasone implant, and separated severe adverse events in the injection procedure from those that were post-injection complications. We evaluated the cause and the outcomes in each case.

● **RESULTS:** In twenty-one procedures (1.69%) we noticed significant complications during and after intravitreal injection of the dexamethasone implant. Complications related to the injection procedure were in one case, that a second implant was injected by mistake in the same eye on the same day. In another case, the implant lodged in the sclera during retraction of the injector needle. Leaking scleral tunnel at the injection site led to hypotony in another case. There were 10 cases of post-injection displacement of the implant into the anterior chamber and one case with a migrated and trapped device between the intraocular lens and an artificial iris. Displacement typically occurred in patients with preexisting risk factors: eyes with complicated intraocular lens implantation, iris reconstruction or iris defects or pseudophakic eyes after vitrectomy were prone to develop this complication. Displacement led to secondary corneal decompensation with pseudohypopyon. One case developed an endophthalmitis, and we observed four cases of retinal detachment. Two eyes presented with long-lasting hypotony due to ciliary insufficiency.

● **CONCLUSION:** Treatment with the dexamethasone implant may cause various expected or unexpected complications that may have serious consequences for the patient and require further surgery. To reduce complications, clinicians should evaluate certain risk factors before scheduling patients for dexamethasone implant treatment and use proper injection techniques.

● **KEYWORDS:** intravitreal implants; dexamethasone implants; Ozurdex; intravitreal injection; slow release drug
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INTRODUCTION

The intravitreal sustained-release, biodegradable, dexamethasone implant (Ozurdex®; Allergan, Inc., Irvine, California, USA) is used for the treatment of macular edema (ME) arising from retinal vein occlusions, diabetic retinopathy, uveitis and off-label also from Irvine-Gass syndrome[1]. The cylindrical implant measures 6.0 mm in length and 0.46 mm in diameter. Common complications like conjunctival or vitreous hemorrhage, cataract progression and increased intraocular pressure (IOP) are already reported[2]. However, the implant itself and the injection procedure can provoke adverse events. We report on ocular complications related to the injection procedure as well as post-injection complications which we found are associated with certain risk conditions that were not previously identified and reported. We present a relatively high number of varied cases and, we describe a unique case of two concomitant dexamethasone implants in the same eye.

SUBJECTS AND METHODS

Ethical Approval The study was conducted according to the tenets of the Declaration of Helsinki and approval by the Institutional Review Board. Informed consent from all participants was obtained.

At two German university hospitals, we retrospectively reviewed the clinical records of 1241 consecutive patients treated with intravitreal dexamethasone implant from 2014 to 2016. We evaluated adverse events associated with the

therapy and report in detail each case where the complication has not been previously described or where we considered it was a case to be highlighted. Some patients had been treated elsewhere and were referred to the clinics after the complication had occurred. Best-corrected visual acuity (BCVA), IOP, ophthalmic history and ocular examination were documented. We established the clinical findings of ocular examination for each case, risk factors and treatment strategies. The adverse events were divided into group 1 (complications related to the injection procedure) and group 2 (complications after the injection procedure). We excluded complications or side effects such as conjunctival or vitreous bleeding, cataract progression or IOP. Patients with high myopia, previous retinal detachment, or ocular surgeries, were also excluded.

RESULTS

From 2014 to 2016, twenty-one different serious complications associated with the dexamethasone implant were included in the study. We report in detail each case where the complication has not been previously described or where we considered it as a case to be highlighted (Tables 1, 2). The mean patient age of the patients was 71.6y (range 20-89y). Thus, we report a complication rate of 1.69%. Three complications were related to the injection procedure (Group 1; cases 1-3), and fifteen cases had post-injection complications (Group 2; cases 4-18). There was one case with endophthalmitis (rate 0.08%). The most important and interesting cases were described in detail. In the group of injection-related adverse events, we had three cases (cases 1-3).

Case 1 was a 20-year-old male patient with chronic panuveitis, ME and secondary glaucoma. He was planned to be treated with bilateral intravitreal injection of a dexamethasone implant on the same day in another clinic. Ten days later, he was referred to our university hospital. The patient asserted that he had no immediate post-injection complaints and that he had undergone uneventful bilateral dexamethasone implants before. BCVA was 20/100 in his right and 20/40 in his left eye; with normal IOP. Surprisingly, on fundoscopy, two dexamethasone implants were observed in the right eye, and no implant was visible in the left eye (Figure 1A). Optical coherence tomography did not show ME in either eye. Hereafter, the patient declined further consultations. Three months later, the patient complained of blurred vision and pain in his right eye. As self-medication, he had used systemic acetazolamide, topical dorzolamide and latanoprost. BCVA had not changed, in fundoscopy the dexamethasone implants were no longer visible in the right eye, IOP was 28 mm Hg in the right and 29 mm Hg in the left eye. He was recommended for further glaucoma surgery, and trabeculectomy was performed on both eyes successively. In the follow-up visits, up to four

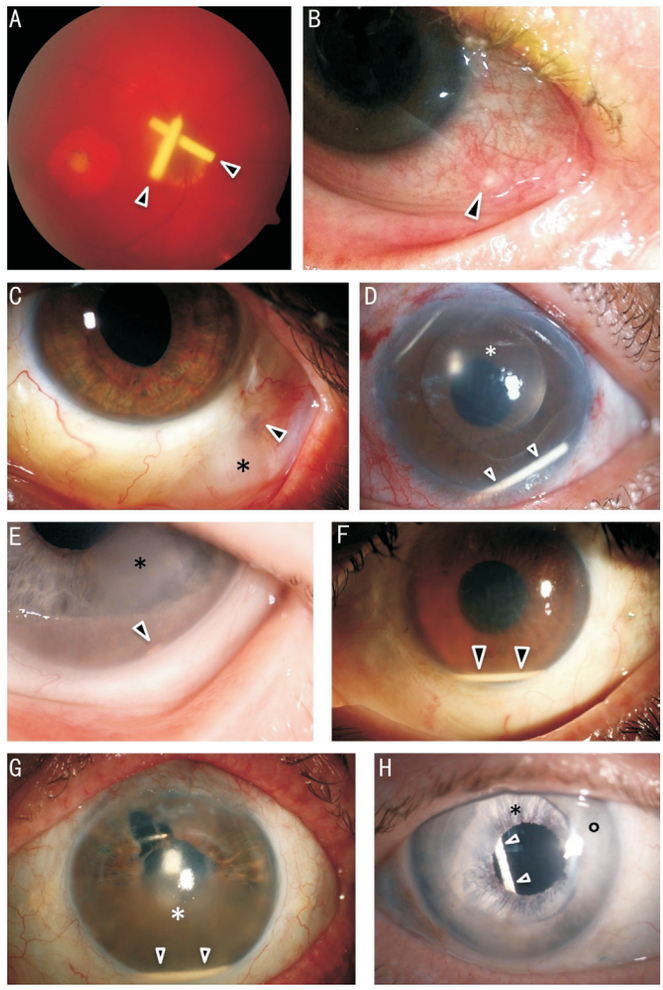

Figure 1 Complications related to and after the dexamethasone injection procedure A: Fundus photography of a patient who had been treated accidentally with two unilateral intravitreal injections of a dexamethasone implant for macular edema on the same day (case 1). The cross-shaped implants are located in the central vitreous body (arrowheads); B: The anterior segment photography shows a small end of the dexamethasone implant (arrowhead) that was stuck in the sclera covered by conjunctiva (case 2); C: Seidel positive wound leakage through the injection site (arrowhead) with consecutive chemosis and filtering bleb (asterisk) (case 3); D: The photo shows the anterior chamber lens (asterisk), the implant in the anterior chamber (arrowheads) with corneal edema and Descemet's folds (case 13). Surgical removal of the implant in this case is shown in Figure 2; E: A small fragment of the implant is visible in the anterior chamber (arrowhead). Corneal edema (asterisk) and endothelial precipitates can also be seen (case 10); F: Dexamethasone implant in the anterior chamber (arrowheads) with incipient corneal decompensation including Descemet's folds and corneal edema (case 6); G: Case of a pseudohypopyon. The eye shows extensive corneal edema (asterisk). The implant in the anterior chamber (arrowheads) can hardly be differentiated from a hypopyon. Patient's ophthalmic history reveals a complicated cataract surgery with a secondary scleral fixed lens implantation and iris suture. At the 11 o'clock position the lens haptic and the iris defect are visible (case 7); H: The implant (arrowheads) is trapped between the artificial iris (asterisk) and the IOL (case 15). The patient was treated due to chronic macular edema. The residual iris can also be seen in the photo (ring).

Table 1 Overview of patient's characteristics with complications after treatment with Ozurdex®

Case	Age/sex	Ophthalmic history	AE	Time after IVI till complaints/ presentation	VA before IVI & after AE	Findings of ophthalmic examination at first presentation	Therapeutic management	VA after therapy	Features in course of disease
Complications related to the injection procedure									
1	20/M	Glaucoma Cyclophotocoagulation	Inadvertent unilateral injection of two implants	3mo	20/100 & 20/100	Fundus with two implants in same eye. IOP 29 mm Hg	Trabeculectomy	20/125	-
2	80/M	-	Scleral stuck of implant	1d	20/32 & 20/32	Small end of the implant being stuck in the sclera	Implant pushed inwardly from outside with a forceps	20/32	-
3	48/F	-PPV -R/L one Ozurdex without any complications	Seidel positive wound leakage	5d	20/100	Seidel positive wound leakage. No choroidal detachment.	Intraoperative scleral tunnel suturing	20/100	-
Post-injection complications									
4	49/M	-Uveitis -IOL -6 IVI of Ozurdex without complications	Hypotony	6wk	5/100 & 5/100	IOP 4 mm Hg, else normal	IOP recovered after 2-3mo	5/100	See case 5, one year later new event similar to this complication
5	49/M	-Uveitis -IOL -6 IVI of Ozurdex without complications -1 IVI of Ozurdex with hypotony (see case 14) -another 1 IVI of Ozurdex without complications	Persistent hypotony	3mo	Hand motion & hand motion	IOP 4 mm Hg, else normal	Wait and see	Hand motion	IOP didn't recover since an observation time of over 1y.
6	58/F	Scleral fixated IOL	Implant in the AC	4d	20/160 & 1/15	Implant in the AC, DCF, corneal edema	Surgical removal was prepared, but intraoperative implant was repositioned in the vitreous. Pilocarpine and prohibition of supine position.	1/15 3	2d later further wandering of implant in the AC. Therapy with pilocarpine 1% eye drops every 10min till surgery. Viscoat injection into the AC and implant removal from the AC with a forceps. 1y later re-injection of Ozurdex with wandering into the AC. VA counting fingers, corneal edema, DCF ++, fundus red
7	74/M	-Surgical removal of vitreous prolapse into the AC after cataract surgery -PPV and secondary, scleral fixated lens implantation due to lens subluxation. Complicated surgery with iris suture	Implant in the AC appears as pseudohypopyon	1mo	20/63 & 1/20	ECC R 1759 and L 2056, implant in the AC L. Extensive corneal edema and corneal decompensation.	Initially, patient was treated with local antibiotic eye drops as implant was not recognized and appeared as hypopyon. Three more days later identification and surgical removal of implant from the AC with a forceps	20/125	6mo later penetrating keratoplasty due to corneal decompensation with stromal scars and VA = 1/10. 10mo after penetrating keratoplasty VA = 1/50.
8	76/F	IOL repositioning + PPV after IOL dislocation and capsule rupture; sulcus implanted lens; iris defect	Implant in the AC appears as pseudohypopyon	3wk	20/32 & hand motion	Implant in the AC, DCF++, corneal edema and corneal decompensation. Iris defects inferior.	Initially, patient was referred to us with hypopyon. Identification and surgical removal of implant from the AC with a forceps. Complicated surgery due to intraoperative fragmentation of implant into many pieces.	CF	-
9	41/M	-PPV due to ERM -PPV+silicon oil+scleral buckling due to retinal detachment -secondary IOL implantation (Verisyse®) due to lens subluxation -Marfan syndrome	Implant in the AC	2wk	20/80 & CF	Corneal edema and bullae, DCF++, pigmented endothelial precipitates, iris defects, inferior YAG-IE, IOL subluxation nasally, implant in the AC.	Implant removal from the AC with a forceps	CF	-

Table 1 Overview of patient's characteristics with complications after treatment with Ozurdex® (continued)

Case	Age/sex	Ophthalmic history	AE	Time after IVI till complaints/ presentation	VA before IVI & after AE	Findings of ophthalmic examination at first presentation	Therapeutic management	VA after therapy	Features in course of disease
10	89/M	-PPV due to retinal detachment -IOL with slight dislocation	Implant in the AC	9d	5/100 & CF	Implant in the AC, DCF++, corneal edema and corneal decompensation. IOL slightly dislocated nasally. Normotension	Implant removal from the AC with a forceps	5/100	1mo later corneal edema resolved
11	76/F	-PPV + silicon oil removal, initial PPV due to retinal detachment -YAG-IE superior -AC-IOL	Implant in the AC	2wk	NA & 1/100	Implant in the AC, DCF++, corneal edema. AC IOL. IOP 22 mm Hg	Positional change maneuvers for reposition failed. Implant removal from the AC with a forceps	1/100	-
12	83/F	-PPV+ secondary IOL implantation (Verisyse®) after complicated phaco with intraoperative lens drop	Implant fragments in the AC	NA	N/A & hand motion	Sclero-corneal cross seam superior, corneal edema, endothelial precipitates, implant fragments in the AC	Removal of implant fragments from the AC with a forceps	1/25	After 12 further days patient presented again with 3 further implant fragments in the AC. Removal of implant fragments from the AC with a forceps was performed again.
13	63/F	IOL-exchange (AC IOL), IE, several PPVs due to ERM and vitreous bleeding	Implant in the AC and high IOP	8d	20/200 & light perception	Corneal edema, DCF++, AC cells+, IOP 38 mm Hg, fundus red	Implant removal from the AC with a forceps	0.05	-
14	56/F	Artificial iris + KPL	Implant in the AC	NA	NA	-	Implant removal from the AC	10/100	After 4wk due to worsening of macular edema scleral suturing of a new Ozurdex implant
15	54/F	Artificial iris + PPV + scleral-fixated IOL + KPL due to penetrating trauma many years ago	Implant between artificial iris and IOL	3mo	20/63 & 1/35	-	Implant spontaneously repositioned in the vitreous.	20/100	See case 13, one year later new event independent from adversity No.12
16	54/F	Artificial iris + PPV + scleral-fixated IOL + KPL due to penetrating trauma many years ago	Implant in the iridocorneal angle	3mo	NA	Almost dissolved implant in the iridocorneal angle. Light corneal opacity.	Observation due to almost dissolved implant.	NA	-
17	77/M	Diabetic retinopathy	Purulent endophthalmitis	N/A	N/A & hand motion	Conjunctiva with hyperemia, cornea with DCF, AC cells, reduced insight on the fundus, white retinal infiltrates, sclerotic vessels	-PPV +intravitreal antibiotic +vitreous aspirate +abrasio -local and systemic antibiotics	CF	-3mo ERM with SRF, PVR and retinal tears. Treatment with ppv + peeling + silicon oil + cryo -1 further month later rubeosis iridis and high IOP (26 mm Hg). Treatment with PALC and antiglaucomatous eye drops
18	31/M, 61/M, 73/F, 76/F	All 4 patients without pre-surgeries or high myopia	Retinal detachment	2mo, 2mo, 3mo, 7mo	20/63 & 1/15; N/A & N/A 20/40 & hand motion NA & NA	Retinal detachment	PPV	20/32; 20/40; 1/25; 20/100	-

Focus is on kind of complication and therapeutic management. AE: Adverse event; DCF: Descemet's folds; AC: Anterior chamber; ECC: Endothelial cell count; ERM: Epiretinal membrane; f: Female; IE: Iridectomy; IOL: Intraocular lens; IOP: Intraocular pressure; IVI: Intravitreal injection; KPL: Keratoplasty; L: Left; m: Male; N/A: Not applicable; PPV: Pars plana vitrectomy; PALC: Peripheral argon laser coagulation; PVR: Proliferative vitreoretinopathy; R: Right; SRF: Sub-retinal fluid; VA: Visual acuity; CF: Counting fingers.

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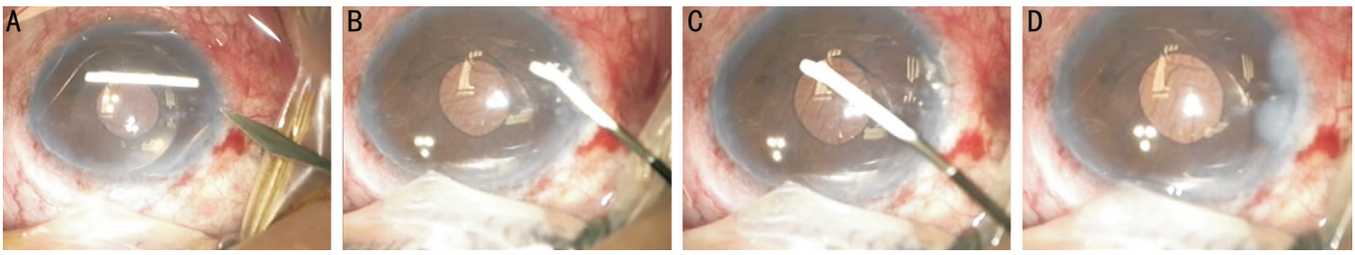

Figure 2 Removal of a dexamethasone implant from the anterior chamber (Case 13, the same patient as in Figure 1D) The implant led to corneal opacity, Descemet's folds and IOP increase. A paracentesis is performed (A), injection of OVD, grasping the implant with a 23G forceps (B), explantation through the paracentesis (C) and hydration of the wound (D).

months after surgery BCVA was 20/125 in the right and 20/63 in the left eye, while the IOP was within normal limits (around 16 mm Hg) without any further complications. ME did not reappear.

Case 2 was an 80-year-old man referred to our clinic after receiving the dexamethasone implant the day before. At presentation, he complained of pain in the treated eye. The BCVA at 20/32 was stable compared to the previous day and the IOP was normal. Clinical examination revealed the implant stuck in the sclera with a protruding end visible in the conjunctiva (Figure 1B, arrowhead). As most of the implant was already in the vitreous cavity, using a sterile field and topical anesthesia, we successfully pushed the implant back into the vitreous with forceps. At follow-up visits up to three months, BCVA and the IOP remained stable, and the implant remained intravitreally located.

Case 3: A 48-year-old female was previously vitrectomized and treated once with the dexamethasone implant without any complication. Six days after the second injections she presented at our clinic with a positive wound leakage at the injection site (Figure 1C, arrowhead) and partial fluid drainage under the conjunctiva (Figure 1C, asterisk). An intraoperative scleral tunnel suturing was performed successfully.

In the group of post-injection adverse events, we had fifteen cases. They can be subdivided in 1) general implant displacement (including migration of the implant from the vitreous cavity into the anterior chamber); 2) miscellaneous-including persistent hypotony, endophthalmitis and retinal detachment (Cases 4, 5 and 17, 18):

The most frequent event was a general displacement of the dexamethasone implant (Cases 6-16) including one entrapment of the implant between an artificial iris and intraocular lens (IOL; Case 15). Several different conditions were associated with this process of migration: scleral fixated IOL, iris-fixated IOL, sulcus implanted lens, lens subluxation due to Marfan syndrome, presence of an anterior chamber IOL (Figure 1D), capsule defect, iris defects or implant fragmentation (Figure 1E, arrowhead). Migration of the implant into the anterior chamber can lead to irreversible endothelial damage with corneal decompensation, and it can produce elevated IOP; where the implant must be removed (Figure 2).

Cases 4 and 5 (complications in the same patient): An extraordinary case of hypotony occurred irrespective of the injection procedure: a 49-year-old male was treated with the dexamethasone implant six times without any complications until he developed hypotony (4 mm Hg) after the last injection (case 4). Further ophthalmic examination showed normal anterior and posterior segment without any wound leakage at the injection site. Diaphanoscopy and ultrasound could exclude ciliary body dialysis. The patient history had recorded a ciliary body insufficiency. IOP recovered spontaneously approximately two months later without any therapy. After another injection of the dexamethasone implant, the same patient once again showed persistent hypotony, which continued at least one year after the injection (mentioned as Case 5).

Case 6: A 58-year-old female patient presented with a complaint of blurred vision. Four days prior, outside Germany, she had a dexamethasone implant injected in her left eye to treat diabetic ME. We noted a scleral-fixated IOL implanted in the affected eye. Her BCVA was 1/15, and the IOP was 17 mm Hg. Examination revealed Descemet's folds, corneal edema, and the dexamethasone implant visible in the lower anterior chamber (Figure 1F). Given the presence of this incipient corneal decompensation, we decided to remove the implant from the anterior chamber under local anesthesia. During surgery, the dexamethasone implant was not visible in the anterior segment. With the patient adopting a supine position, it had repositioned spontaneously in the vitreous. We prescribed pilocarpine 2% eye drops and advised her to avoid the prone position as far as possible. Two days later she presented with the same problem. Again, we attempted to remove it from the anterior chamber, but this time, we were prepared for vitrectomy, knowing the high risk of recurrent implant luxation. The patient received topical pilocarpine 2% every 10min for one hour before surgery. Viscoat® was injected into the anterior chamber to prevent descent of the dexamethasone implant into the posterior segment. Thus,

the implant was successfully removed with forceps from the anterior chamber. One year later, an ophthalmologist from another clinic, applied a new dexamethasone implant. Two days later, the patient was referred to us with the implant in the anterior chamber. We removed it using the procedure we had used before.

Cases 7 and 8: Two other patients with a dislocated implant in the anterior chamber were misdiagnosed as uveitis with hypopyon. Initially, the extensive corneal edema (Figure 1G, asterisk) prevented identification of the implant (Figure 1G, arrowheads). This pseudo-hypopyon was realized later in the follow-up visits, and the dexamethasone implant was explanted. One of these patients developed an irreversible corneal decompensation with stromal scarring culminating in penetrating keratoplasty half a year later.

Other adverse events were also associated with implant motion (Cases 9 to 16): A 63-year-old female underwent several vitrectomies, lens exchange with anterior chamber lens and iridectomy (Case 13). The dexamethasone implant moved into the anterior chamber. Patient developed corneal edema and Descemet's folds. Surgical removal of the implant from the anterior chamber is shown in Figure 2. In another case, a 54-year-old female with a history of numerous ophthalmic surgeries following an ocular trauma many years prior, including implantation of a scleral-fixated artificial iris and IOL. She received a dexamethasone implant to treat chronic ME and presented later with the implant trapped between the artificial iris (Figure 1H, asterisk) and the scleral-fixated IOL (Case 15; Figure 1H, arrowheads). Later she was retreated with the dexamethasone-implant and, this time, the implant was found in the iridocorneal angle (Case 16). On both occasions the implant was surgically removed.

The last two cases (Cases 17 and 18) were one with a postoperative endophthalmitis and another with a retinal detachment following the dexamethasone implantation.

DISCUSSION

The common complications of intravitreal injection of the dexamethasone implant—such as a rise in IOP, cataract formation or subconjunctival hemorrhage—are all in most cases transient complications and manageable. We present the first account of varied and extraordinary complications, which result under certain conditions from either the injection procedure or appear as post-injection adverse reactions, and we describe the clinical management of these cases.

In general, if patients have a high risk for complications, the necessity of strict ophthalmic follow-up examinations should be clarified with the patient. Furthermore, the surgeon should consider the patient's indication for intraocular steroids for patients with risk factors like glaucoma, unstable iris-lens-diaphragm and reduced compliance.

From all of these observations, we are able to draw conclusions and make recommendations on future clinical conduct: We describe for the first time an inadvertent unilateral injection of two implants (Case 1). The reason for this event could be most likely medical negligence, but also insufficient communication with the patient: due to linguistic barriers, dementia, or general anesthesia. It is not clear whether this patient developed an elevated IOP from having two implants or would he have had it if he had just one. Furthermore, we do not know if two implants in one eye would have a stronger effect on resolving the ME. Fortunately, we did not observe any functional or morphological damage and visual acuity remained stable. From observation of this case, we can suggest a recommendation that the injection procedure for bilateral interventions should always be made in a fixed order of approach-for example, always beginning with the right eye first and then going on to the second eye to make another injection.

Case 2 scleral protrusion of the implant, a repositioning with further surgery could prove mandatory, depending on the position of the implant. An implant lodged in the sclera is easy to reposition with a forceps or another instrument. In general, when carefully performed, a subretinal or intralenticular displacement and thus damage to adjacent ocular structures or a fragmentation of the implant can be avoided. Nevertheless, in cases of intralenticular injection of the implant, the patient should be treated with cataract surgery[3-4]. This case underlines the importance of an appropriate injection technique. Care must be taken to use the delivery system properly. The variable injection force can hypothetically lead to an erroneously positioning of the implant in the injection site in the sclera as well as to retinal damage in the direction of the implant delivery.

Post-injection hypotony (Cases 4 and 5) is quite difficult to treat if the reason is not a leaking injection site like in Case 3. The implant itself already gives steroid-treatment. A ciliary detachment can be diagnosed by ultrasound and can be treated by surgical reattachment or at least by waiting. This case shows that routine examinations after the dexamethasone implant procedure are recommended.

There are already reports in the literature of implant displacement into the anterior chamber (Cases 6-16)[8-9,12]. At first, ophthalmologists should be aware of risk patients for this adverse event. It is not always obvious, in which eyes the implant could tend to luxate, for example in Case 15 it was trapped between the artificial iris and IOL though in apparently stable conditions. If injection of the dexamethasone implant is necessary in these eyes, then the recommendation to avoid wandering of the implant is to fix it to the sclera[10]. We tried this by suturing the implant to the sclera, but the dissolving implant broke up and tended again to move into the anterior chamber.

Table 2 Complications related to the injection procedure and post-injection complications with clinical presentation of the adverse events, associated reasons and management

Adverse event	Reason	Management	Literature
Complications related to the injection procedure			
Implant was outside of the eyeball	Early release	Injection of a new implant	
Implant trapped in the sclera	- Retraction of the needle while injecting - Inadequate position of the needle - Inadvertent eye or head movements by the patient	Repositioning by pushing the implant inwards	
Implant inintralenticular, lens touch		Cataract surgery. Cave: capsule defects can lead to nucleus drop during cataract surgery or in case of lens touch to Argentinian flag sign	[3-4]
Implant was in the anterior chamber		Surgical removal. Cave: increased risk for retinal detachment	
Implant was sub-retinal			
Two implants in the same eye	Iatrogenic, instead of bilateral injection	Surgical removal if it leads to increased eye pressure	
Bulbus hypotony with or without choroidal detachment	- No accurate scleral tunneling - Prior vitrectomy	Observation Scleral tunnel suturing	[5]
Eccentric/macular hole	Kinetic energy with mechanical impact of the implant especially in vitrectomized patients	- Adequate position of the needle - Exclusion of vitrectomized patients	[6-7]
Post injectional complications			
Anterior chamber or irido-corneal angle - could occur as pseudohypopyon - can lead to corneal decompensation	Rupture of the posterior lens capsule Aphakia Subluxated IOL Scleral fixated IOL Sulcus implanted IOL Iris fixated IOL Anterior chamber IOL Zonular dehiscence (*i.e.* in myopic eyes, Marfan-Syndrome) Iris defect (*i.e.* iridectomy) Prior vitrectomy	No corneal edema: - Positional change maneuvers Corneal edema: - Surgical removal from the anterior chamber being prepared for vitrectomy as intraoperative relapse of implant is possible - Scleral fixation of the implant - Local therapy for high IOP and corneal decompensation; if this is insufficient keratoplasty could be necessary	[8-12]
Posterior chamber	Artificial iris	- Surgical removal	
Foveal adhesion	Prior vitrectomy	Displacement of the implant with - positional maneuvers placing the patient in an upright, supine and lateral position intermittently - surgical intervention	[13-14]
Split of the implant	-	Close-mesh ophthalmic examinations if patient of risk group for wandering of the implant (see above)	[15-18]
Worsening of vitreomacular traction or macular hole	Vitreomacular adhesion or traction	If no spontaneous resolve in follow-ups and worsened vision treatment of macular hole or traction with vitrectomy	[19]
Hypotony	Ciliary body insufficiency	Contact lens	
Retinal detachment	- Inadequate position of the needle	Retinal detachment surgery	
Endophthalmitis	Insufficient hygiene including inadequate disinfection. No accurate scleral tunneling Leaky injection site	PPV + vitreous sample for antibiogram + intravitreal antibiotics + local and systemic antibiotics	[20]

IOL: Intraocular lens; IOP: Intraocular pressure, PPV: Pars plana vitrectomy.

As soon as it has migrated into the anterior chamber, this requires immediate treatment because of the high risk for corneal decompensation, which can eventually lead to keratoplasty. The right diagnosis can be hampered as it can appear as pseudohypopyon[2]. There are different treatment opportunities, depending on the clinical status. If there is no corneal edema a relapse of the implant into the vitreous can be supported by placing the patient, in mydriasis, and a supine position with intermittent positional changes for 15 to 30min. From our experience, after a successful intravitreal repositioning, and to reduce the high risk of a remigration of the implant into the anterior chamber, we recommend topical pilocarpine 1% twice daily and a recommendation, if possible, to avoid the prone position. If corneal edema is present at the time of the migration of the dexamethasone implant into the anterior chamber, we suggest its urgent surgical removal. Different surgical techniques are conceivable[12]. Due to the rigidity of the implant soon after injection it could be removed with a forceps (Figure 2). At a later stage, the implant becomes softer. Then the risk that it could split in small fragments is higher. In such a situation, aspiration with the vitreous cutter could be facilitative. Surgeons should be prepared for vitrectomy since the implant might vanish into the vitreous cavity during surgery. If fragments are missed and if these remnants appear in the anterior chamber, subsequent repeated surgery may be necessary.

Khurana *et al*[9] describe the YAG laser-induced fragmentation of an implant if it adheres visibly between the iris and the intraocular lens. Subsequent pieces fall posteriorly and have the risk to appear in the anterior chamber again with the consecutive reactions mentioned above.

In special conditions, the patient may be advised to keep to a

certain posture, for example, to adopt a prone, supine or lateral position. This can be tried for intravitreal malposition of an implant like foveal or papillary adhesion, before deciding for vitrectomy[13].

A postoperative endophthalmitis (Case 17) and retinal detachment (Case 18) have to be detected in the follow up schedule procedure and managed using standard treatment options for either of these conditions.

Despite the overall very low risk of complications, the ophthalmologist must be clear about the selection of suitable patients for the injection procedure and be aware of the possibility of postoperative complications[6,21-23]. Likewise, the patient should be mandatorily informed about the additional possible complications, which we described here. Overall, however, at 1.69%, severe complications are rarely observed and amenable to control. It is expected that similar complications can occur in using other similarly sized and similarly shaped implants like fluocinolone acetonide (Iluvien®, Alimera)[24]. With this knowledge, the dexamethasone slow-release device remains a good and helpful treatment option for a wide range of ocular diseases.

In conclusion, ophthalmologists should be aware of potential complications during and after injection of the dexamethasone implant. Our report provides information to identify patients at risk, determine suitable procedures before treatment, and appropriate alternatives in managing adverse events. Careful injection procedures and strict measures in patients at risk will result in a significant reduction in complications.

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REFERENCES

1 Herrero-Vanrell R, Cardillo JA, Kuppermann BD. Clinical applications of the sustained-release dexamethasone implant for treatment of macular edema. *Clin Ophthalmol* 2011;5:139-146.

2 Kreissig I, Degenring RF, Jonas JB. Intravitreal triamcinolone acetonide Complication of infectious and sterile endophthalmitis. *Ophthalmologe* 2006;103(1):30-34.

3 Chhabra R, Kopsidas K, Mahmood S. Accidental insertion of dexamethasone implant into the crystalline lens—12mo follow-up. *Eye (Lond)* 2014;28(5):624-625.

4 Fasce F, Battaglia Parodi M, Knutsson KA, Spinelli A, Mauceri P, Bolognesi G, Bandello F. Accidental injection of dexamethasone intravitreal implant in the crystalline lens. *Acta Ophthalmol* 2014;92(4):e330-e331.

5 Alagöz N, Alagöz C, Yılmaz I, Yıldırım Y, Baz Ö, Altan Ç, Yazıcı AT, Taşkapılı M. Immediate intraocular pressure changes following intravitreal dexamethasone implant. *J Ocular Pharmacol Ther* 2016;32(1):44-49.

6 Christensen L, Sanders R, Olson J. "magic bullet": eccentric macular hole as a complication from dexamethasone implant insertion. *Case Rep Ophthalmol Med* 2016;2016:1706234.

7 de Benedetto U, Battaglia Parodi M, Knutsson KA, Lattanzio R, Bandello F, Iacono P. Macular hole after injection of dexamethasone intravitreal implant for macular oedema due to central retinal vein occlusion. *Acta Ophthalmol* 2013;91(1):e75-e77.

8 Jonas JB, Schmidbauer M. Steroid implant in anterior chamber of an aphakic vitrectomized eye. *Graefes Arch Clin Exp Ophthalmol* 2013;251(1):385-386.

9 Khurana RN, Appa SN, McCannel CA, Elman MJ, Wittenberg SE, Parks DJ, Ahmad S, Yeh S. Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. *Ophthalmology* 2014;121(1):67-71.

10 Mateo C, Alkabes M, Burés-Jelstrup A. Scleral fixation of dexamethasone intravitreal implant (OZURDEX®) in a case of angle-supported lens implantation. *Int Ophthalmol* 2014;34(3):661-665.

11 Stepanov A, Codenotti M, Ramoni A, Prati M, Jiraskova N, Rozsival P, Bandello F. Anterior chamber migration of dexamethasone intravitreal implant (Ozurdex®) through basal iridectomy (Ando) in a pseudophakic patient. *Eur J Ophthalmol* 2016;26(3):e52-e54.

12 Bansal R, Bansal P, Kulkarni P, Gupta V, Sharma A, Gupta A. Wandering Ozurdex(®) implant. *J Ophthalmic Inflamm Infect* 2012;2(1):1-5.

13 Afshar AR, Loh AR, Pongsachareonnont P, Schwartz DM, Stewart JM. Dexamethasone intravitreal implant trapped at the macula in a silicone oil-filled eye. *Ophthalmology* 2013;120(12):2748-2749.e1.

14 Itoh Y, Srivastava SK, Ehlers JP. Management of foveal adhesion of a dexamethasone implant. *Acta Ophthalmol* 2016;94(5):e376-e377.

15 Agrawal R, Fernandez-Sanz G, Bala S, Addison PK. Desegmentation of Ozurdex implant in vitreous cavity: report of two cases. *Br J Ophthalmol* 2014;98(7):961-963.

16 Bhagat R, Zhang J, Farooq S, Li XY. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. *J Ocular Pharmacol Ther* 2014;30(10):854-858.

17 Rishi P, Mathur G, Rishi E. Fractured Ozurdex™ implant in the vitreous cavity. *Indian J Ophthalmol* 2012;60(4):337-338.

18 Roy R, Hegde S. Split Ozurdex implant: a caution. *Canadian Journal of Ophthalmology* 2013;48(1):e15-e16.

19 Bakri SJ, Omar AF. Evolution of vitreomacular traction following the use of the dexamethasone intravitreal implant (Ozurdex) in the treatment of macular edema secondary to central retinal vein occlusion. *J Ocul Pharmacol Ther* 2012;28(5):547-549.

20 Arıkan Yorgun M, Mutlu M, Toklu Y, Cakmak HB, Cağıl N. Suspected bacterial endophthalmitis following sustained-release dexamethasone

intravitreal implant: a case report. *Korean J Ophthalmol* 2014;28(3): 275-277.

21 Georgalas I, Petrou P, Pagoulatos D, Papaconstantinou D, Tservakis I. Central serous chorioretinopathy in the fellow eye as a complication of intravitreal dexamethasone implant for the treatment of Irvine-Gass syndrome. *Clin Exp Optom* 2016;99(6):601-603.

22 López-Herrero F, Moruno-Rodriguez A, Molina-Sócola FE, Medina-Tapia A, Sánchez-Vicente JL. Accidental intralenticular insertion as a complication of intravitreal dexamethasone implant. *Arch Soc Esp Oftalmol* 2017;92(9):e58.

23 Uwaydat SH, Sallam AB, Wang H, Goyal S. Retinal indentation by a dexamethasone implant in a gas-filled eye: report of an unusual complication. *JAMA Ophthalmol* 2017;135(10):1125-1127.

24 Papastavrou VT, Zambarakji H, Dooley I, Eleftheriadis H, Jackson TL. Observation: fluocinolone acetonide (iluvien) implant migration into the anterior chamber. *Retin Cases Brief Rep* 2017;11(1):44-46.