Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-195 Levofloxacin und Dexamethason

Stand: September 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Levofloxacin und Dexamethason
[Zur Vorbeugung und Behandlung von Entzündungen sowie zur Vorbeugung von Infektionen im Zusammenhang mit Kataraktoperationen]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegt ein Beschluss zu Bromfenac zur Behandlung der postoperativen Augenentzündung nach Kataraktextraktion bei Erwachsenen vom 19.01.2012 vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Levofloxacin und Dexamethason Ducressa®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Ducressa Augentropfenlösung ist indiziert zur Vorbeugung und Behandlung von Entzündungen sowie zur Vorbeugung von Infektionen im Zusammenhang mit Kataraktoperationen bei Erwachsenen.
Infektionsprophylaxe	
Cefuroxim S01AA27 Aprokam	**Antibiotische Prophylaxe** der postoperativen **Endophthalmitis** nach Kataraktoperation.
Polymyxin-B Neomycin Gramicidin S03AA30 Polyspectran®	Ophthalmologischer Bereich Bakterielle Infektionen des äußeren Auges (einschließlich Anhangsgebilde) mit Polymyxin-B-, Gramicidin- bzw. Neomycin-empfindlichen Erregern sowie **Infektionsprophylaxe, z. B. nach Operationen**, peripherer Keratitis, Blepharitis, Verätzungen. […]
Povidon-Iod D08A G02 Braunol®7,5 % Lösung zur Anwendung auf der Haut	Zur einmaligen Anwendung: Desinfektion der intakten äußeren Haut oder **Antiseptik der Schleimhaut wie z. B. vor Operationen**, Biopsien, Injektionen, Punktionen, Blutentnahmen und Blasenkatheterisierungen.
Vorbeugung und/oder Behandlung von Entzündungen	
Nicht-steroidale Antiphlogistika	
Diclofenac S01BC03 z.B. Diclofenac	Zur **Vorbeugung postoperativer Entzündungen** nach Kataraktoperationen. Zur Aufrechterhaltung der Pupillenerweiterung (Mydriasis) bei Kataraktoperationen. Zur Behandlung von Augenschmerzen bei photorefraktiven Operationen über bis zu 24 Stunden nach der Operation.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Devatis	
Nepafenac S01BC10 NEVANAC	NEVANAC 1 mg/ml wird bei Erwachsenen angewendet zur: – **Prophylaxe und Behandlung postoperativer** Schmerz- und **Entzündungszustände** bei Kataraktoperationen. – Verminderung des Risikos postoperativer Makulaödeme in Zusammenhang mit Kataraktoperationen bei Diabetikern (siehe Abschnitt 5.1). Stand Fachinformation August 2018
Indometacin S01BC01 z.B. Indometacin Dr. Mann	**- Nicht infektiöse Entzündungen des vorderen Augenabschnittes** nach Augenoperationen. -Zur Vermeidung einer Miosis während operativer Eingriffe. -Behandlung von Schmerzzuständen am Auge unmittelbar nach einer photorefraktiven Hornhautexzision und in den ersten drei Tagen nach dem Eingriff.
Ketorolac S01BC05 KetoVision	KetoVision 5 mg/ml Augentropfen werden angewendet zur **Prophylaxe und Reduktion von Entzündungen** und damit verbundenen Symptomen nach einer Augenoperation. KetoVision 5 mg/ml Augentropfen werden angewendet bei Erwachsenen.
Flurbiprofen S01BC04 OCUFLURO.K.	- Zur Vermeidung einer Miosis während operativer Eingriffe. - Entzündungen nach Lasertrabekuloplastik. **- Entzündungen des vorderen Augenabschnittes nach Augenoperationen.** Bei Vorliegen einer Infektion oder wenn die Gefahr einer Infektion besteht, sollte gleichzeitig mit Ocuflur O.K. eine entsprechende Behandlung (z.B. mit Antibiotika) erfolgen.
Kortikoidsteroide	
Rimexolon S01BA13 Vexol	VEXOL ist bei **Entzündungszuständen** nach Augenoperationen, bei Uveitis anterior und zur Behandlung von Entzündungen der palpebralen und bulbären Bindehaut, der Hornhaut und des vorderen Augenabschnitts indiziert, die auf eine Kortikosteroidtherapie ansprechen. Die Entzündung sollte nicht-infektiöser Natur sein. In schwereren Fällen, und wenn der hintere Augenabschnitt betroffen ist, wird subkonjunktivale Injektion oder eine systemische Therapie empfohlen (siehe unter 4.4)
Dexamethason S01BA01 z.B. Dexamethason-Augensalbe	1. Schwere nichtinfektiöse entzündliche so-wie allergische Erkrankungen des vorderen Augenabschnittes wie Konjunktivitis, Keratitis, Episkleritis, Skleritis, Uveitis anterior (Iritis/Iridozyklitis), Uveitis intermedia (Parsplana-Syndrom) 2. Zur **Abschwächung entzündlicher Lokalreaktionen nach Operationen** (z. B. Keratoplastik, Linsenimplantation) 3. Verätzungen und Verbrennungen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
JENAPHARM®	
Fluorometholon S01BA07 EFFLUMIDEX®	Nichtbakterielle oder allergische Entzündungen des vorderen Augenabschnittes. **Nichtbakterielle Entzündungen nach Operationen**
Prednisolon S01BA04 z.B. INFLANEFRAN FORTE	INFLANEFRANFORTE wird bei Erwachsenen verwendet zur: - symptomatischen Behandlung schwerer nicht infektiöser, entzündlicher Erkrankungen des Auges, z.B. schwere allergische Konjunktivitis, schwere und mittelschwere Konjunktivitis vernalis, Keratoconjunktivitis scrophulosa, Acne-rosacea-Keratitis, Keratitis parenchymatosa, Keratitis disciformis; - symptomatische Behandlung von Uveitis, Iritis, Iridocyclitis; - **Verminderung postoperativer entzündlicher Erscheinungen**, z.B. nach Katarakt-Operation
Loteprednoletabonat S01BA14 Lotemax®	Zur **Behandlung postoperativer Entzündungen** nach chirurgischen Eingriffen am Auge.
Kombinationspräparate: Antiinfektiva und Kortikosteroide	
Tobramycin und Dexamethason S01CA01 TOBRADEX	**Vorbeugung und Behandlung von Entzündungen und Vorbeugung von Infektionen** in Zusammenhang mit Kataraktoperationen bei Erwachsenen und Kindern ab 2 Jahren.
Dexamethason und Gentamicin S01CA01 z.B. Dexa-Gentamicin	Entzündung des vorderen Augenabschnittes, bei denen gleichzeitig eine durch Gentamicin-empfindliche Erreger verursachte Infektion vorliegt oder **die Gefahr einer bakteriellen Infektion** besteht. […]
Dexamethason, Neomycin, Polymyxin-B S01CA01	Entzündungen des vorderen Augenabschnittes, die der Behandlung mit einem Corticoid bedürfen und bei denen gleichzeitig eine durch Polymyxin-B- und/oder Neomycin- empfindliche Erreger verursachte Infektion des äußeren Auges vorliegt oder **die Gefahr einer bakteriellen Infektion besteht, z. B. postoperativ** zur Kontrolle immunologischer Prozesse und zur Infektionsprophylaxe, periphere Keratitis, Blepharitis, Verätzungen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
ISOPTO-MAX®	
Dexamethason, Neomycin, S01C A01 dispadex®	Infektionen des vorderen Augenabschnittes verursacht durch Neomycin empfindlichen Erregern,z.B. bakterielle Konjunktivitis, die gleichzeitig einer Glucocorticoid-Behandlung bedürfen. Entzündliche Erkrankungen des vorderen Augenabschnittes, die auf Glucocorticoide ansprechen und bei denen die Gefahr einer Infektion besteht, z.B. zur Behandlung von Entzündungszuständen nach chirurgischen Eingriffen am Auge.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-195 (Levofloxacin und Dexamethason)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. August 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCVA	Best-corrected visual acuity
BSS	Balanced salt solution
CME	Cystoid macular edema
ECC	Endothelial cell count
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICC	Intracameral cefuroxime
ICM	Intracameral moxifloxacin
ICV	Intracameral vancomycin
IOL	intraocular lens
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MO	Macular Oedema
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal anti-inflammatory drugs
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
VA	Visual acuity
WHO	World Health Organization

1 Indikation

Vorbeugung und Behandlung von Entzündungen sowie zur Vorbeugung von Infektionen im Zusammenhang mit Kataraktoperationen bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Entzündungen oder Infektionen im Zusammenhang mit Kataraktoperationen* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 17.07.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 766 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt acht Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2012 [2].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. Januar 2012 - Bromfenac

Anwendungsgebiet

Behandlung der postoperativen Augenentzündung nach Kataraktextraktion bei Erwachsenen

Zweckmäßige Vergleichstherapie

Dexamethason Augentropfen

Fazit / Ausmaß des Zusatznutzens

Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie gilt gemäß § 35a Absatz 1 Satz 5 SGB V als nicht belegt.

3.2 Cochrane Reviews

Gower EW et al., 2017 [3].

Perioperative antibiotics for prevention of acute endophthalmitinis after cataract surgery (Review)

Fragestellung

To evaluate the eIects of perioperative antibiotic prophylaxis for endophthalmitis following cataract surgery compared with no prophylaxis or other form of prophylaxis.

Methodik

Population:

- participants undergoing cataract surgery

Intervention vs Komparator:

- preoperative antibiotics, intraoperative (intracameral, subconjunctival, or systemic), or postoperative antibiotic prophylaxis for acute endophthalmitis
  - any prophylaxis versus no prophylaxis;
  - preoperative versus postoperative or intraoperative prophylaxis or combinations;
  - •specific antibiotics used in included trials;
  - mode of perioperative antibiotic delivery
- We excluded studies that evaluated antiseptic preoperative preparation using agents such as povidone iodine. In addition, excluded studies that evaluated antibiotics for treating acute endophthalmitis a,er cataract surgery.

Endpunkte:

- Endophthalmitis:
- Visual acuity (VA)
- Adverse eIects
- Quality of life measures

Recherche/Suchzeitraum:

- CENTRAL, Medline, Embase, LILACS, WHO, ICTRP till 6 December 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs (N=101005)

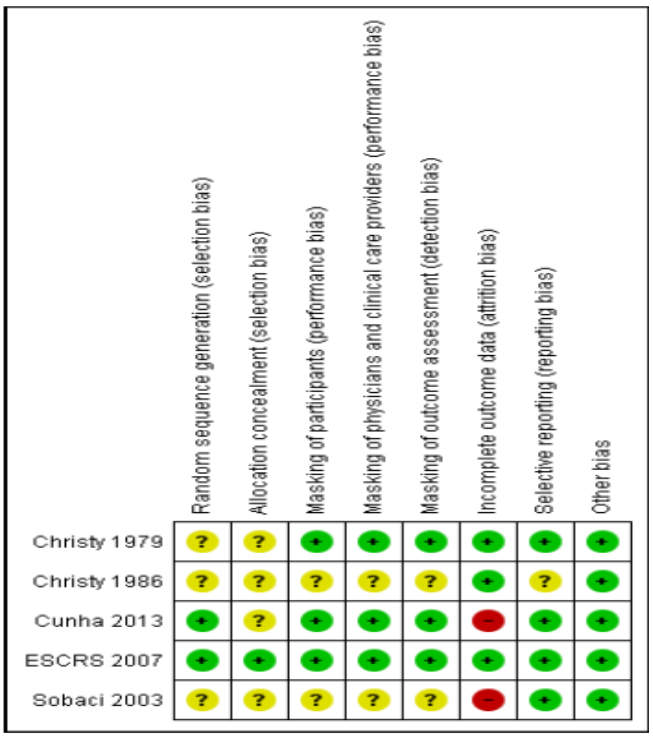
Charakteristika der Population:

- Sobaci 2003 was conducted in Turkey and compared antibiotics (vancomycin and gentamycin) in balanced salt solution (BSS) irrigating infusion fluid with BSS-only irrigating infusion fluid in 644 eyes of 640 participants. All were treated with ofloxacin and diclofenac

sodium four times on the day prior to surgery. Povidone iodine was utilized for antisepsis at the time of surgery and a solution of ofloxacin, dexamethasone, and indomethacin was give postoperatively.

- ESCRS 2007 conducted at multiple sites throughout Europe and Turkey, implemented a two-by-two factorial design to evaluate intracameral cefuroxime injected at the end of surgery and topical levofloxacin given immediately preoperatively (within one hour of surgery) and up to 15 minutes following surgery in 16,603 participants. […] In ESCRS 2007, the two interventions studied were intracameral cefuroxime and topical levofloxacin. […] Povidone iodine was used for antisepsis at the time of surgery and topical levofloxacin was given to all participants starting the morning a,er surgery. Follow-up was for six weeks postoperation.

Qualität der Studien:



Studienergebnisse:

Perioperative prophylaxis versus no prophylaxis

Perioperative prophylaxis versus no prophylaxis								
Study ID	**No. eyes and participants**	**Follow-up**	**Comparison (intervention vs comparator)**	**Risk of endophthalmitis by study group**		**RR (95% CI) Treatment vs control**		**Certainty of the evidence (GRADE)**
				Presumed cases*	**Proven cases****	**Presumed cases***	**Proven cases****	
Sobaci 2003	644 eyes of 640 participants	6 weeks	**Treatment:** BSS with antibiotics (vancomycin 20 mg/mL and gentamicin 8 mg/mL)	Not reported	0/322 (0%) eyes	Not reported	0.20 (0.01 to 4.15)	⊕⊝⊝⊝ **Very low**[1,2]
			Control: BSS-only irrigating infusion fluid	Not reported	2/322 (0.62%) eyes			
ESCRS 2007	16,603 eyes of 16,603 participants	6 weeks	**Treatment 1:** combined intracameral cefuroxime and topical levofloxacin	2/4052 (0.05%) eyes	1/4052 (0.02%) eyes	0.14 (0.03 to 0.63)	0.10 (0.01 to 0.78)	⊕⊕⊕⊕ **High**
			Treatment 2: intracameral cefuroxime 0.9%	3/4056 (0.07%) eyes	2/4056 (0.05%) eyes	0.21 (0.06 to 0.74)	0.20 (0.04 to 0.91)	⊕⊕⊕⊕ **High**
			Treatment 3: topical levofloxacin 0.5%	10/4049 (0.25%) eyes	7/4049 (0.17%) eyes	0.72 (0.32 to 1.61)	0.70 (0.27 to 1.84)	⊕⊕⊕⊝ **Moderate**[3]
			Control: placebo drops	14/4054 (0.35%) eyes	10/4054 (0.25%) eyes			

Comparisons of combinations of antibiotics with specific antibiotics

Study ID	**No. eyes and participants**	**Follow-up**	**Interventions**	**Risk of endophthalmitis by study group**		**RR (95% CI) Treatment 1 vs treatment 2**		**Certainty of the evidence (GRADE)**
				Presumed cases*	**Proven cases****	**Presumed cases***	**Proven cases****	
Christy 1979	6618 eyes of 6618 participants	1 week	**Treatment 1:** combined prophylaxis (topical regimen + periocular penicillin at the time of surgery)	5/3309 (0.15%) eyes	Not reported	0.33 (0.12 to 0.92)	Not reported	⊕⊕⊕⊝ **Moderate**[4]
			Treatment 2: topical regimen alone (chloramphenicol-sulfadimidine)	15/3309 (0.45%) eyes	Not reported			
ESCRS 2007	16,603 eyes of 16,603 participants	6 weeks	**Treatment 1:** combined intracameral cefuroxime and topical levofloxacin	2/4052 (0.05%) eyes	1/4052 (0.02%) eyes	**Treatment 1 vs treatment 2:** 0.67 (0.11 to 3.99)	**Treatment 1 vs treatment 2:** 0.50 (0.05 to 5.52)	⊕⊕⊕⊝ **Moderate**[3]
			Treatment 2: intracameral cefuroxime 0.9%	3/4056 (0.07%) eyes	2/4056 (0.05%) eyes	**Treatment 2 vs treatment 3:** 0.30 (0.08 to 1.09)	**Treatment 2 vs treatment 3:** 0.29 (0.06 to 1.37)	⊕⊕⊕⊝ **Moderate**[3]
			Treatment 3: topical levofloxacin 0.5%	10/4049 (0.25%) eyes	7/4049 (0.17%) eyes	**Treatment 1 vs treatment 3:** 0.20 (0.04 to 0.91)	**Treatment 1 vs treatment 3:** 0.14 (0.02 to 1.16)	⊕⊕⊕⊕ **High**

Proportion of eyes with final visual acuity greater than 20/40 following endophthalmitis

- Among the five presumed cases of postoperative endophthalmitis who received intracameral cefuroxime injections, two (40%) had final VA better than 20/40. Among the 24 presumed cases of postoperative endophthalmitis who did not receive intracameral cefuroxime injections, 14 (58.3%) had final VA better than 20/40. The difference between antibiotic injection and no injection groups was uncertain (RR 0.69, 95% CI 0.22 to 2.11).

- There were similar results for culture-proven cases between antibiotic injection (1/3 (33.3%) eyes) and no injection (10/17 (58.1%) eyes) groups (RR 0.57, 95% CI 0.11 to 2.95). We assessed the certainty of evidence for this outcome as moderate, downgrading for imprecision.

Anmerkung/Fazit der Autoren

This systematic review underscores the broad scope of prophylaxis regimens considered to be of potential use in preventing endophthalmitis following cataract surgery. Among the included studies, the mode of antibiotic administration ranged widely from topical administration preoperatively to intraocular injections during surgery.

Among the five studies, the ESCRS 2007 results are most applicable to 21st century surgical practice, as it used contemporary surgical techniques and study drugs that are readily available in Europe. Its design allowed for examination of both topical and intracameral antibiotics, and included a sample size sufficient to yield statistically significant results.

ESCRS 2007 {published data only}
BarryP, GardnerS, SealD, GettinbyG, LeesF, PetersonM, et al. Clinical observations associated with proven and unproven cases in the ESCRS study of prophylaxis of postoperative endophthalmitis a,er cataract surgery. Journal of Cataract and Refractive Surgery 2009;35(9):1523-31.
BarryP, SealDV, GettinbyG, LeesF, PetersonM, RevieCW, et al. ESCRS study of prophylaxis of postoperative endophthalmitis a,er cataract surgery: preliminary report of principal results from a European multicenter study. Journal of Cataract and Refractive Surgery 2006;32(3):407-10.
*Endophthalmitis Study Group, European Society of Cataract and Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. Journal of Cataract and Refractive Surgery 2007;33(6):978-88.
PleyerU, GeldsetzerK. Will intracameral cefuroxime become the new standard in endophthalmitis prevention?. Klinische Monatsblätter für Augenheilkunde 2008;225(11):934-40.
SealDV, BarryP, GettinbyG, LeesF, PetersonM, RevieCW, et al. ESCRS study of prophylaxis of postoperative endophthalmitis a,er cataract surgery: case for a European multicenter study. Journal of Cataract and Refractive Surgery 2006;32(3):396-406.

Sobaci 2003 {published data only}
SobaciG, TuncerK, TaWA, OzyurtM, BayerA, KutluU. The elect of intraoperative antibiotics in irrigating solutions on aqueous humor contamination and endophthalmitis a,er phacoemulsification surgery. European Journal of Ophthalmology 2003;13(9-10):773-8.

Kommentare zum Review

Einschluss von Studien mit z.T. nicht zugelassenen AM

Lim BX et al., 2016 [5].

Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Fragestellung

Is there evidence to support the prophylactic use of topical NSAIDs either in addition to, or instead of, topical steroids postoperatively to reduce the incidence of macular oedema (MO) and associated visual morbidity.

Methodik

Population:

- adult participants had undergone standard surgery for age-related cataract

Intervention:

- NSAIDs in addition to topical steroids

Komparator:

- topical steroids alone

Endpunkte:

- primary outcome: poor vision outcome due to MO in the study eye at three months defined as best corrected visual acuity (BCVA) not improving to 6/9 or better
- secondary outcome: quality of life, central retinal thickness from preoperative assessment in the study eyes
- adverse events

Recherche/Suchzeitraum:

- CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 8), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to September 2016), Embase (January 1980 to September 2016), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to September 2016)

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 34 RCTs (N=5532)

Charakteristika der Population:

- We identified 34 studies that were conducted in the Americas, Europe, the Eastern Mediterranean region and South-East Asia. Over 5000 people were randomised in these trials. The majority of studies probably enrolled one eye per participant, a small subset (4 trials) enrolled a proportion of people with bilateral surgery.
- Twenty-eight of these 34 studies compared non-steroidal anti-inflammatory drugs (NSAIDs) plus steroids with steroids alone. Six studies compared NSAIDs (on their own or with placebo) with steroids. A variety of NSAIDs were used, including ketorolac, diclofenac, nepafenac, indomethacin, bromfenac and pranopfen.
- Follow-up ranged from one month to 12 months. The majority of studies (n = 23) followed up to two months or less.

Qualität der Studien:

- We graded the evidence as low- to very low-certainty.
- In general, the trials were poorly reported and it was difficult to judge the extent to which bias had been avoided. We did not judge any of the studies at low risk of bias for all domains.
- Many trials were not properly masked and, in a few studies, there were problems with attrition bias and selective outcome reporting.

- For outcomes that had more data we identified the possibility of publication bias with an asymmetric funnel plot.
- There were also problems with directness. For example, many studies reported "CMO" but were not clear whether or not this was 'clinically significant', or indeed what this meant in terms of whether it caused both symptoms and signs. And in many of the older studies this could not be verified by optical coherence tomography (OCT).

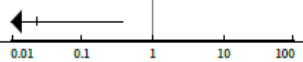
Studienergebnisse:

NSAID + steroids vs steroids

- Poor vision at 3 months: There was low-certainty evidence that people receiving topical NSAIDs in combination with steroids may have a lower risk of poor vision due to macular oedema (MO) at three months (risk ratio (RR) 0.40, 95% confidence interval (CI) 0.27 to 0.61; eyes = 1360; studies = 5; I2 = 5%)..
- Poor vision at 12 months: There were very little data for 12 months (only one study reported poor vision due to MO at this time point) and we judged this to have very low-certainty evidence.: RR 1.32; (95 CI: 0.09 to 20.37)
- Inflammation:

Analysis 1.5. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 5 Inflammation.

Study or subgroup	NSAIDs/steroids n/N	Steroids n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cervantes-Coste 2009	0/30	0/30		Not estimable
Chatziralli 2011	2/70	0/68		4.86[0.24,99.39]
Zhang 2008	0/110	21/110		0.02[0,0.38]

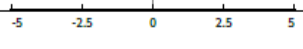


NSAID vs steroids

- Poor vision: None of the six studies comparing NSAIDs alone with steroids reported on poor vision due to MO at three months or 12 months.
- Two studies reported BCVA at three months, and the results of these trials were inconsistent but both found differences of less than 0.1 logMAR between groups.
- Quality of life was only reported in one of the 34 studies, and it was not fully reported other than to comment on lack of differences between groups.
- In general, no major adverse events were noted - the main consistent observation was burning or stinging.
- Inflammation:

Analysis 2.3. Comparison 2 NSAIDs versus steroids, Outcome 3 Inflammation (flare).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Steroids N	Steroids Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Asano 2008	65	8.5 (6)	62	8 (3.8)		0.47[-1.26,2.2]
Endo 2010	31	3.9 (3.8)	31	6.3 (4)		-2.4[-4.33,-0.47]
Miyake 2007	25	8.1 (3.8)	25	9 (3)		-0.9[-2.8,1]
Miyake 2011	30	12 (5.5)	29	19.3 (10.7)		-7.3[-11.66,-2.94]
Miyanaga 2009	25	7.6 (2.8)	23	8.5 (6.5)		-0.9[-3.77,1.97]



Anmerkung/Fazit der Autoren

Using topical NSAIDs may reduce the risk of developing macular oedema a(er cataract surgery, although it is possible that current estimates as to the size of this reduction are exaggerated due to selective non-reporting of negative studies. It is unclear the extent to which this reduction has an impact on the visual function and quality of life of patients. There is little evidence to suggest any important effect on vision after surgery.

The value of adding topical NSAIDs to steroids, or using them as an alternative to topical steroids with a view to reducing the risk of poor visual outcome after cataract surgery is uncertain. This is reflected in wide variations in modern practice.

Kommentare zum Review

Einschluss von Studien mit z.T. nicht zugelassenen AM

Juthani VV et al., 2017 [4].

Non-steroidal anti-inflammatory drugs versus corticosteroids for controlling inflammation aer uncomplicated cataract surgery (Review)

Fragestellung

To evaluate the comparative effectiveness of topical NSAIDs (alone or in combination with topical corticosteroids) versus topical corticosteroids to control intraocular inflammation after uncomplicated phacoemulsification for cataract extraction. To assess postoperative best-corrected visual acuity (BCVA), patient-reported discomfort, symptoms, or complications (such as elevation of IOP), and cost-effectiveness with the use of postoperative NSAIDs or corticosteroids.

Methodik

Population:

- participants underwent phacoemulsification only for cataract extraction

Intervention:

- topical NSAIDs
- topical NSAIDs and corticosteroids

Komparator:

- topical corticosteroids

Endpunkte:

- Intraocular inflammation and BCVA
  - 1. the proportion of participants with intraocular inflammation at one-week after surgery;
  - 2. the proportion of participants with BCVA of 20/40 or better at one-week after surgery.
- The proportion of participants with CME, as measured by ocular coherence tomography or fluorescein angiography, at one-week after surgery (Cystoid macular edema is frequently used as a surrogate for active intraocular inflammation.)
- Adverse events

Recherche/Suchzeitraum:

- Cochrane, Medline, Embase, PubMed, Lilacs, clinicaltrials.gov, WHO, 16 December 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

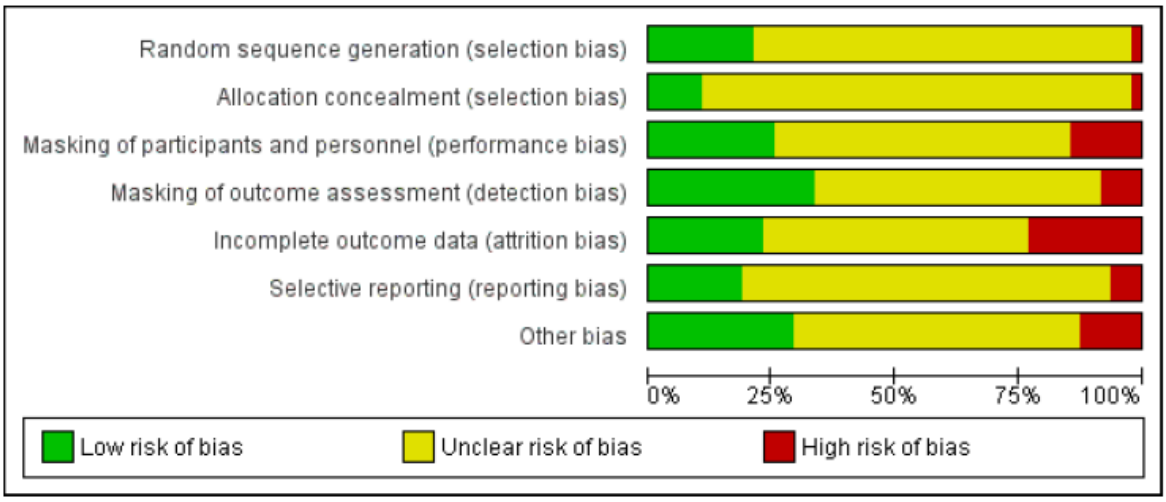
- 17 RCTs

Charakteristika der Population:

- We included studies that enrolled participants who received phacoemulsification for cataract. Some studies included a group of participants who received other types of cataract surgery, in which case we used only the data from the participants who underwent phacoemulsification.

Qualität der Studien:

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



- In general, we graded the evidence as being of low and moderate certainty. The reasons for downgrades included imprecision and heterogeneity in factors such as study design, medications used, and regimens studied..
- Many of the included studies were also poorly reported, so that it was difficult to judge the degree of bias likely present in the various domains. In our certainty estimates, we downgraded for risk of bias when the analysis included poorly-reported studies.

Studienergebnisse:

NSAIDs versus corticosteroids

- Inflammation defined by presence of corneal edema
  - Only one study that compared an NSAID with a corticosteroid reported on the presence of corneal edema at one week.

- In the NSAID group, 4 of 39 participants (10.3%) and, in the corticosteroid group, 10 out of 75 participants (13.3%) showed signs of corneal edema (Trinavarat 2003). There was insuffcient evidence to conclude that one treatment group had a lower proportion of corneal edema at one week post-surgery than the other (RR 0.77, 95% CI 0.26 to 2.29).
- We judged the certainty of the evidence for this outcome to be low, downgraded one level each due to imprecision and high risk of performance and detection bias; this was reported as an unmasked study.

- Cystoid macular edema at one month after surgery
  - 4 studies; Participants who were treated with an NSAID had a lower risk of CME at one month compared with participants who were treated with a corticosteroid (RR 0.26, 95% CI 0.17 to 0.41;
  - The certainty of the evidence for the outcome of CME at one month postoperatively was low. We did downgrade based on risk of bias for the studies in this analysis, as they were poorly reported, details of masking and analysis were unclear, and in one there was a high risk of attrition bias. We also downgraded the evidence one level due to indirectness, because our outcome of interest was CME at one week, and the data we were able to combine was for one month. Additionally, two of the studies included in the meta-analysis used fluorometholone as the corticosteroid in the comparison, which is a very weak corticosteroid and therefore a weak comparator. These two studies contributed 30% of the weight of the meta-analysis
- BCVA of 20/40 or better at one week after surgery
  - none of the included studies reported BCVA as a dichotomous variable that reported on the proportion of participants with BCVA of 20/40 or better at one-week after surgery.
- Adverse events
  - None of the studies in this comparison reported on adverse events.

<u>Combination of NSAIDs plus corticosteroids versus corticosteroids alone</u>

- Inflammation defined by presence of corneal edema
  - One RCT: At each of the four time points, there was statistical uncertainty as to which group had a lower risk of developing corneal edema (RR 1.07, 95% CI 0.98 to 1.16 at one week; RR 0.52, 95% CI 0.24 to 1.14 at two weeks; RR 0.97; 95% CI 0.20 to 4.65 at three weeks; and RR 2.92, 95% CI 0.12 to 70.35 at four weeks).
  - Downgraded one level to moderate due to concerns about reporting bias
- BCVA of 20/40 or better at one week aer surgery
  - None of the included studies reported on the proportion of participants that had BCVA of 20/40 or better
- Cystoid macular edema at one month after surgery
  - We included seven studies in the meta-analysis for the proportion of participants who had CME at one month postoperatively (Jung 2015; Li 2011; Miyanaga 2009; Moschos 2012; Ticly 2014; Wittpenn 2008; Zaczek 2014).
  - This analysis favored the combination of an NSAID plus a corticosteroid over a corticosteroid alone for an approximately 50% lower risk of CME present at one month after surgery; however there was statistical uncertainty (RR 0.50, 95% CI 0.23 to 1.06)
- Adverse events

- Only 2 studies reported on adverse events. 1 reported that there were no adverse events related to NSAID use, but that 1 participant randomized to NSAIDs plus corticosteroid had heterogeneous retinal detachment as a complication of cataract surgery.
- Another study used the COMTOL questionnaire to ask participants about the frequency and severity of side effects; 3 of the top 5 most commonly reported side effects were markers of ocular discomfort: burning, redness, and blurred vision.
- The adverse events reported in this study were not separated by intervention group.

Anmerkung/Fazit der Autoren

The evidence for the treatment of postoperative inflammation after uncomplicated phacoemulsification is insufficient to inform practice. From the 48 trials included in this review, we could not ascertain the equivalence or superiority of non-steroidal anti-inflammatory drugs (NSAIDs) with or without corticosteroids versus corticosteroids for the treatment of postoperative inflammation; we were unable to make conclusions about our primary outcome.

[…] There may be some risk reduction of CME with NSAIDs alone (low-certainty evidence) or in combination with corticosteroids (low-certainty evidence) in the first month after phacoemulsification.

Kommentare zum Review

Einschluss von Studien mit z.T. nicht zugelassenen AM

3.3 Systematische Reviews

Bowen RC et al., 2018 [1].

Comparative analysis of the safety and efficacy of intracameral cefuroxime, moxifloxacin and vancomycin at the end of cataract surgery: a meta-analysis

Fragestellung

The aim of this study was to evaluate the safety and efficacy of intracameral cefuroxime (ICC) intracameral moxifloxacin (ICM) and intracameral vancomycin (ICV) as prophylactic pharmaco-therapy for prevention of POE

Methodik

Population:

- phacoemulsification cataract surgery

Intervention:

- IC antibiotics (ie, cefuroxime, moxifloxacin or vancomycin) at the end of cataract surgery.

Komparator:

- non-IC antibiotics (topical, subconjunctival or non-specified) at the end of cataract surgery.

Endpunkte:

- incidence of postcataract surgery endophthalmitis, the effects of geographic location, and the addition of topical antibiotics on POE incidence

Recherche/Suchzeitraum:

- BIOSIS Previews, CINAHL, ClinicalTrials.gov, Cochrane Library, Dissertations & Theses, EMBASE, PubMed, ScienceDirect and Scopus were searched from inception to January 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias.

Ergebnisse

Anzahl eingeschlossener Studien:

- Efficacy Analysis: 17 studies The European Society of Cataract & Refractive Surgeons (ESCRS) study was the only RCT4; 1
- Safety analysis: 33 studies met the inclusion criteria for the safety and toxicity analysis with 2 RCTs

Charakteristika der Population:

Cefuroxime doses ranged from 1 to 10 mg/0.1 mL, vancomycin doses ranged from 0.0375 to 1 mg/0.1 mL, and moxifloxacin doses ranged from 15 to 500 mcg/0.1 mL. Postoperative follow-up ranged from 1 day to 12 months.

Qualität der Studien:

- Efficacy analysis: The overall quality of the RCT was graded as high due to the study design, low risk of bias, large measure of effect and direct comparisons.
- Safety analysis: Of the 33 studies analysed for risk of bias, the principal causes of moderate to high bias were confounding variables and protocol deviations. Selection, attrition and reporting bias were determined to be low to moderate risk of bias. Lack of homogeneity between studies (eg, differences in study methods, species and antibiotic concentrations) was the greatest challenge in comparing studies.

Studienergebnisse:

Efficacy of IC antibiotics

- Incidence of endophthalmitis: RCT (OR, 0.21; 95% CI 0.08 to 0.54; P=0.001); Quality of evidence: High (due to large effect)

Safety of IC antibiotics

- Postoperative safety profile of intracameral cefuroxime (ICC)
  - Retina: No macular thickening (P=0.34) at 5 weeks postoperatively
- Postoperative safety profile of intracameral moxifloxacin (ICM versus balanced sodium solution (BSS))
  - Structure cornea: No difference in endothelial cell count (ECC) or central corneal thickness at 3 months (P>0.05).
  - anterior chamber: ICM versus BSS. Not significantly different from controls (P>0.05).
  - Visual acuity (VA): All eyes had VA 20/30 or better.

27. Gupta MS, McKee HD, Saldaña M, et al. Macular thickness after cataract surgery with intracameral cefuroxime. J Cataract Refract Surg. 2005; 31:1163–6. [PubMed: 16039491]
28. Lam PT, Young AL, Cheng LL, et al. Randomized controlled trial on the safety of intracameral cephalosporins in cataract surgery. Clin Ophthalmol. 2010; 4:1499–504. [PubMed: 21191447]
48. Lane SS, Osher RH, Masket S, et al. Evaluation of the safety of prophylactic intracameral moxifloxacin in cataract surgery. J Cataract Refract Surg. 2008; 34:1451–9. [PubMed: 18721703]

Anmerkung/Fazit der Autoren

IC antibiotics alone may be as effective as IC plus postoperative topical antibiotics; however, the lack of direct comparison and the variety of topical antibiotics could suggest an alternative interpretation. These data showed that although very rare, ICV has been associated with haemorrhagic occlusive retinal vasculitis (HORV). ICC had minimal toxicity events at standard doses. ICM was the most studied antibiotic for safety and found to have a low toxicity profile at all studied concentrations.

Zhao X et al., 2017 [8].

Comparison of the efficacy and patients' tolerability of Nepafenac and Ketorolac in the treatment of ocular inflammation following cataract surgery: A meta-analysis of randomized controlled trials

Fragestellung

We undertook a meta-analysis to evaluate the efficacy and patient tolerability of Nepafenac and Ketorolac for the prevention and treatment of pain and inflammation following cataract surgery, in order to provide a reference for the decision-making of ophthalmologists.

Methodik

Population:

- visually significant cataract, intervention: cataract surgery

Intervention:

- Nepafenac

Komparator:

- Ketorolac

Endpunkte:

- best corrected visual acuity (BCVA, log MAR scale), anterior chamber inflammation, inflammation free rate, central macular thickness (CMT), intraoperative mydriasis, ocular discomfort, peak drug concentrations and prostaglandin E2 (PEG2) levels, conjunctival hyperemia and other complications;

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from their earliest entries through December, 2016

Qualitätsbewertung der Studien:

- 12-item scale: (1)Method of randomization; (2)Concealed allocation; (3)Patient blinding; (4)Provider blinding; (5)Outcome assessor blinding; (6)Drop-out rate; (7)Patient allocated as plan; (8)Free of selective outcome reporting; (9)Same baseline; (10)Co-interventions avoided or similar; (11)Acceptable compliance; (12)Same time of outcome assessment. Y = Yes, N = No, A trial with a score of 7 or more was considered high quality, more than four but no more than seven was considered moderate quality, and no more than four was considered low quality.

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs (574 patients were in the Nepafenac group and 591 in the Ketorolac group)

Charakteristika der Population:

- The sample sizes of the included studies were between 50 and 200 patients. In each study, the demographic characteristics of the two groups were similar.

Qualität der Studien:

Table 2. 12-item scale critical appraisal scores.

Author	12-item scale critical appraisal score												
	1	2	3	4	5	6	7	8	9	10	11	12	Quatily
Sahu, S 2015	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	High
Duong, HV 2007	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Malik, A 2016	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	High
Ramakrishnan, S 2016	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Tzelikis, PF 2015	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Almeida, DR 2012	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Nardi, M 2007	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	High
Walters, T 2007	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	High
Bucci, FA 2011	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Bucci, FA 2011	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Zanetti, FR 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

- The results showed that the average score for the quality of included studies was 10.55±0.93 and all of them were of high quality.

Studienergebnisse:

- Best corrected visual acuity
  - For BCVA at postoperative 1 day, 1 week and 1 month, fixed-effect models were used as no heterogeneity was detected. The forest plots of these 3 time periods also indicated that there was no statistical difference between the Nepafenac group and the Ketorolac group
- Inflammation free rate
  - Forest plots of these 3 time periods indicated that the Nepafenac group's inflammation free rate had no statistical difference with the Ketorolac group (2 RCTs)
- Ocular discomfort and conjunctival hyperemia
  - Two studies [7, 22] described the postoperative ocular discomfort rate, the pooling result by fixed-effect model (P = 0.160, I2 = 49.4%) manifested that the ocular discomfort rate of the Nepafenac group was significantly lower than the Ketorolac group (RR = 0.589, 95% CI:0.436~0.794, P = 0.001,
- Intraoperative mydriasis
  - Two studies [16, 23] described these two drugs' influence on intraoperative mydriasis. The pooling result of a fixed-effect model (P = 1.00, I2 = 0%) manifested that there was no statistical difference between the Nepafenac and Ketorolac groups in the maintenance of intraoperative mydriasis (WMD = 0.000, 95%CI: - 0.355~0.355, P = 1.000,
- Central macular thickness
  - Two studies [16, 21] included 141 patients in the Nepafenac group and 145 patients in the Ketorolac group described the perioperative CMT.
  - The forest plots of these 3 time periods manifested that there was no statistical difference between the Nepafenac group and the Ketorolac group

3 Sahu S, Ram J, Bansal R, Pandav SS, Gupta A. Effect of topical ketorolac 0.4%, nepafenac 0.1%, and bromfenac 0.09% on postoperative inflammation using laser flare photometry in patients having phacoemulsification. Journal of cataract and refractive surgery. 2015; 41(10):2043±2048. doi: 10.1016/j. jcrs.2015.10.061 PMID: 26703278
4. Duffin RM, Camras CB, Gardner SK, Pettit TH. Inhibitors of surgically induced miosis. Ophthalmology. 1982; 89(8): 966±979. PMID: 7133642
5. O' Brien TP. Emerging guidelines for use of NSAID therapy to optimize cataract surgery patient care. Current medical research opinion. 2005; 21(7): 1131±1137. doi: 10.1185/030079905X50651 PMID: 16004683
6. Heier JS, Topping TM, Baumann W, Dirks MS, Chern S. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. Ophthalmology. 2000; 107(11): 2034±2039. http://dx.doi.org/10.1016/S0161-6420(00)00365-1. PMID: 11054327
7. Nardi M, Lobo C, Bereczki A, Cano J, Zagato E, Potts S, et al. Analgesic and anti-inflammatory effectiveness of nepafena 0.1% for cataract surgery. Clinical Ophthalmology. 2007; 1(4):527±533. PMID: 19668532
14 Walters T, Raizman M, Ernest P, Gayton J, Lehmann R. In vivo pharmacokinetics and in vitro pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac. Journal of cataract and refractive surgery. 2007; 33(9):1539±1545. doi: 10.1016/j.jcrs.2007.05.015 PMID: 17720067
15. Bucci FJ, Waterbury LD. A randomized comparison of to-aqueous penetration of ketorolac 0.45%, bromfenac 0.09% and nepafenac 0.1% in cataract patients undergoing phacoemulsification. Current medical research opinion. 2011; 28(12):2235±2239.
16. Ramakrishnan S, Baskaran P, Talwar B, Venkatesh R. Prospective, Randomized Study Comparing the Effect of 0.1% Nepafenac and 0.4% Ketorolac Tromethamine on Macular Thickness in Cataract Surgery Patients With Low Risk for Cystoid Macular Edema. Asia-Pacific journal of ophthalmology (Philadelphia, Pa.). 2015; 4(4): 216±220.
17. Duong HV, Westfield KC, Chalkley TH. Ketorolac tromethamine LS 0.4% versus nepafenac 0.1% in patients having cataract surgery. Prospective randomized double-masked clinical trial. Jouranl of cataract and refractive surgery. 2007; 33(11):1925±1929.
20. Malik A, Sadafale A, Gupta YK, Gupta A. A comparative study of various topical nonsteroidal anti-inflammatory drugs to steroid drops for control of post cataract surgery inflammation. Oman journal of ophthalmology. 2016; 9(3):150±156. doi: 10.4103/0974-620X.192268 PMID: 27843229
21. Tzelikis PF, Vieira M, Hida WT, Motta AF, Nakano CT, Nakano EM, et al. Comparison of ketorolac 0.4% and nepafenac 0.1% for the prevention of cystoid macular oedema after phacoemulsification: prospective placebo-controlled randomised study. British journal of ophthalmology. 2015; 99(5):654±658. doi: 10.1136/bjophthalmol-2014-305803 PMID: 25385061
22. Almeida DR, Khan Z, Xing L, Bakar SN, Rahim K, Urton T, et al. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. Journal of cataract and refractive surgery. 2012; 38(9):1537±1543. doi: 10.1016/j.jcrs.2012.04.034 PMID: 22795976
23. Zanetti FR, Fulco EA, Chaves FR, Costa Pinto AP, Arieta CE, Lira RP. Effect of preoperative use of topical prednisolone acetate, ketorolac tromethamine, nepafenac and placebo, on the maintenance of intraoperative mydriasis during cataract surgery: a randomized trial. Indian journal of ophthalmology. 2012; 60(4):277±281. doi: 10.4103/0301-4738.98705 PMID: 22824596
24. Bucci FJ, Waterbury LD. Prostaglandin E2 inhibition of ketorolac 0.45%, bromfenac 0.09%, and nepafenac 0.1% in patients undergoing phacoemulsification. Advances in therapy. 2011; 28(12): 1089±1095. doi: 10.1007/s12325-011-0080-7 PMID: 22105509

Anmerkung/Fazit der Autoren

Compared with Ketorolac, topical Nepafenac has a superior efficacy in patients' tolerability following cataract surgery. However, these two drugs are equally desirable in the management of anterior chamber inflammation, visual rehabilitation and intraoperative mydriasis. Given the limitations in our study, further researches with larger sample sizes and focus on more specific indicators such as peak aqueous concentrations of drugs or PEG2 levels are required to reach a firmer conclusion.

3.4 Leitlinien

NICE, 2017 [6].

Cataracts in adults: management

Zielsetzung/Fragestellung

This guideline covers managing cataracts in adults aged 18 and over. It aims to improve care before, during and after cataract surgery by optimising service organisation, referral and surgical management, and reducing complications. It further aims to improve the availability of information for people with cataracts before, during and after cataract surgery.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert. Originalpublikation aus dem Jahr 2008.

Recherche/Suchzeitraum:

1. Cochrane Database of Systematic Reviews –CDSR (Wiley)□Cochrane Central Register of Controlled Trials –CENTRAL (Wiley)□Database of Abstracts of Reviewsof Effects –DARE (Wiley)□Health Technology Assessment Database –HTA (Wiley)□EMBASE (Ovid)□MEDLINE (Ovid)□MEDLINE In-Process (Ovid)□PsychINFO (Ovid)

- July 2015 and November 2016. The re-run searches took place in January 2017

LoE

- Grade

GoR

The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

- Interventions that must (or must not) be used: We usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally we use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
- Interventions that should (or should not) be used – a ‘strong’ recommendation: We use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer…’) when we are confident that an intervention will not be of benefit for most patients.

- Interventions that could be used: We use ‘consider’ when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Empfehlungen

12.5 Interventions to prevent endophthalmitis

12.5 What is the effectiveness of prophylactic antiseptics and antibiotics to prevent endophthalmitis after cataract surgery?

1.8.4 Use preoperative antiseptics in line with standard surgical practice.

1.8.5 Use intracameral cefuroxime during cataract surgery to prevent endophthalmitis.

Trade-off between benefits and harms

The committee was not surprised that there were no RCT evidence for **antiseptics** as they are used extensively as part of standard surgical practice to prevent infection (in both cataract and other types of surgery). It may therefore be unethical not to offer people antiseptics or to randomise people to a pure placebo group in research trials. The routine use of antiseptic prophylaxis was also confirmed in the 2 RCTs of antibiotics, where antiseptics were used as prophylaxis at the time of surgery. The committee agreed that, although there is no evidence on the use of antiseptic prophylaxis, a strong (‘use’) recommendation should still be made due to the widespread practice. It also agreed that, since there was no evidence to suggest antiseptic use should be any different in people with cataract surgery, the use should be in line with standard general surgical practice.

For the study by ESCRS, the committee discussed the evidence for both clinically diagnosed and culture-proven endophthalmitis, where significant findings were only seen in the clinically diagnosed endophthalmitis **with intracameral cefuroxime** and in none of the culture-proven cases. The committee discussed and agreed that clinically diagnosed cases may not always be culture-positive. Examples of possible reasons for this could be that the culture techniques used are not sensitive enough or the sample taken is not large enough to have captured an adequate amount of the bacteria to grow on the culture plate. The committee was therefore not concerned about the non-significant results for culture-proven endophthalmitis. The committee agreed that, as a significant reduction in clinically diagnosed endophthalmitis with intracameral cefuroxime was evident in the evidence and from the clinical experience of committee members, intracameral injection is also more comfortable for the patient, a strong (‘use’) recommendation should be made. […]

Quality of evidence

The committee agreed that the ESCRS study was well-designed and executed but for the Sobaci et al. (2003) study, the committee had some concern that excluding people where the surgical technique was modified may have excluded people at the highest risk of infection. They also noted the small study sample size in the Sobaci et al. study and agreed that the trial would need to be much larger in order to provide any meaningful evidence. The committee discussed the lack of evidence on postoperative antibiotics, and that this may be due to the fact that they are provided as part of standard good clinical practice in the UK (although there is wide variation in practice around the world). In addition, the committee recognised that patients are invariably receiving other drops (e.g. steroids), which are likely provided in combination with postoperative antibiotic drops and often in a single drop product. For this reason, and in the absence of evidence, the committee agreed that it would be inappropriate to make a recommendation for postoperative antibiotics at this stage but instead it would useful to make a recommendation for future research

Other consideration

The committee discussed the risk of antibiotic resistance but agreed that the risk is low here because the doses are so low, and none of the commonly used antibiotics are ones that are critical for use in other situations. The committee was therefore not concerned about any antibiotic resistance issues as a result of the recommendations made.

Table 52 Summary of included studies for the effectiveness of prophylactic antiseptics and antibiotics to prevent endophthalmitis

Study & location	Population	Comparison(s)	Antibiotics or antiseptics	Placebo
ESCRS 2007 Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey and the UK	16,603 people undergoing phacoemulsification cataract surgery	Intracameral antibiotics vs. topical antibiotics (pre- and postoperative) vs. combined intracameral and topical antibiotics vs. placebo	Intervention #1: intracameral cefuroxime 0.9% (injected into the anterior chamber at the end of surgery) Intervention #2: topical levofloxacin 0.5% (instilled one drop one hour before surgery, one drop half an hour before surgery, and three more drops at 5-minute intervals immediately after surgery) Intervention #3: combined intracameral cefuroxime and topical levofloxacin	Intervention #4: placebo drops (no sham injection was given)
Sobaci et al. 2003 Turkey	644 eyes of 640 people undergoing phacoemulsification cataract surgery	Intraoperative antibiotics vs. no antibiotics	Intervention #1: balanced salt solution (BSS) with antibiotics (20 mg/mL vancomycin and 8 mg/mL gentamicin	Intervention #2: BSS-only irrigating infusion fluid

12.6 Interventions to prevent cystoid macular oedema

What is the effectiveness of prophylactic topical corticosteroids and/or NSAIDs to prevent inflammation and cystoid macular oedema after phacoemulsification cataract surgery?

49. Consider topical steroids in combination with non-steroidal anti-inflammatory drugs (NSAIDs):

- after cataract surgery for people at increased risk of cystoid macular oedema, for example, people with diabetes or uveitis
- to manage cystoid macular oedema.

50. Offer topical steroids and/or NSAIDs after cataract surgery to prevent inflammation and cystoid macular oedema.

Trade-off between benefits and harms

The committee noted that the evidence was only available in a low-risk (routine) population and that majority of the studies had excluded the higher-risk population, such as people at high risk of inflammation or those with uveitis, who have a predisposition for CMO. The committee discussed whether the evidence could be generalised and applied to the high-risk population and it agreed that, based on committee members' clinical experience, they would expect to see similar overall relative benefits in both groups (although absolute effects would be greater, owing to higher underlying event rates), despite the lack of evidence in the high-risk group.

The committee also discussed the use of topical steroids and NSAIDs in current clinical practice and agreed that both groups of drugs are routinely used in prophylaxis and treatment. In particular, the committee highlighted that NSAIDs with or without steroids are commonly administered to people with diabetes and for treatment of symptomatic CMO, in which setting they have been shown to be effective. However, the committee also acknowledged that some clinicians may worry about prescribing NSAIDs due to side effects such as stinging, burning, and conjunctival hyperaemia which could potentially lead to poor compliance. These types of side effects were also reported in some of the included studies. Discussing the evidence, the committee agreed that, although NSAIDs with or without steroids were shown to be better than steroids alone in reducing the risk of CMO, in people with a low preoperative risk of CMO, the effects shown would not be sufficient to justify the routine use of combination NSAID and steroid therapy for all people undergoing cataract surgery, particularly given the low quality of much of the evidence base. Hence, based on the evidence-base and the current clinical practice of providing either topical steroids and/or NSAIDs as prophylaxis to people undergoing cataract surgery, the committee agreed to make a recommendation to offer topical steroids and/or NSAIDs for all people following cataract surgery.

From the knowledge and clinical experience of committee members, combination therapy is commonly used in people who are at higher risk of CMO. The majority of the studies intentionally excluded people who are at high risk, and therefore the only relevant evidence came from populations of people with diabetic retinopathy. The committee agreed that it was reasonable to extrapolate this evidence to other populations at high preoperative risk of CMO, such as people with other retinal disease or uveitis, and therefore a 'consider' recommendation was made for combination therapy in people at high risk of CMO. No evidence was identified on the timing/duration of treatment, and therefore the committee agreed it was not possible to make any recommendations on this topic.

Quality of evidence

The committee discussed that it may be difficult to generalise the evidence to the most common settings in the UK because the majority of the evidence was only available in populations at low preoperative risk for CMO. Nevertheless, the committee agreed that it would expect to see a similar overall relative response in both groups. The committee noted that the evidence presented consisted of comparisons between active treatments, rather than comparisons to no treatment or placebo. However, it agreed that it would be considered unethical not to give some prophylactic treatment, and therefore agreed this omission did not adversely affect the quality of the evidence base.

Evidence statements – Inflammation

Very low-quality evidence from 5 RCTs containing 346 participants found no meaningful difference between NSAIDs and steroids in controlling postoperative inflammation (measured as flare [photons/ms]) after cataract surgery.

Low quality-evidence from 1 RCT containing 47 participants indicates that, compared with steroids alone, NSAIDs plus steroids are more effective in controlling postoperative inflammation (measured as flare [photons/ms]) after cataract surgery.

Very low-quality evidence from 2 RCTs containing 198 participants found no meaningful difference between NSAIDs plus steroids and steroids alone in the risk of postoperative inflammation (measured as number of events) after cataract surgery.

Evidence statements –Best corrected distance visual acuity (BCVA)

Very low-quality evidence from 3 RCTs containing 220 participants found no meaningful difference between NSAIDs and steroids on the improvement of BCVA [logMAR] after cataract surgery.

Very low-quality evidence from 7 RCTs containing 782 participants found no meaningful difference between NSAIDs plus steroids and steroids alone on the improvement of BCVA [logMAR] after cataract surgery.

Evidence statements –Adverse events

Very low-quality evidence from 5 RCTs containing 346 participants found no meaningful difference between NSAIDs and steroids in the risk of adverse events.

Very low-quality evidence from 10 RCT containing 1,467 participants found no meaningful difference between NSAIDs plus steroids and steroids alone in the risk of adverse events.

Olsen et al., 2017 [7].

AMERICAN ACADEMY OF OPHTHALMOLOGY

Cataract in the Adult Eye Preferred Practice Pattern®

Zielsetzung/Fragestellung

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that identify characteristics and components of quality eye care.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Konsensusprozess nicht detailliert beschrieben, externe Begutachtung dargelegt;
- Empfehlungen der Leitlinie sind ersichtlich; die Verbindung zu der zugrundeliegenden Evidenz ist dargestellt, jedoch sind die Empfehlungen nicht explizit hervorgehoben
- Regelmäßige Überprüfung der Aktualität gesichert. Die Leitlinie ist 5 Jahre nach Publikation gültig

Recherche/Suchzeitraum:

- PubMed Searches (limits: English, Publication date 1/10/11 – 7/13/2015)

LoE

To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

GoR

Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

Sonstige methodische Hinweise

- Konsensfindung nur allgemein beschrieben.

Empfehlungen

Infection Prophylaxis

There is increasing evidence that supports the use of intraocular antibiotics to reduce the risk of endophthalmitis. (I-, good quality, strong recommendation)

> The partially masked and randomized European Society of Cataract and Refractive Surgeons (ESCRS) study of the prophylactic effect of intracameral cefuroxime injection at the conclusion of the procedure and/or perioperative levofloxacin eye drops on the incidence of endophthalmitis after phacoemulsification was halted early because of a beneficial effect using intracameral cefuroxime. Based on data from 13,698 patients with complete follow-up records, investigators found that the odds ratio for developing endophthalmitis was 4.59 (95% CI, 1.74–12.08; P=0.002) in the group not receiving intracameral cefuroxime injection.351 […] One study used serial aqueous taps in cataract patients to determine that a single intracameral bolus of 1 mg of vancomycin achieved aqueous drug levels exceeding the minimum inhibitory concentration for most gram-positive bacteria for longer than 24 hours. However, the use of vancomycin as an endophthalmitis prophylaxis is strongly discouraged based on the recent finding of hemorrhagic occlusive retinal vasculitis (HORV) development after seemingly uncomplicated cataract surgery.401 Several studies support the safety of intracameral moxifloxacin injection for endophthalmitis prophylaxis, and three retrospective studies suggest efficacy.346,347,392,400,402-404
>
> Although the evidence is limited, retrospective studies suggest that topical antibiotic prophylaxis may be effective,336,346
>
> Evidence of the benefit of injecting subconjunctival antibiotics at the conclusion of surgery is supported by two retrospective surveys. However, this is associated with risks that include pain, globe perforation, hemorrhage, and intraocular toxicity from subconjunctival leakage through the incision with the potential for macular infarction when aminoglycosides are used.342,414,415
>
> Topical fourth-generation fluoroquinolones have theoretical advantages of broad-spectrum coverage, bactericidal activity, and improved intraocular penetration, and they were the most frequent topical prophylactic antibiotics used by the ASCRS survey respondents.411 […] Furthermore, one very large study based on 315,246 surgeries did not show a difference in efficacy between topical gatifloxacin, ofloxacin, or polymyxin/trimethoprim. However, the use of topical aminoglycosides was associated with double the rate of postoperative endophthalmitis, suggesting they are not a good choice for prophylaxis.346 This study also found that although topical antibiotics did not increase the efficacy of intracameral antibiotics, the lack of antibiotics altogether had twice the incidence of postoperative endophthalmitis when compared with topical antibiotics alone, and the use of no antibiotics had four times the incidence when compared with intracameral antibiotic use.
>
> There is mounting evidence that injecting intracameral antibiotics as a bolus at the conclusion of surgery is an efficacious method of endophthalmitis prophylaxis. The evidence supporting subconjunctival antibiotic prophylaxis is relatively weak. As an alternative to intracameral or subconjunctival injection, topical antibiotic instillation may be more protective when initiated on the day of surgery instead of on the first postoperative day. Due to the lack of sufficiently large prospective clinical trials, and the impracticality of conducting such trials, there is insufficient evidence to recommend a specific antibiotic drug or method of delivery for endophthalmitis prophylaxis. However, increasing evidence supports the role of intracameral antibiotic use.424

There is good evidence for the use of a 5% solution of povidone iodine in the conjunctival cul de sac to prevent infection.369,423 (II-, moderate quality, strong recommendation)

In conclusion, the surgeon must ensure that antisepsis of the periocular surface, typically with povidone iodine, is achieved and that all incisions are closed in a watertight fashion at the end of the procedure.336 (II-, moderate quality, strong recommendation)

> Importantly, nonrandomized controlled trials and a prospective trial with the unoperated eye as the control have provided evidence that using topical 5% povidone iodine in the conjunctival cul de sac reduced the bacterial load and the incidence of postoperative infection.368-370 Lower concentrations of povidone iodine are less effective in reducing conjunctival bacterial colony counts.371-373 The presence of lidocaine gel prior to povidone iodine instillation appears to diminish its antimicrobial efficacy.374 Although topical antibiotics prior to surgery do decrease the bacterial load on the ocular surface, 1 day was as effective as 3 days of preoperative antibiotics in one randomized study, and topical povidone iodine alone was as effective as povidone iodine combined with preoperative topical antibiotics in another randomized clinical study.375-381 So, it is unlikely that preoperative topical antibiotics add anything to the effect of appropriately used topical 5% povidone just prior to surger

It would appear that antibiotic use on the day of surgery is important rather than waiting until the next day.336 Specific prophylactic antibiotic strategies in the perioperative period lack sufficient scientific evidence to make a recommendation at this time.

Although topical antibiotics prior to surgery do decrease the bacterial load on the ocular surface, 1 day was as effective as 3 days of preoperative antibiotics in one randomized study, and topical povidone iodine alone was as effective as povidone iodine combined with preoperative topical antibiotics in another randomized clinical study.375-381 So, it is unlikely that preoperative topical antibiotics add anything to the effect of appropriately used topical 5% povidone just prior to surgery.

Toxic anterior segment syndrome (TASS)

Toxic anterior segment syndrome (TASS) is a sterile postoperative inflammatory reaction that typically presents within 12 to 48 hours following surgery and can mimic infectious endophthalmitis.[…] Toxic anterior segment syndrome usually responds to anti-inflammatory medication, but permanent intraocular damage can occur. However, if there is sufficient suspicion of an infectious etiology, cultures of the anterior chamber and vitreous should be obtained to test for infectious etiologies, and antibiotic treatment should be initiated.426 […]

Prolonged inflammation

There are several potential etiologies for prolonged postsurgical inflammation. Persistent iritis has been associated with retained lens fragments,655 previous history of uveitis,656 and a subacute infection with Propionibacterium acnes.657 Other infectious agents, such as fungi, can cause indolent infection and inflammation. Malposition or misplacement of IOLs of specific design may also lead to persistent intraocular inflammation.

The surgeon should ensure proper orientation of IOLs to prevent corneal complications. (III, good quality, strong recommendation) Insufficient postoperative anti-inflammatory medication may also be a contributory cause.658

Cystoid macular edema (CME)

Because CME is generally associated with postsurgical inflammation, topical anti-inflammatory medications are used to prevent CME as well as to treat established CME. There is evidence that NSAIDs, alone or in combination with topical corticosteroids, decrease the likelihood of postoperative CME. There are studies showing benefit to early visual recovery but no level I evidence yet demonstrating a long-term benefit (i.e., 3 months or more).395,711-728

At present, there is no firmly established protocol for preventing postsurgical CME. Aside from retinitis pigmentosa, there are no known genetic predispositions. The perioperative prophylactic use of NSAIDs for prevention of CME has been advocated for high-risk eyes based on a number of studies.710,732 Administration of NSAIDs before and immediately after surgery may hasten the recovery of vision in the first few weeks following surgery. However, there is no level I evidence that visual outcome is improved by the routine use of prophylactic NSAIDs at 3 months or more after cataract surgery.725 (II+, moderate quality, strong recommendation)

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 7 of 12, July 2020) am 17.07.2020

#	Suchfrage
1	[mh ^"ophthalmologic surgical procedures"]
2	[mh "cataract extraction"]
3	(((cataract* OR lens*) AND (extract* OR aspirat* or operat* or remov* or surg* or excis* or implant*)) OR “enzymatic zonulolysis” OR phakectomy OR lensectomy OR phaoemulsif* OR phakoemulsif*):ti,ab,kw
4	#1 OR #2 OR #3
5	[mh "eye infections"]
6	(endophthalmitis* OR ophthalmia* OR trachoma* OR keratoconjunctivitis*):ti,ab,kw
7	#5 OR #6
8	[mh uveitis]
9	(uveitis* OR panuveitis* OR panophthalmitis* OR iridocyclitis* OR iritis* OR choroiditis* OR chorioretinitis*):ti,ab,kw
10	#8 OR #9
11	#4 OR #7 OR #10
13	#11 with Cochrane Library publication date from Jul 2015 to Jul 2020

Systematic Reviews in Medline (PubMed) am 17.07.2020

#	Suchfrage
1	ophthalmologic surgical procedures[mh:noexp]
2	cataract extraction[mh]
3	((cataract*[tiab] OR lens*[tiab]) AND (extract*[tiab] OR aspirat*[tiab] OR operat*[tiab] OR remov*[tiab] OR surg*[tiab] OR excis*[tiab] OR implant*[tiab])) OR enzymatic zonulolysis[tiab] OR phakectom*[tiab] OR lensectom*[tiab] OR phaoemulsif*[tiab] OR phakoemulsif*[tiab]
4	#1 OR #2 OR #3
5	eye infections[mh]
6	endophthalmitis*[tiab] OR ophthalmia*[tiab] OR trachoma*[tiab] OR keratoconjunctivitis*[tiab]
7	#5 OR #6
8	uveitis[mh]
9	uveitis*[tiab] OR panuveitis*[tiab] OR panophthalmitis*[tiab] OR iridocyclitis*[tiab] OR iritis*[tiab] OR choroiditis*[tiab] OR chorioretinitis*[tiab]
10	#8 OR #9
11	(#7 OR #10) AND (cataract*[tiab] OR lens*[tiab])
12	#4 OR #11
13	(#12) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR

	integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
14	((#13) AND ("2015/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 17.07.2020

#	Suchfrage
1	ophthalmologic surgical procedures[mh:noexp]
2	cataract extraction[mh]
3	((cataract*[tiab] OR lens*[tiab]) AND (extract*[tiab] OR aspirat*[tiab] OR operat*[tiab] OR remov*[tiab] OR surg*[tiab] OR excis*[tiab] OR implant*[tiab])) OR enzymatic zonulolysis[tiab] OR phakectom*[tiab] OR lensectom*[tiab] OR phaoemulsif*[tiab] OR phakoemulsif*[tiab]
4	#1 OR #2 OR #3
5	eye infections[mh]
6	endophthalmitis*[tiab] OR ophthalmia*[tiab] OR trachoma*[tiab] OR keratoconjunctivitis*[tiab]
7	#5 OR #6
8	uveitis[mh]
9	uveitis*[tiab] OR panuveitis*[tiab] OR panophthalmitis*[tiab] OR iridocyclitis*[tiab] OR iritis*[tiab] OR choroiditis*[tiab] OR chorioretinitis*[tiab]
10	#8 OR #9
11	#7 OR #10

12	#4 OR #11
13	(#12) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
14	(((#13) AND ("2015/07/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

Referenzen

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8. **Zhao X, Xia S, Wang E, Chen Y.** Comparison of the efficacy and patients' tolerability of nepafenac and ketorolac in the treatment of ocular inflammation following cataract surgery: a meta-analysis of randomized controlled trials. PLoS One 2017;12(3):e0173254.

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2020-B-195

Kontaktdaten

Deutsche Ophthalmologische Gesellschaft (DOG), in Abstimmung mit Deutschsprachige Gesellschaft für Intraokularlinsen-Implantation (DGII), Berufsverband der Augenärzte (BVA)

Indikation gemäß Beratungsantrag

Behandlung von Patient*innen mit Augentropfen im Zusammenhang mit Kataraktoperationen

Was ist der Behandlungsstandard im Zusammenhang mit Katarakt-Operationen ?

Bisher gibt es noch keine verfügbare AWMF-Leitlinie zur perioperativen Therapie der Katarakt-Operation. Eine S2e-Leitlinie ist in der Phase der Beratung und Erstellung.
Im Zusammenhang mit Katarakt-Operationen findet eine Behandlung von Patienten mit Augentropfen mit unterschiedlichen Überlegungen statt:

a) **Infektions-Prophylaxe** (Endophthalmitis)
Für eine Empfehlung muss berücksichtigt werden, dass es kaum Evidenz für eine prophylaktische Gabe antibiotischer Augentropfen in der perioperative Phase gibt.[1]
Methodisch erschweren verschiedene Faktoren die Durchführung kontrollierter Studien, die eine Vermeidung intraokularer Infektionen nach der Linsenchirurgie belegen könnten. Die absolute **Inzidenz** einer **Endophthalmitis** ist sehr niedrig, mit Inzidenzen zwischen 0.29 bis 1.79 auf 1000 Operationen.[2-4] Die funktionellen Auswirkungen sind aber oft schwerwiegend.[5-6] Oft wird eine Clusterung der Ereignisse (gehäuftes zeitliches Auftreten z.B. durch Kontaminationen verwendeter Materialien) beobachtet.[7-8] Die periokuläre Flora wurde meist als primäre Quelle sporadischer postoperativer Infektionen identifiziert.[9] Große Stichproben, eine multizentrische Erfassung und aussagekräftige Zeiträume sind für die Nachbeobachtung erforderlich. Eine Differenzierung gegenüber nicht infektiösen Entzündungen erschwert zusätzlich die Analysen; unterschiedliche Definitionen und Ausprägungen werden zudem in der Literatur beschrieben. Die intersektorale und teils sehr unterschiedlich gehandhabte perioperative Versorgung des Patienten erschwert eine zuverlässige Erhebung von Daten. Gerade das Auftreten mit zeitlichem Abstand oder räumlicher Entfernung steht einer zuverlässigen Erfassung entgegen. Studien erlauben zum Teil den Einschluss einzeitig bilateraler Operationen. Außerdem können andere Faktoren wie operative Technik (Schnittführung) und individuelle Risiken nur schwer harmonisiert werden.
Die Maßnahme mit der größten Evidenz ist die präoperative Anti-Sepsis mit **Povidon-Iod** (5%ige Konzentration zum Ausspülen der Bindehaut, Abstreichen der Haut mit 10%iger Lösung).[10] Angesichts des Zusammenhangs zwischen der Bakterienflora der Augenoberfläche und dem Keimspektrum der Endophthalmitis[9] bietet Povidon-Iod eine signifikante Reduktion (nicht Eradikation) der Keimlast.[11-12] Eine Reduktion potentieller Erreger über die Vorbereitung

Kontaktdaten

Deutsche Ophthalmologische Gesellschaft (DOG), in Abstimmung mit Deutschsprachige Gesellschaft für Intraokularlinsen-Implantation (DGII), Berufsverband der Augenärzte (BVA)

Indikation gemäß Beratungsantrag

Behandlung von Patient*innen mit Augentropfen im Zusammenhang mit Kataraktoperationen

mit Povidon-Iod hinaus kann die Gabe antibiotischer Augentropfen nicht erreichen.[13-14]
Inzwischen wird auch die Wirksamkeit einer Gabe von Antibiotika in das Auge (zum Zeitpunkt der Operation) durch verschiedene Hinweise unterstützt. Die nur teilweise maskierte und randomisierte Studie der *European Society of Cataract and Refractive Surgeons* (ESCRS) wurde wegen der prophylaktischen Wirkung von intrakameralen Cefuroxim-Injektionen zum Abschluss des Eingriffs und/oder perioperativen Levofloxacin-Augentropfen abgebrochen:[15] Auf der Grundlage der Daten (n=13.698 Patienten mit vollständiger Nachbeobachtung) war die Wahrscheinlichkeit einer Endophthalmitis ohne Cefuroxim-Injektion um 4,59 (95% CI, 1,74-12,08) erhöht. Die Inzidenz in der Kontrollgruppe war allerdings höher als in anderen Studien. Retrospektive Arbeiten beschrieben jedoch auch eine deutliche Verringerung der schweren Entzündungsereignisse, nachdem mit der intrakameralen Gabe von Cefuroxim begonnen worden war.[16-22] Kleinere prospektive Studien unterstützen die Beobachtung.[23]
Die Verabreichung antibiotischer Augentropfen vor und/oder nach einer Katarakt-Operation wird – gerade nach oder trotz der Gabe intraokularer Antibiotika - kontrovers diskutiert. Die Tropfpräparate können zwar die bakterielle Siedlung verringern, es ist jedoch fraglich, ob diese Wirkung – über die prä-operative Antisepsis hinaus – erforderlich oder hilfreich ist. Es ist „sehr unsicher“,[1] ob die Gabe antibiotischer Augentropfen das Risiko einer Endophthalmitis verringert, erst recht wenn diese zusätzlich zu einer Gabe von Antibiotika im Rahmen der Operation erfolgen.
Gegenüber einer theoretischen Verringerung der Keimlast stehen theoretische Nachteile wie

- die Entwicklung von **Resistenzen** nach der lokalen Applikation von Breitspektrum-Antibiotika.[24]
- die **Kosten** für die Präparate und ihre Verabreichung (Pflegedienst etc.)[25]
- die Entwicklung allergischer Reaktionen auf die Wirk- oder Inhaltstoffe[26,27]
- zusätzliche Risiken für die Schädigung der Oberfläche, insbesondere für den Fall einer unsachgemäßen Anwendung (Manipulation am Auge)[28]

Insgesamt soll daher aufgrund der geringen Evidenz eines Nutzens, der auch Nachteile gegenüberstehen, keine Routine-mäßige Anwendung antibiotischer Augentropfen erfolgen. Eine Therapie mit Antibiotika sollte in begründeten Einzelfällen erfolgen, z.B. wenn in der perioperativen Therapie einer bakteriellen Entzündung der Bindehaut/Lider besteht, nach Auftreten intraoperativer Komplikationen (Kapselruptur, Glaskörperprolaps, Vitrektomie), eine Unverträglichkeit gegenüber Povidon-Iod bekannt ist oder Hinweise auf eine intraokulare Infektion in den Tagen nach einer Katarakt-Operation vorliegen.

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b) Antiphlogistische Wirkung

Die Gruppe zur Verfügung stehender Wirkstoffe reicht von nicht-steroidalen Wirkstoffen (Ketorolac, Diclofenac, Nepafenac, Flurbiprofen, Salicylsäure) über oberflächen-wirksame Steroide (Fluormetholon, Loteprednol, Hydrocortison) bis hin zu Dexamethason und Prednisolon.

Die NSAID sollen teilweise der peri-operativen Vermeidung einer Pupillenverengung dienen und/oder das Auftreten von Verklebungen der Iris und Kapsel/Linsen-Vorderfläche verhindern. Weil die Anwendung zum Teil in den zugrundeliegenden Studien vor der Operation begonnen wurde, weisen die Fachinformationen teilweise auf einen „präoperativen Behandlungsbeginn“ (Diclofenac) hin.

Die Behandlung dient vor allem der Vermeidung bleibender/relevanter Komplikationen nach komplizierten Operationen oder bei Risikogruppen. Es stellt sich die Frage, ob der alleinige oder kombinierte Einsatz aber auch nach **unkomplizierter Katarakt-Chirurgie** von Nutzen ist.

Ein Cochrane-Report von 2017 identifizierte 48 randomisierte kontrollierte Studien (RCTs), die aber nur selten klare Ergebnisse in Bezug auf die Entzündung (dichotome Variablen wie Vorderkammer-Zellen, Hornhautödem) beschrieben und insbesondere keinen Nachweis eines funktionellen Vorteils (bestkorrigierter Visus) erfassen konnten.[29] Hinweise aus 4 RCTs deuten aber darauf hin, dass die Häufigkeit eines Makulaödems nach unkompliziertem Operationsverlauf erniedrigt wurde. Eine vergleichende Bewertung der Kombination von NSAID und Kortikosteroiden gegenüber einer Monotherapie mit Kortikosteroiden ist mangels aussagekräftiger Studien nicht möglich. Viele berichtete Studien weisen methodische Schwächen (Definition oder Verblindung der Tropfschemata, Zeitpunkte zur Nachbeobachtung, Verwendung etablierter Klassifikationen) auf.

Eine frühere Meta-Analyse aus Dänemark beschreibt hochwertige Evidenz dafür, dass die Verwendung von NSAID im Vergleich zur Anwendung steroid-haltiger Augentropfen die Rate für das postoperative Makulaödem deutlich erniedrigt (3.8% vs. 25.3%).[30] Ein HTA-Bericht der *American Academy of Ophthalmology* von 2015 weist auf die hohe Rate einer Spontanremission eines Makulaödems hin und stellt daher den langfristigen Nutzen einer NSAID-Therapie zur Verhinderung des Sehkraftverlustes in Frage:[31] Die Verabreichung von NSAID kann die Sehverbesserung in den ersten Wochen nach einer Kataraktoperation beschleunigen, ohne dass es Studiendaten mit Belegen für einen Effekt auf die langfristige Funktionsentwicklung gibt. In Bezug auf die zentrale Netzhautdicke beschrieben bisherige Studien keinen klinisch relevanten Vorteil.[32] Angesichts der methodischen Limitationen und eines möglichen Verzerrungspotentials der Studien, könnten systematische Reviews die klinische Wirksamkeit der NSAID überschätzen.[33-34]

Zusammenfassend kann die anti-entzündliche Therapie mit NSAID die Inzidenz eines postoperativen zystoiden Makulaödems für Patienten mit einem relativen Risiko verringern und

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dazu beitragen, eine Entzündung nach der Operation zu kontrollieren. Die Evidenz wurde vor allem mit Studien über eine Laufzeit von 1-3 Monaten gezeigt.[35]

Berücksichtigt werden müssen außerdem die seltenen potenziellen Komplikationen an der Hornhaut, die von leichter Stippung bis zur Einschmelzung reichen können.[36,37] Daher sollte die Verordnung vor dem Hintergrund des individuellen Nutzen betrachtet werden. Ein abschließender Vergleich der alleinigen Gabe von NSAID mit der Kombination von topischen Kortikosteroiden ist mangels aussagekräftiger Studien (noch) nicht möglich.

Konkrete Beispiele für Situationen mit einem Therapiebedarf sind:

- Das *Toxic Anterior Segment Syndrom* (TASS) stellt als Entzündung des vorderen Augenabschnitts eine wichtige Differentialdiagnose der infektiösen Endophthalmitis dar. Die sterile postoperative Entzündungsreaktion entwickelt sich typischerweise innerhalb von 12 bis 48 Stunden nach der Operation. Ödeme der Hornhaut, eine zelluläre Infiltration der Vorderkammer, Fibrin und Hypopyon können beobachtet werden. Als Ursache werden hitzestabile gramnegative Endotoxine (Wasser), chemische Reinigungsmittel und Enzyme (Reinigung der Instrumente), denaturiertes Viscoelastikum (Rückstände auf Kanülen oder Instrumenten), der pH-Wert oder Osmolalität verwendeter Lösungen und Kontaminationen der Kunstlinse diskutiert.[38]
  Mit dem Einsatz intrakameraler Antibiotika sind häufiger Berichte eines TASS aufgetaucht, die z.B. mit Verdünnungsfehlern dokumentiert wurden.[39,40] Am häufigsten wurde TASS in Verbindung mit unzureichender Reinigung und Aufbereitung ophthalmologischer Instrumente in Verbindung gebracht.[41,42] Eine entsprechende Entzündungsreaktion erfordert sicher eine intensive Therapie mit topischen Steroiden und hat dann eine gute Visusprognose.[43]
- Allgemeine, intraoperative und okuläre Risikofaktoren erhöhen die Wahrscheinlichkeit eines *Makulaödems* nach einer Katarakt-Operation. Das postoperative zystoide Makulaödem, auch Irvine-Gass-Syndrom genannt, wird in einer Häufigkeit von 1.17 - 4.2% der operierten Augen (je nach verwendeter Definition und Kohorte) berichtet.[37,44,45] Oft entwickeln sich diese Ödeme in den ersten drei Monaten nach einer Katarakt-Operation. Patienten mit Diabetes haben ein deutlich erhöhtes Risiko: Einerseits besteht ein nahezu linearer Trend zwischen dem Schweregrad einer diabetischen Retinopathie und dem Risiko eines postoperativen Ödems. Das relative Risiko ist für Menschen mit einer Retinopathie mit 6.23 [95% Konfidenzintervall: 5.12-7.58] im Vergleich zu Patienten ohne Diabetes erhöht; doch selbst Patienten ohne diabetische Retinopathie haben ein signifikant erhöhtes Risiko.[46] Andere okuläre Erkrankungen wie z.B. eine Uveitis oder retinale Gefäßerkrankungen werden von einer Störung der Blut-Netzhaut-Schranke begleitet.[37] Auch komplizierte Operationen sind mit einem erhöhten relativen Risiko der Ödem-Entwicklung verbunden.[46] Eine Rationale der prophylaktischen Therapie ist die

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Beobachtung, dass chronische Ausprägungen eines zystoiden postoperativen Ödems schlechter auf die Therapie mit Augentropfen ansprechen.[48]

c) Schmerzen

Unter anderem eine Verletzung der Hornhaut-Oberfläche kann im Einzelfall Schmerzen nach einer Katarakt-Operation verursachen. Abgesehen von einer oralen Schmerztherapie sind einzelne Wirkstoffe auch zur Linderung postoperativer Schmerzen zugelassen (z.B. Nepafenac zur „Prophylaxe und Behandlung postoperativer Schmerzzustände“ oder Diclofenac zur „Behandlung von Augenschmerzen bei photorefraktiven OPs über bis zu 24 Stunden nach der Operation“).[49]

Augentropfen sind daher eine Option, um systemische Medikamente mit entsprechenden Nebenwirkungen zu vermeiden einzusparen.[50]

d) Oberflächenpflege

Zahlreiche Erkrankungen der Augenoberfläche sind mit einer Tränenmindersekretion oder erhöhten Instabilität des Tränenfilms verbunden, z.B. Graft-versus-host Disease, das okuläre Pemphigoid oder Zustand nach Verätzungen. Bei Menschen mit einem trockenen Auge (Benetzungsstörung), gerade aber auch bei schweren Ausprägungen der Erkrankungen der Augenoberfläche kann es in zeitlicher Folge nach einer Katarakt-Operation zu einer Verschlechterung der Benetzungssituation kommen.[51] Daher ist in bestimmten Situationen eine intensivierte Behandlung mit Tränenersatzmitteln gefordert, um das kompromittierte Hornhautepithel zu schützen.[52] Allerdings existieren kaum Studien, die unterschiedliche Präparate systematisch miteinander vergleichen.[53,54]

Zusammenfassung:

Für den Behandlungsstandard nach einer Katarakt-Operation muss insgesamt ein Spektrum unterschiedlicher Anwendungsgebiete berücksichtigt werden. Die klare Abgrenzung wird dadurch erschwert, dass individuell unterschiedliche Faktoren für die Entscheidung über die Gabe anti-entzündlicher Augentropfen zu berücksichtigen sind. Zur Vorbeugung und Behandlung von Entzündungen, aber auch zur Vorbeugung oder Therapie von Infektionen ist zu differenzieren, welche Risikofaktoren wie z.B. Alter, Operationsverlauf, systemische oder okuläre Vorerkrankungen vorliegen.

Die postoperative Therapie beinhaltet in der Regel steroidale und/oder nichtsteroidale Augentropfen über zwei bis vier Wochen.[55]

In bestimmten **Szenarien** wie einem protrahierten Vorderkammer-Reiz, der Verletzung der Oberfläche, Infektionen und/oder Entzündungen der Bindehaut, Schmerzen, dem Rezidiv einer Herpes-Infektion, bei erhöhtem Risiko eines postoperativen Makulaödems oder aber der Entwicklung eines zystoiden Makulaödems kann eine medikamentöse Therapie mit den

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genannten Präparaten angeraten sein. Es liegt in der Entscheidung des operierenden Chirurgen, die Therapie in Abhängigkeit des Operationsverlaufs und der post-operativen Befunden anzupassen.

Zu den **Komplikationen** der postoperativen Medikation gehören ein erhöhter Augeninnendruck mit Kortikosteroiden und allergische Reaktionen.[56,26,27] Signifikante Hornhautreaktionen, einschließlich Epitheldefekten und stromalen Ulzerationen und Einschmelzungen, sind selten für topische okuläre NSAIDs berichtet worden.[36,57-60] Für die Auswahl einer zweckmäßigen Vergleichstherapie (ZVT) ist das beabsichtigte Anwendungsgebiet und die Substanzgruppe (Steroid vs. NSAID) sinnvollerweise zu berücksichtigen, um die relevanten Raten der Nebenwirkungen vergleichen zu können.

Wie sieht die Versorgungspraxis in Deutschland aus?

Am häufigsten werden die Antiphlogistika als Augentropfen in der perioperativen Phase eingesetzt. Zur Prävention einer Infektion werden antibiotische Augentropfen nur in begründeten Ausnahmefällen eingesetzt, allerdings schon zur Behandlung einer manifesten Entzündung (Konjunktivitis, Blepharitis, Endophthalmitis, etc.) im Anschluss an die Operation.

Im Vergleich zur Bewertung von Nepafenac (Nevanac®)[61] 2013 dürften sich die Zahlen der verordneten Augentropfen geringfügig erhöht haben. Der demographische Wandel hat zu einer geringen Erhöhung der Anzahl an Katarakt-Operationen zulasten der GKV und des Anteils der Menschen mit Diabetes geführt.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen zur Vorbeugung und Behandlung von Entzündungen sowie zur Vorbeugung von Infektionen im Zusammenhang mit Kataraktoperationen die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Die wichtigsten Kriterien für eine Behandlung zur Vorbeugung oder Behandlung einer Entzündung wurden oben bereits genannt. Unter anderem sind hier die Faktoren relevant, die das Risiko für ein postoperatives zystoides Malulaödem erhöhen:[37]

Allgemeine Risikofaktoren	Intraoperative Risikofaktoren/ Komplikationen	Okuläre Begleiterkrankungen
Diabetes	Ruptur der Hinterkapsel	Uveitis
Arterielle Hypertonie	Glaskörper-Prolaps/Stränge	Diabetische Retinopathie
Hohes Alter	Phako-Energie (harte Linse)	Retinale Venenverschlüsse
Männliches Geschlecht	Verletzungen der Iris, Floppy Iris	Epiretinale Gliose
	Linsenreste in Vorderkammer/Glaskörperraum	Zustand nach vitreoretinaler Chirurgie oder Netzhautablösung
	Lange Operationsdauer	Ödem des Partnerauge
		Therapie mit Prostglandin-Analoga

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