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ORIGINAL RESEARCH

Efficacy of Topical Non-Selective and COX-2 Selective NSAIDs in Accelerating Resolution of Acute Central Serous Chorioretinopathy: A Retrospective Analysis

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Purpose: To evaluate whether topical nonsteroidal anti-inflammatory drugs (NSAIDs) accelerate the resolution of acute central serous chorioretinopathy (CSCR) compared with observation.

Patients and methods: This retrospective cohort study reviewed patients diagnosed with acute CSCR (2018–2023) (n = 145). Patients received either topical ketorolac (n = 26, nonselective NSAID, four times daily) or observation alone (n = 63). Historical data (2007–2013) (n = 111) comparing COX-2 selective NSAIDs (bromfenac or nepafenac, n = 38) with observation (n = 73) were analyzed for comparison. Main outcome was time to complete subretinal fluid resolution on optical coherence tomography (OCT) and visual acuity (VA) recovery to 20/20. Outcomes were analyzed using Kaplan–Meier survival curves and Cox proportional-hazards regression.

Results: Baseline demographics were similar between NSAID-treated and observed groups (mean age 45 years, ~82% male, baseline visual acuity ~20/40). In the recent cohort, NSAID treatment with ketorolac significantly accelerated fluid resolution compared with observation (median 74 vs 115 days; hazard ratio 1.70, 95% CI 1.05–2.75, $p = 0.033$). Historical data revealed a greater treatment effect with COX-2 selective NSAIDs (mean resolution 42 days vs 131 days with observation, $p < 0.0001$). When combined, NSAIDs significantly shortened CSCR duration compared to observation alone (mean 62 vs 132 days, $p < 0.001$), with COX-2 selective NSAIDs showing superior efficacy ($p < 0.01$ vs ketorolac). Visual acuity outcomes at final resolution were excellent (~20/20) and similar between groups. No significant adverse events occurred, and 12-month recurrence rates were similar between NSAID-treated and observed groups.

Conclusion: Topical NSAIDs, especially COX-2 selective agents, may accelerate resolution of acute CSCR compared to observation alone. The earlier recovery of normal vision and anatomical resolution may benefit patients clinically by reducing morbidity associated with prolonged retinal detachment. Prospective studies are warranted to confirm these findings and refine treatment protocols for acute CSCR.

Keywords: anti-inflammatory therapy, choroid, subretinal fluid, pharmacokinetics, Retina, ophthalmology

Introduction

Central serous chorioretinopathy (CSCR) is a retinal disorder characterized by idiopathic serous detachment of the neurosensory retina, most often affecting healthy adults (especially middle-aged men) and frequently associated with type-A personality traits, psychosocial stress, and exogenous or endogenous corticosteroid exposure.[1] In acute CSCR, patients typically present with blurred central vision, metamorphopsia, and a relative central scotoma due to accumulation of subretinal fluid. The pathogenesis is thought to involve choroidal vascular hyperpermeability and retinal pigment epithelium (RPE) barrier dysfunction, leading to focal serous detachments. In most cases, acute CSCR is self-limited:

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over 75% of acute episodes resolve spontaneously within 3–6 months, with the majority of patients regaining near-normal visual acuity.[2] Consequently, the standard management for an initial episode of acute CSCR is observation with reassurance and modification of risk factors, since spontaneous recovery is expected within a few months.[2] However, a significant subset of patients (estimated ~15–20%) experience a more prolonged or recurrent course that can progress to a chronic form with persistent subretinal fluid beyond 4–6 months, placing them at risk for permanent RPE damage and vision loss.[2] For such cases, therapeutic intervention (eg verteporfin photodynamic therapy or oral mineralocorticoid antagonists) is often pursued to expedite fluid reabsorption and prevent complications.[3,4] However, mineralocorticoid receptor antagonists such as eplerenone have shown mixed or limited efficacy in chronic CSCR. For example, the VICI trial reported no significant benefit of eplerenone over placebo, exposing the need for alternative treatment approaches even in acute cases.[5]

Given the potential morbidity of extended macular detachment in CSCR, there is interest in treatments that might hasten resolution even in the "acute" phase. Various therapies have been explored, including focal laser photocoagulation, half-dose photodynamic therapy (PDT), anti-corticosteroid approaches (such as oral eplerenone), and subthreshold micropulse laser, primarily for chronic or severe CSCR.[3,4] To date, no pharmacologic treatment has been universally adopted for acute CSCR, and clinical practice for initial episodes remains largely conservative. One novel approach is the off-label use of topical NSAIDs. NSAIDs inhibit cyclooxygenase (COX) enzymes and are widely used in other retinal conditions (eg pseudophakic cystoid macular edema) to reduce retinal vascular leakage.[6] It has been hypothesized that NSAIDs might similarly promote faster resolution of subretinal fluid in CSCR by modulating choroidal inflammation and vascular permeability. COX-2 in particular is upregulated during inflammatory stress and mediates the synthesis of prostaglandin E_2 (PGE_2), a prostanoid that can increase choroidal endothelial permeability and disrupt the outer blood–retinal barrier. Blocking COX-2 could thus mitigate these effects and facilitate resolution of subretinal fluid.[7] Moreover, emerging evidence suggests a possible role of inflammation in CSCR and related pachychoroid conditions; for instance, peripapillary pachychoroid syndrome (an allied pachychoroid disorder) has been successfully treated with topical corticosteroids[8] further suggesting that inflammation is a common pathophysiological factor across the pachychoroid spectrum, including CSCR.

Previous investigations have provided preliminary support for this concept. Bahadorani et al reported that acute CSCR patients treated with topical bromfenac or nepafenac (both relatively COX-2 selective NSAIDs) showed a significantly greater reduction in central macular thickness at 4–5 weeks compared to untreated controls ($p < 0.01$).[9] In that small series, NSAID-treated eyes demonstrated a faster rate of subretinal fluid resolution over the short term, suggesting a potential benefit of NSAIDs in acute CSCR. Nonetheless, NSAIDs are not currently part of the standard treatment paradigm for CSCR, and data on their efficacy have been limited to small cohorts.

In this context, we conducted a large retrospective analysis to evaluate the efficacy of topical NSAIDs for acute CSCR. Our study leveraged two distinct patient cohorts: a recent multi-center cohort (2018–2023) in which one retina practice routinely treated acute CSCR with a topical NSAID while others managed similar cases with observation, and a historical cohort (2007–2013) from a different set of practices where an exploratory use of COX-2 selective NSAIDs for CSCR had been documented. We aimed to compare the clinical course of acute CSCR between NSAID-treated eyes and observation-only controls, with particular attention to differences between COX-2 selective and non-selective NSAID therapies. We hypothesized that NSAID treatment would accelerate the resolution of subretinal fluid relative to observation, and that COX-2 selective agents might confer a greater therapeutic effect due to their more targeted anti-inflammatory action. Our findings may help clarify the role of NSAIDs as a potential early intervention in acute CSCR, an approach that could shorten disease duration and improve visual outcomes for patients who would otherwise simply wait for spontaneous recovery.

Methods

Study Design and Population

We performed a retrospective cohort study of patients diagnosed with acute CSCR at two large retina-only practices and one academic center. The analysis was divided into two periods: (1) a contemporary cohort from January 2018 to June 2023, and (2) a historical comparison cohort from 2007 to 2013 (previously collected data from an exploratory

study). The study was approved by Sterling IRB, with a waiver of informed consent for this retrospective review. All study conduct adhered to the tenets of the Declaration of Helsinki and complied with applicable privacy laws.

Inclusion and Exclusion Criteria

Adults aged ≥18 years with a first episode of acute CSCR were eligible. We defined acute CSCR as a symptomatic serous detachment of the central macula confirmed by multimodal imaging (including optical coherence tomography, OCT) with symptom onset ≤4 weeks prior to diagnosis, and without clinical signs of chronicity. All included patients achieved complete resolution of subretinal fluid and recovery of vision to 20/20 within 12 months of onset. At baseline, all patients had best-corrected visual acuity (BCVA) worse than 20/20 and a subfoveal neurosensory retinal detachment on spectral-domain OCT measuring at least 250 μm in height (Zeiss Stratus OCT) or 300 μm (Zeiss Cirrus OCT). Exclusion criteria included any evidence of chronic or recurrent CSCR (eg prior CSCR episodes or long-standing RPE atrophy/gravitational tracks), duration of symptoms >3 months at presentation, any concomitant maculopathy (such as choroidal neovascularization or diabetic macular edema), or use of any CSCR-specific treatment (eg PDT, thermal laser, oral eplerenone) before the endpoint of fluid resolution.

Treatment and Control Groups

In the 2018–2023 cohort, management approach was determined by practice location. Patients followed at Medical Center Ophthalmology Associates (San Antonio, TX) were offered treatment with a topical NSAID, while patients at the other participating practice (Georgia Retina, Atlanta, GA) were managed with observation alone. Treated eyes received topical ketorolac tromethamine 0.5% four times daily (QID) from diagnosis until complete resolution of subretinal fluid. QID dosing was selected to maximize posterior segment tissue penetration, supported by pharmacokinetic evidence demonstrating that frequent dosing maintains therapeutic drug concentrations at the retina and choroid due to enhanced scleral absorption and rapid anterior segment clearance.[10–12] Ketorolac was chosen at this center based on availability and clinical familiarity; notably, ketorolac is a relatively non-selective COX inhibitor (blocking both COX-1 and COX-2). Patients in the observation group received no medicinal intervention and were monitored with periodic follow-up exams. In both groups, any exogenous corticosteroid use was discontinued when possible, and no high-dose carotenoid or other supplement was prescribed.

For comparative purposes, we also analyzed data from an earlier cohort (2007–2013) at the same San Antonio practice, where a different NSAID treatment paradigm had been employed. In that period, topical relatively COX-2 selective NSAIDs (either bromfenac 0.09% or nepafenac 0.1%, both dosed QID) were used to treat acute CSCR, while collaborating centers managed their CSCR cases with observation only. These historical data were originally collected as part of an exploratory study on NSAIDs in CSCR. Key inclusion criteria and outcome definitions were similar between the two periods, allowing a qualitative comparison between COX-2 selective NSAID therapy (2007–2013) and less COX-selective NSAID therapy (2018–2023). No patient from the historical cohort was included in the recent cohort analysis (ie, there were no duplicate patients).

Outcome Measures and Follow-Up

All patients underwent a comprehensive ophthalmic examination and multimodal imaging at baseline, including color fundus photography and fluorescein angiography (FA) and/or indocyanine green angiography (ICGA) if needed to confirm the diagnosis of CSCR, as well as spectral-domain OCT. Follow-up visits occurred approximately every 4 weeks until resolution of subretinal fluid, then every 1–3 months thereafter up to 12 months. At each visit, OCT imaging was obtained to assess subretinal fluid, and BCVA was measured using Snellen or ETDRS visual acuity charts.

The primary outcome was the time to complete resolution of subretinal fluid on OCT, accompanied by recovery of BCVA to 20/20 (or to the patient's pre-CSCR baseline vision if it was worse than 20/20). Time to resolution was calculated in days from initial diagnosis to the first visit at which the OCT showed no subretinal fluid at the macula. If an eye had persistent fluid at 12 months, it was considered not to have met the primary endpoint within the "acute" phase and was censored at that time. We also recorded the final BCVA at the time of fluid resolution (or at 12 months for any censored cases).

Secondary outcomes included comparisons of resolution time between eyes treated with COX-2 selective NSAIDs versus non-selective NSAIDs, and between each treatment subgroup and its respective observation control. We also evaluated the proportion of eyes achieving 20/20 BCVA at final follow-up and any change in central retinal thickness on OCT from baseline to resolution. Additionally, any recurrences (re-accumulation of subretinal fluid after initial complete resolution) during the 12-month follow-up were noted. Safety was assessed by documenting any ocular surface or retinal adverse events possibly related to NSAID use (such as corneal epithelial complications or intraocular pressure elevation).

Statistical Analysis

Baseline characteristics of the treatment and observation groups were compared to assess group equivalence. Continuous variables (eg age, baseline BCVA, baseline OCT thickness) were compared with independent-samples *t*-tests (or Mann–Whitney *U*-tests if distributions were non-normal). Categorical variables (sex, presence of risk factors) were compared with chi-square tests.

Time-to-event data (days to fluid resolution) were analyzed using Kaplan–Meier survival curves and the Log rank test to compare distributions between groups. Eyes that had not resolved by 12 months were censored at 365 days for this analysis. We also performed a Cox proportional-hazards regression, stratifying by cohort (historical vs recent), to estimate the hazard ratio (HR) for resolution with NSAID treatment relative to observation. The proportional hazards assumption was evaluated by inspecting log–minus–log plots.

Results

Baseline Characteristics

In total, 89 eyes were included in the 2018–2023 cohort (26 treated with ketorolac, 63 observed) and 111 eyes in the 2007–2013 cohort (38 treated with a COX-2 selective NSAID and 73 eyes managed with observation from external control sites). Baseline data from the historical cohort similarly showed no major differences between the treated and control groups in terms of age, sex, baseline visual acuity (~20/40 Snellen), or OCT thickness. Table 1 summarizes the baseline demographics of the two study groups (NSAID vs observation) in the recent cohort.

Table 1 Baseline Characteristics of Acute CSCR Patients (2018–2023 Cohort)

Parameter	NSAID Treatment (n = 26)	Observation (n = 63)	*p*-value
Age, years (mean ± SD)	45.3 ± 8.7	46.0 ± 9.1	0.75
Male sex, %	81% (21/26)	83% (52/63)	0.84
Symptom duration, days	18 ± 9	20 ± 11	0.40
Baseline BCVA (Snellen)	~20/40*	~20/40*	0.66
Baseline BCVA (logMAR)	0.32 ± 0.15	0.30 ± 0.14	0.66
Baseline OCT thickness (μm)	421 ± 98	436 ± 105	0.52
Any risk factors present, %	54%	47%	0.48
Recent steroid use	15%	14%	0.91
Hypertension	23%	29%	0.55
"Type A" stress profile	54%	52%	0.85

Notes: *BCVA values are approximated to Snellen for clarity (all patients had BCVA <20/20 by inclusion criteria; mean logMAR ~0.3).

Resolution of Subretinal Fluid – NSAIDs vs Observation

All patients were followed until complete resolution of subretinal fluid or up to 12 months, whichever came first. In the 2018–2023 cohort, ketorolac-treated eyes demonstrated a significantly faster resolution of acute CSCR compared to observed eyes. The median time to resolution was 74 days (IQR 59–102) in the NSAID group versus 115 days (IQR 87–165) in the observation group. Figure 1 displays the Kaplan–Meier survival curves for time to resolution in the two groups. By 3 months from diagnosis, approximately 80% of NSAID-treated eyes had resolved, compared to only ~50% of eyes under observation. The Log rank test indicated a statistically significant difference in favor of NSAID treatment ($\chi^2 = 4.8$, $p = 0.029$). Cox proportional-hazards analysis yielded a hazard ratio (HR) of 1.70 (95% confidence interval 1.05–2.75, $p = 0.033$) for the treatment effect – meaning that at any given time, the probability of having resolved CSCR was about 70% higher in eyes receiving ketorolac than in eyes managed with observation.

In absolute terms, the mean time to resolution was 89 ± 55 days with ketorolac versus 133 ± 68 days with observation (a difference of ~44 days). This difference was also reflected in a two-sample *t*-test (which, despite the right-skewed distribution of resolution times, showed $p = 0.031$ for the difference in means). The fastest resolution in a treated eye occurred at 27 days, whereas the fastest in an observed eye was 40 days; conversely, the slowest resolution among treated eyes was 264 days (one outlier case approaching the chronic threshold), compared to 329 days in the observation group (several eyes bordering on chronic). By the 12-month mark, 100% (26/26) of NSAID-treated cases had completely resolved, while 63 of 63 (100%) of the "acute" observation cases had also resolved by definition (note: eyes that remained unresolved at 1 year were not included in this acute analysis, as they were considered chronic a priori and censored).

The 2007–2013 cohort analysis echoed these findings with an even more dramatic effect size. Eyes treated with a relatively COX-2 selective NSAID (bromfenac or nepafenac) had a mean time to resolution of 42 ± 15 days, whereas those in the contemporaneous observation group took 131 ± 60 days on average to resolve. The difference was highly significant (unpaired *t*-test, $p < 0.0001$). In that earlier cohort, the median resolution time with COX-2 NSAIDs was approximately 40 days, compared to ~125 days with observation. These summary statistics indicate a markedly accelerated course with relatively COX-2 selective treatment. Indeed, Figure 2 (a box-and-whisker plot of resolution times from both cohorts combined) illustrates that the distribution of resolution times for the COX-2 NSAID group was entirely lower than that of either the observation or ketorolac groups.

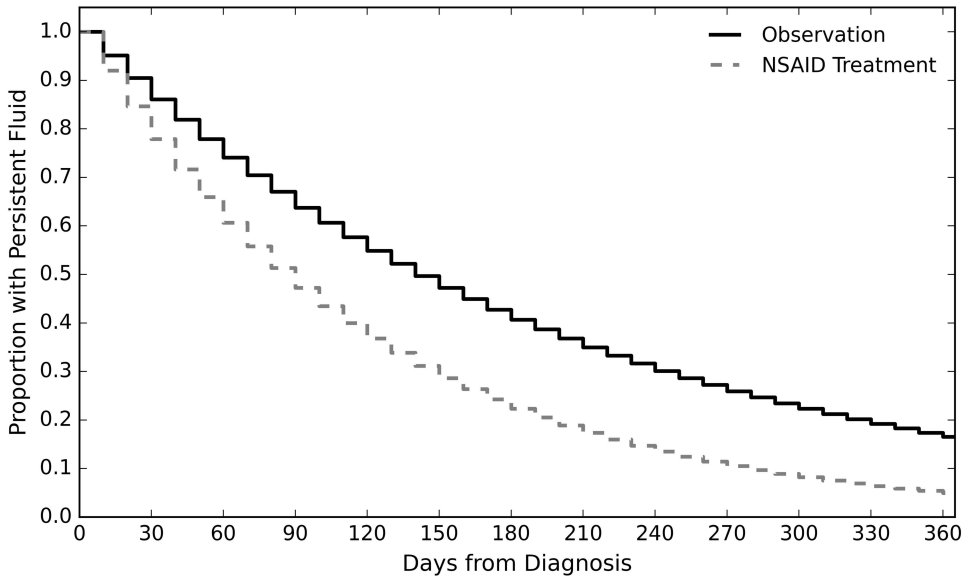

Figure 1 Kaplan–Meier survival curves for time to subretinal fluid resolution in acute CSCR (2018–2023 cohort). The solid black line represents eyes treated with ketorolac (n = 26), and the gray line represents eyes managed with observation alone (n = 63). The y-axis shows the proportion of eyes without resolution of subretinal fluid over time (in days). NSAID-treated eyes exhibited significantly faster fluid resolution than observed eyes (Log rank test, p = 0.03).

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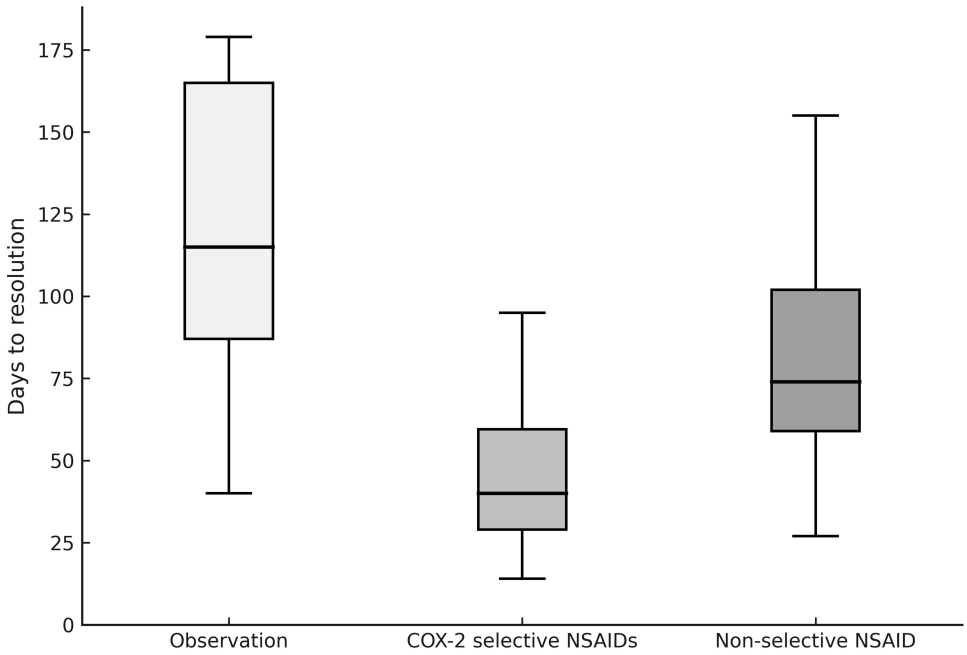

Figure 2 Distribution of time to resolution of subretinal fluid across all study groups. Box-and-whisker plot comparing resolution times for observation (n = 136 eyes), COX-2 selective NSAIDs (bromfenac or nepafenac; n = 38 eyes), and non-selective NSAID (ketorolac; n = 26 eyes). The median (line), interquartile range (box), and 1.5× IQR (whiskers) are shown for each group, ending at the minima and maxima. Both NSAID-treated groups resolved significantly faster than observation; the COX-2 selective NSAIDs were associated with the shortest time to resolution ($p < 0.0002$ vs observation; $p < 0.02$ vs non-selective NSAID).

When comparing the two NSAID treatment strategies directly, relatively COX-2 selective NSAIDs were associated with faster fluid resolution than the less-selective ketorolac. As shown in Figure 3, the mean time to resolution was less than half for the COX-2 group (42 days) relative to the less-selective group (89 days). We note that these two groups were drawn from different time periods and patient populations; thus, this comparison is exploratory rather than from

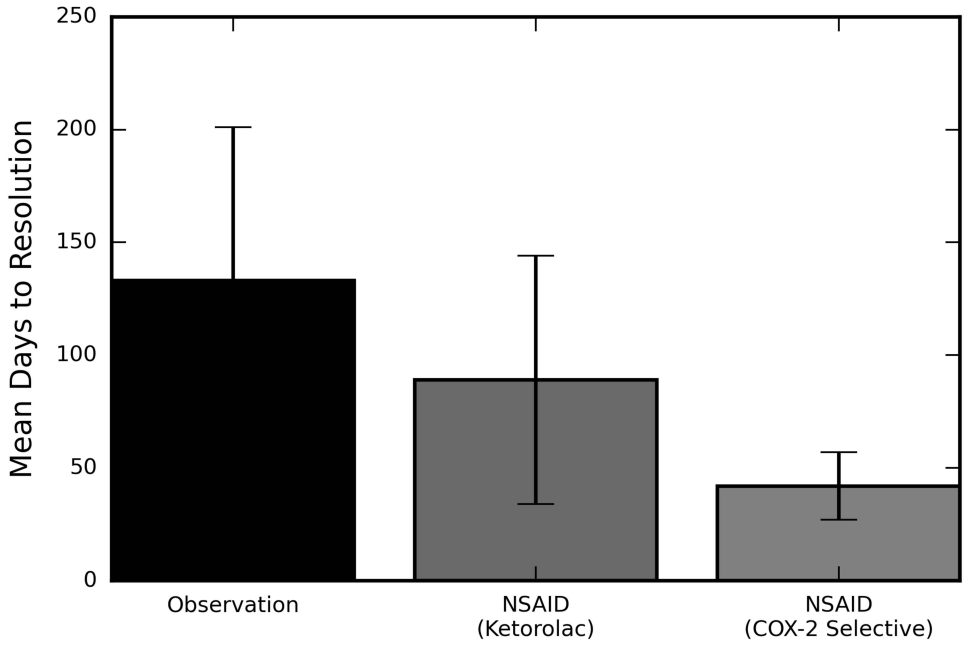

Figure 3 Mean time to subretinal fluid resolution by NSAID class. Bar chart comparing the mean resolution time in days for acute CSCR treated with COX-2 selective NSAIDs (bromfenac or nepafenac; n = 38) versus a non-selective NSAID (ketorolac; n = 26). Error bars represent standard deviations. COX-2 selective therapy was associated with a significantly shorter time to resolution compared to non-selective therapy ($p < 0.01$).

a single randomized dataset. Nonetheless, the stark difference suggests a possible pharmacologic advantage for COX-2 inhibition in resolving CSCR. A two-sample analysis (allowing for unequal variances) confirmed that the difference in means was statistically significant ($p = 0.004$).

To further explore treatment impact, we pooled all NSAID-treated cases (from both cohorts) and compared them against all observed cases. Across the combined population, NSAID therapy of any type significantly reduced the time to resolution compared to observation (mean 62 days vs 132 days, $p < 0.001$; log-rank $p = 0.0003$). In stratified Cox analysis, the benefit of treatment remained significant in both the historical and recent subgroups. Notably, among NSAID-treated eyes, those receiving bromfenac or nepafenac generally cleared subretinal fluid by around 3 months at the latest, whereas a few ketorolac-treated eyes approached the 6–9-month range before resolving. No eye in either treated group progressed to chronic CSCR (≥12 months of persistent fluid), whereas in the overall observed population, a fraction (~30% of the initial 119 acute cases) did not fully resolve by 1 year and required alternative interventions (these were the cases excluded as chronic in the primary analysis).

Visual Acuity Outcomes

By the time of fluid resolution, most patients in both groups experienced substantial visual recovery. In the 2018–2023 cohort, the final BCVA at resolution (or at 12 months for censored cases) was 20/20 or better in 25 of 26 eyes (96%) treated with NSAIDs and in 59 of 63 eyes (94%) that were observed ($p = 0.64$ for the difference in proportions). The single treated eye that did not reach 20/20 had baseline amblyopia (final BCVA 20/30). The few observed eyes that ended slightly worse than 20/20 had mild residual RPE changes; their final BCVA ranged from 20/25 to 20/30. The mean BCVA improvement from baseline was +3.1 ± 1.7 ETDRS lines in the NSAID group and +2.8 ± 1.9 lines in the observation group ($p = 0.55$). In essence, once subretinal fluid resolved, vision normalized in nearly all cases, regardless of treatment, as expected for acute CSCR. There was a trend toward earlier visual recovery in the NSAID group corresponding to the earlier anatomic resolution, for example, at the 2-month follow-up, 85% of treated eyes had improved by ≥2 lines vs 60% of observed eyes, paralleling the fluid clearance timeline, but by the final visit, the visual outcomes were equivalent.

In the 2007–2013 cohort, final BCVA was likewise 20/20 in the vast majority of eyes in both the NSAID and control groups (so long as they resolved within the acute phase). There was no indication that NSAID therapy adversely affected visual potential; on the contrary, by shortening the duration of macular detachment, it is conceivable that early treatment could reduce subtle photoreceptor damage. However, in our data the final acuity outcomes were excellent across the board, making it difficult to detect any meaningful difference in ultimate vision between treated vs untreated acute cases. We did note that one patient in the observation group of the historical cohort had a mild persistent visual acuity deficit (20/40 final) despite fluid resolution, possibly due to longer-standing detachment causing minor photoreceptor injury; no similar cases occurred in the NSAID-treated group. Overall, the visual prognosis was favorable in all acute cases, consistent with prior knowledge, and NSAID treatment did not change the final visual acuity outcome so much as it influenced the timing of recovery.

Recurrences and Additional Treatments

During the follow-up period, we monitored for CSCR recurrences (reappearance of subretinal fluid after complete resolution). By 12 months, 5 of 26 eyes (19%) in the ketorolac-treated group experienced a recurrence, compared to 12 of 63 eyes (19%) in the observation group – essentially identical one-year recurrence rates. In the historical cohort, recurrence within one year was noted in 3 of 38 (8%) NSAID-treated eyes and 6 of 73 (8%) observed eyes, again no significant difference. These recurrent cases were generally managed with a repeat course of NSAIDs or continued observation; in some that evolved into chronic CSCR, definitive therapies such as PDT were eventually applied. Importantly, the use of NSAIDs in the acute phase did not predispose to a higher relapse rate once the medication was discontinued; if anything, there was a slightly longer average recurrence-free interval in treated eyes (though this was not statistically significant given the sample size).

A total of 18 patients from the initial observation groups (combined cohorts) eventually required rescue treatment because their CSCR did not resolve spontaneously within approximately 6–9 months (ie they progressed toward chronic

CSCR). Of those, 14 underwent low-fluence PDT and 4 received oral eplerenone, per treating physician preference. These cases were outside the acute timeframe and were not included in the primary analyses; however, it is notable that the need for rescue therapy was confined to the observation arms. None of the NSAID-treated eyes had persistent fluid beyond 12 months requiring rescue (all resolved by around 9 months at most). This suggests that early NSAID intervention may reduce the proportion of patients progressing to chronic CSCR – a hypothesis that would need confirmation in a controlled prospective study.

Safety

Topical NSAIDs were generally well tolerated in our cohorts. No patient discontinued NSAID therapy due to side effects. No corneal complications (such as clinically significant epitheliopathy or ulceration) were observed, and there were no cases of intraocular pressure elevation attributable to NSAID use. Some patients noted mild transient stinging upon drop instillation (particularly with ketorolac, consistent with its known side effect profile), but this did not limit adherence. One patient on bromfenac reported mild dry-eye symptoms that improved with lubricating drops. Importantly, there were no retinal or choroidal adverse events linked to NSAID use – for example, we observed no cases of CSCR worsening, no macular hemorrhages, and no apparent delays in fluid resolution that would suggest any detrimental effect of the medication.

It is worth noting that COX-2 selective NSAIDs (bromfenac, nepafenac) have historically been considerably more expensive than generic ketorolac, which influenced the choice of agent in the contemporary cohort. At the time of the 2007–2013 study, bromfenac and nepafenac were used off-label despite high cost; by 2018, cost considerations led to the predominant use of generic ketorolac for a broader patient population. In our data, the higher-cost medications appeared more efficacious, raising a cost-benefit question. Fortunately, in recent years more affordable generic formulations of bromfenac have become available, which may enable wider use of relatively COX-2 selective therapy in the future without prohibitive expense.

Discussion

In this large retrospective analysis, we found that topical NSAID therapy significantly accelerated the resolution of acute CSCR, shortening the course of the disease by several weeks on average. Eyes treated with NSAIDs (either COX-2 selective or less-selective) had a markedly faster resolution of subretinal fluid compared to those managed with observation alone. Notably, the effect was most pronounced with relatively COX-2 selective NSAIDs, which were associated with roughly a 2–3-month reduction in fluid duration. These findings support the hypothesis that inflammation-mediated pathways contribute to the pathophysiology of CSCR and can be therapeutically targeted to expedite recovery. These results align with reports of successful treatment of peripapillary pachychoroid syndrome (an allied condition) using topical corticosteroids,[6] suggesting that inflammation is a common pathophysiological factor in the pachychoroid spectrum, including CSCR. However, given the retrospective and non-randomized nature of our study, a placebo effect or the natural course of the disease could partly account for the observed differences; thus, our results should be interpreted with appropriate caution and considered hypothesis-generating rather than conclusive. Prospective randomized trials are needed to confirm a true causal benefit of NSAID therapy.

Our study builds upon prior preliminary reports. Bahadorani et al (2019) first demonstrated in a small controlled series that topical bromfenac or nepafenac could hasten anatomical improvement in acute CSCR.[9] Our results corroborate and extend that observation in a larger multi-center context and additionally provide a comparison between different NSAID types.

The pharmacokinetic rationale for utilizing QID dosing of topical NSAIDs, specifically ketorolac, is well-supported by studies demonstrating limited corneal penetration and a need for scleral absorption to reach therapeutic concentrations in the posterior ocular structures.[10–12] Frequent dosing addresses the rapid turnover of drug concentration at the ocular surface due to tear film dynamics and nasolacrimal drainage, which quickly reduce available drug levels.[10–12] Such pharmacokinetic considerations have informed clinical practice in managing inflammatory retinal conditions requiring sustained posterior segment therapeutic drug levels.[13]

The proposed mechanism by which NSAIDs aid CSCR resolution centers on the choroidal circulation. CSCR has been linked to elevated choroidal hydrostatic pressure and hyperpermeability, possibly driven by sympathetic stimuli and endogenous corticosteroids. COX-2–derived prostaglandins (especially PGE_2) have been implicated in increasing choroidal blood flow and permeability. By blocking COX-2, NSAIDs likely reduce PGE_2 levels, thereby stabilizing the choroidal vasculature and the RPE barrier. This is supported by experimental evidence that PGE_2 can cause endothelial contraction and disrupt tight junctions, whereas COX-2 inhibition prevents these changes in models of blood–retinal barrier breakdown.[14] Furthermore, it has been observed that stress hormones (like cortisol and epinephrine), which are known risk factors in CSCR, can upregulate inflammatory mediators; for example, expression of the prostaglandin E_2 receptor EP2 (PTGER2) increases in vitro with corticosteroid exposure, implicating this molecular link in CSCR pathogenesis.[15] This provides a plausible biological rationale for why dampening the COX-2/PGE_2 pathway could counteract the effects of stress in precipitating CSCR, and why COX-2 selective drugs might have a more pronounced effect: they specifically target the inflammatory component most relevant to fluid leakage in CSCR.

It is important to contextualize our findings with the natural history of CSCR. The majority of acute CSCR cases will indeed resolve on their own given sufficient time.[2] In our observation groups, essentially all patients who met our acute inclusion criteria did eventually regain normal vision without active treatment. Thus, the benefit of NSAIDs is not in achieving resolution that would otherwise never occur, but in achieving it faster. This is not a trivial benefit: a shorter disease duration can translate into less visual disability for the patient (many CSCR patients are of working age and may struggle with weeks of distorted vision), and potentially less microscopic damage to photoreceptors or RPE from prolonged detachment. While final visual acuity was similar with or without treatment in our study, we speculate that beyond a certain point (perhaps beyond 4–6 months of detachment), permanent retinal changes do occur. This suggests that by ensuring that acute CSCR resolves in, say, 2–3 months instead of 5–6 months, NSAID treatment could reduce the chance of crossing that threshold into chronic damage. Moreover, about one-fifth of observed "acute" cases in our series ended up requiring rescue therapy as they approached chronic status, whereas none of the NSAID-treated cases did – hinting that timely NSAID intervention might prevent some eyes from entering into chronic CSCR that mandates more invasive treatment like PDT.

Our data also allow some inferences about recurrence and long-term management. The recurrence rates were similar between treated and untreated acute cases (~20% within a year). This suggests that a course of topical NSAIDs given during the acute phase, then stopped after resolution, does not appear to affect the underlying propensity for CSCR to recur. In other words, NSAIDs can hasten resolution of the current episode but likely do not immunize against future episodes once therapy is discontinued. Whether a longer prophylactic course of NSAIDs after resolution would reduce recurrences is unknown; in practice, continuous long-term NSAID use may be limited by tolerability and patient adherence. Nonetheless, if a patient does have a recurrence, a short repeat course of NSAIDs could again be employed to expedite recovery. We observed that recurrences in previously treated eyes still responded to re-initiation of NSAID therapy (though our numbers were small).

It is worth addressing the safety and systemic implications of using topical NSAIDs in this manner. Topical ophthalmic NSAIDs primarily act locally with minimal systemic absorption, and indeed we did not note any systemic side effects. Locally, NSAIDs can in rare cases cause corneal toxicity, especially with prolonged use, but no such issues arose in our cohorts where use was generally limited to a few months. Importantly, unlike systemic corticosteroid-suppressing therapies for CSCR (such as eplerenone or ketoconazole) that carry systemic risks (eg electrolyte imbalance or liver enzyme elevation), topical NSAIDs do not have significant systemic side effects. Therefore, from a risk–benefit standpoint, topical NSAIDs represent a relatively low-risk intervention in acute CSCR. The main drawbacks historically have been cost (for the newer COX-2 agents) and a modest degree of patient discomfort with frequent drop instillation over multiple months. However, with emerging generics and proper patient education, these barriers can be mitigated.

Our study has several limitations inherent to its retrospective design. First, treatment allocation was not randomized but determined by practice patterns and patient/provider preference. This introduces potential biases – for example, there could be unmeasured differences in patient characteristics between the sites (although our baseline comparisons did not find significant ones). We attempted to minimize bias by verifying that baseline disease severity was comparable between groups and by including a historical control for the relatively COX-2 selective NSAID group, but a prospective

randomized trial would be the definitive way to confirm efficacy. Second, the historical and contemporary cohorts were analyzed partly in parallel; while this allowed insight into drug differences, changes in imaging technology and follow-up protocols over time could confound the comparison. We addressed this by focusing primarily on within-cohort comparisons (NSAID vs control in each period) and treating the cross-cohort observations as exploratory. Third, our definition of "acute" CSCR involved selecting only those observation patients who resolved within a year. This was done to create a fair comparison (since treatment was not given beyond acute cases in the NSAID groups), but it may introduce a selection bias. We essentially excluded the worst-performing observation cases (those that stayed chronic). This bias would, if anything, underestimate the benefit of NSAIDs, because the observation group in our analysis is the only subset that required removal of cases greater than one year in duration. Despite this, NSAIDs still showed a benefit. In a real-world scenario, treating all acute CSCR cases upfront might prevent some of those chronic non-resolvers altogether. Fourth, we relied on clinical documentation for some endpoints like exact date of symptom onset or subtle chronic signs. It's possible a few patients had longer prodromal symptoms or mild prior episodes that were not recognized, which could affect how "acute" their disease truly was. A prospective study could ensure stricter inclusion criteria in this regard.

Considering these limitations, our results should be interpreted as hypothesis-generating but clinically suggestive. The magnitude of effect observed, particularly with COX-2 selective NSAIDs, is compelling and aligns with a biologically plausible mechanism. To our knowledge, this is the largest dataset examining NSAID use in CSCR, and it provides a foundation for designing a prospective trial. For instance, a randomized controlled trial could be designed in which patients with acute CSCR receive either a COX-2 selective NSAID or placebo drops for 3 months, with the primary outcome being time to OCT-confirmed resolution. Such a study would confirm whether the benefit seen retrospectively holds true and is clinically meaningful in a controlled setting.

If NSAIDs are confirmed effective, it would represent a simple and accessible therapy to implement. Topical NSAIDs are widely available and familiar to ophthalmologists. They could be instituted at the time of CSCR diagnosis, offering patients a chance at quicker recovery rather than the traditional "do nothing and wait" approach. This is analogous to how we manage other retinal conditions (for example, one would not leave cystoid macular edema untreated if a safe treatment exists). While PDT remains a gold standard for chronic CSCR, it is expensive and not without risk (and is typically reserved for chronic cases due to those considerations). NSAIDs, in contrast, could fill a niche for early intervention in acute CSCR, potentially reducing the number of patients who ever need PDT or systemic medications.

Our findings also raise interesting questions about COX-1 vs COX-2 roles in ocular physiology. COX-1 is constitutively expressed and contributes to normal homeostasis (for example, COX-1 activity produces prostaglandins that maintain choroidal blood flow and perhaps modulate intraocular pressure).[5] COX-2, on the other hand, is induced by stress and inflammation. It may be that selectively inhibiting COX-2 curtails the pathological fluid leakage in CSCR while sparing COX-1's physiological role, whereas non-selective inhibition blocks both, potentially reducing some beneficial effects or necessitating higher dosing to achieve the desired outcome. This could explain the superior results with bromfenac/nepafenac that we observed. These drugs also have higher lipophilicity and better penetration into ocular tissues compared to ketorolac, which may allow greater drug availability at the choroid and retina.[12,13] Ketorolac, although effective to a degree, might simply not achieve sufficiently high posterior segment concentration or COX-2 blockade to match the others. In clinical practice, one might opt for a COX-2–preferential agent if available and affordable for the patient.

In terms of clinical practice implications: Ophthalmologists might consider prescribing a course of topical NSAIDs for patients with acute CSCR, particularly those who are highly symptomatic or for whom a quicker recovery is desired. This could be done in conjunction with the usual advice of reducing stress and avoiding corticosteroids. It is important to note that the drops are off-label for CSCR but have a sound rationale and minimal downsides aside from cost.

Finally, our study further contributes to the notion that inflammation plays a key role in CSCR. Historically, CSCR was often thought of primarily as a hemodynamic phenomenon related to catecholamine surges. More recent research, and our findings, highlight that inflammatory signaling (perhaps triggered by those catecholamines or by cortisol) is intimately involved in breaking down the outer blood–retinal barrier in CSCR. This opens the door to other anti-inflammatory interventions as well. For example, investigational treatments targeting mineralocorticoid receptors (like eplerenone) aim to counteract the effect of endogenous corticosteroids in CSCR, however those trials (eg the VICI trial)

have yielded mixed results with one major study showing no significant benefit of eplerenone over placebo for chronic CSCR.[5] Topical NSAIDs act further downstream in the inflammatory cascade and might be more directly impactful in the acute phase. Another avenue could be topical carbonic anhydrase inhibitors, which some reports suggest may shorten CSCR episodes by reducing subretinal fluid (though evidence for this is still scant). Regardless, it is becoming clear that "benign neglect" may not be the only approach to acute CSCR. Patients often express a desire for active treatment rather than watchful waiting, and if a safe treatment can indeed speed their recovery, it represents a meaningful improvement in care.

Conclusion

In summary, we found that topical NSAIDs, especially relatively COX-2 selective formulations, significantly accelerated the resolution of acute central serous chorioretinopathy in a large retrospective analysis. NSAID-treated eyes recovered in a matter of weeks, versus a few months in untreated eyes, without adversely affecting final visual outcomes. These results suggest a promising role for NSAIDs as an early intervention to reduce the duration of CSCR episodes and potentially prevent chronic complications. While final visual acuity was excellent in both treated and untreated acute cases, the benefit of faster restoration of normal vision and avoidance of prolonged macular detachment is clinically relevant. Relatively COX-2 selective NSAIDs (such as bromfenac or nepafenac) may offer greater efficacy in this context than less-selective NSAIDs, aligning with their targeted anti-inflammatory action. Prospective randomized trials are warranted to confirm these findings and to establish evidence-based guidelines for managing acute CSCR. In the meantime, retina specialists might consider an off-label trial of topical NSAID therapy in acute CSCR patients, given the favorable risk profile. Our study contributes to the evolving paradigm that acute CSCR need not simply be observed; instead, pharmacologic modulation of choroidal inflammation can expedite recovery. If confirmed, this treatment strategy could improve quality of life for patients during CSCR episodes and reduce the healthcare burden of prolonged follow-up and monitoring.

Abbreviations

BCVA, best-corrected visual acuity; COX, cyclooxygenase; CSCR, central serous chorioretinopathy; FA, fluorescein angiography; ICGA, indocyanine green angiography; IQR, interquartile range; logMAR, logarithm of the minimum angle of resolution; NSAID, non-steroidal anti-inflammatory drug; OCT, optical coherence tomography; PDT, photodynamic therapy; PGE_2, prostaglandin E_2; PTGER2, prostaglandin E_2 receptor 2 (EP2); QID, four times daily; RPE, retinal pigment epithelium; SD, standard deviation.

Ethics

This study was conducted with approval from the Sterling IRB, which waived the requirement for individual informed consent due to the retrospective nature of the research. All procedures adhered to the tenets of the Declaration of Helsinki and to applicable federal and state privacy regulations.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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