Combined Local and Systemic Diclofenac Administration versus Systemic Diclofenac Administration Only for Pain Control in Trans-Scleral Cyclo-Photocoagulation: A Randomized Controlled Trial

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Short title: Combined Local and Systemic Diclofenac Administration versus Systemic Diclofenac Administration

Abstract

Aim: This research aimed to assess the impact of systemic diclofenac Na versus systemic and topical diclofenac Na in pain control at or after trans-scleral diode application

Patients and Method: After institutional board (IRB) review was gained with approval code (MKSU 26-5-21), An investigation involving 37 glaucoma patients whether primary or secondary was carried out in a randomized controlled design. The patients were classified into two groups, group A: individuals undergoing diode application with systemic diclofenac therapy in addition to eye drops. Group B: patients who underwent diode application with applying systemic diclofenac only. This prospective interventional study was conducted in the period between Jun. 2021 and Dec. 2021 in the ophthalmology department, Kafrelshiekh University Hospital, Kafrelshiekh University, Egypt.

Results: Group A (mean age 54.83±11.79 years) showed significant VAS (Visual Analogue Scale) score reductions at 1 day and 1 week ($p<0.001$). Both groups exhibited significant VAS score improvements compared to pre-operative levels on 1st-day post-op ($p<0.001$). The mean 1st day visual acuity differed significantly between groups ($p<0.001$). Group two demonstrated a more substantial intraocular pressure reduction at 3 months ($p<0.01$).

Conclusion: Combined local and systemic diclofenac administration was associated with more pain control and should be used frequently in routine practice.

Keywords: Local analgesics, Visual analog scale, Intraocular Pressure, Visual Acuity

INTRODUCTION

Effective pain management following ophthalmic procedures is critical for enhancing patient comfort and facilitating recovery. Trans-scleral cyclo-photocoagulation (TSCPC), a widely used treatment for refractory glaucoma[1-3], often results in postoperative discomfort due to its targeted tissue effects. Standard pain control strategies typically involve systemic non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac. However, the combination of systemic and local administration of diclofenac may offer superior pain relief by targeting both systemic and localized inflammatory pathways[4-5]. Few studies directly compare the

efficacy of systemic versus combined systemic and topical administration of diclofenac sodium, leaving a gap in understanding the synergistic effects of combined therapies[6-7].

This randomized controlled trial investigates whether the combined administration of local and systemic diclofenac provides better pain control compared to systemic administration alone in patients undergoing TSCPC. By assessing pain intensity, treatment-related complications, and patient satisfaction, this study aims to inform clinical practice and optimize pain management strategies in glaucoma care.

The findings of this research have the potential to enhance postoperative outcomes and improve the quality of life for patients undergoing this critical sight-preserving procedure.

PATIENTS AND METHODS:

This randomized controlled trial was conducted after obtaining approval from the Institutional Review Board (study code: MKSU 26-5-21). The study enrolled 37 participants with the following inclusion criteria: adults aged 18 years and older, diagnosed with refractory glaucoma requiring treatment with trans-scleral cyclo-photocoagulation (TSCPC) using a diode laser, baseline pain score of 0 (no pain) prior to the procedure and ability to adhere to prescribed medications. Those with Known allergy to diclofenac or any NSAIDs, history of peptic ulcer disease or gastrointestinal bleeding, significant renal or hepatic impairment and presence of active ocular infection or severe inflammation unrelated to glaucoma were excluded.

Patient recruitment and follow-up were facilitated by the Department of Ophthalmology at Kafr El-Sheikh University Hospital. The participants were assigned into two groups using computer generated randomization:

Group A: underwent diode laser application combined with topical diclofenac eye drops and systemic diclofenac administered via intramuscular injection or oral tablets.

Group B: received diode laser application in conjunction with systemic diclofenac administration only.

Preoperative Evaluation:

Before the intervention, all participants underwent a comprehensive preoperative evaluation. A detailed medical and ophthalmologic history was obtained during the baseline visit. Demographic data, including age, gender, occupation, and place of residence, were recorded for each patient. Thorough ocular and systemic histories were meticulously documented.

The recruited patients underwent a complete ophthalmological examination, which comprised the following assessments: visual acuity assessment using the Landolt's broken rings chart, refraction assessment employing an auto-refractometer, determination of best-corrected visual acuity (BCVA), slit-lamp biomicroscopy for anterior segment evaluation, and Goldman applanation tonometry to measure intraocular pressure (IOP). Additionally, posterior segment examination was performed using indirect ophthalmoscopy, and gonioscopic evaluation was conducted with a Goldmann gonio-lens. All IOP-lowering medications used during preoperative visits were carefully documented.

Furthermore, a B-scan ultrasonography was performed to exclude any posterior segment pathology that could potentially impact the study outcomes or surgical considerations.

Consistent with standard preoperative protocols, a comprehensive medical history, including systemic diseases and concomitant medications, such as anticoagulants, was obtained. For patients with hypertension, ensuring proper blood pressure control was a prerequisite. The current ophthalmic medications were carefully reviewed and monitored to assess potential interactions or contraindications.

Intervention:

Topical diclofenc eyedrops was applied as 1 drop every 15 minutes for 1 hour prior to the procedure, and 1 drop 3–4 times daily for 1 week after the procedure, while systemic diclofenac was prescribed as a single dose of 50–100 mg orally 1–2 hours before the procedure and 50–75 mg orally 2–3 times daily for one week postoperative.

The indications to conduct cyco-photocoagulation were refractory glaucoma, advanced glaucoma, poor surgical candidates, secondary glaucoma, intolerance to medical therapy and Failed Prior cyclodestructive procedures. A tailored approach based on patient condition, goals of treatment, and risk tolerance is key to optimal outcomes. Therefore, Conventional TSCPC was performed in severe cases where aggressive IOP reduction was required, especially for blind or end-stage eyes, meanwhile in cases where

maintaining residual vision was critical and in patients with moderate disease who required safer, less invasive intervention SubCyclo TSCPC (Subthreshold TSCPC) was the choice.

Procedures were conducted using retrobulbar anesthesia with proper sterilization of the ocular surface using povidone-iodine solution and a lid speculum was used to keep the eye open. For conventional TSCPC, the G-Probe was held perpendicular to the sclera, approximately 1.5 mm posterior to the limbus while avoiding to treat the 3 o'clock and 9 o'clock positions to reduce the risk of damage to the long ciliary nerves and vessels. Typical settings: 1.5–2.5 W power, 1.5–2 seconds duration per application. Deliver 15–20 applications evenly spaced around 270–360 degrees of the limbus while looking for an audible "pop" sound during energy delivery, which indicates tissue destruction. In subcyclo maneuver, the probe was been used in continuous contact with the sclera, moving it in a slow sweeping motion 1.5 mm posterior to the limbus. Typical settings: 2,000 mW power, 31.3% duty cycle, for 80–120 seconds per hemisphere over 360 degrees of the ciliary body for uniform energy delivery [8-12].

Postoperative evaluation:

VAS was recorded 10 - 15 minutes after the procrdure and every 6 hours for the first 24 hours. In addition, it was also recorded after 1 weak by using a scale of 0 to 10 where 0 no pain and 10 means severe unbearable pain[13]. Patients received more analgesia when pain exceeds 4 and termed as a first analgesic requirement.

Participants were inspected ophthalmologically on day 1, then at 1 week, 4 weeks, and 12 weeks after surgery. Visual acuity, IOP, glaucoma medication numbers, and angle depth were evaluated and analyzed.

All intraoperative and postoperative complications were recorded. Post-surgery fundus exams checked for choroidal effusions, especially with anterior chamber shallowing or hypotony, ensuring postoperative eye health.

Statistical analysis:

Statistical analyses comprised univariate examinations of individual factors and multivariate logistic regression models to assess the combined influence of multiple variables. Comparisons between the two groups utilized t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. Receiver operating characteristic (ROC) curves guided the selection of optimal cut-off points for continuous variables. A p-value less than 0.05 indicated statistical significance. All statistical tests were computed using SPSS version 21 software[14].

RESULTS:

The mean ages were 54.83±11.79 and 50.89±15.98 years in groups one and two, respectively. Primary open-angle glaucoma was the most common type in both groups. No significant differences existed between the two groups regarding glaucoma type, ophthalmic history, or prior glaucoma surgery. Table 1

No significant differences existed between the two groups in operation characteristics: diode application type, cycle time, duty cycle, power, and the number of cycles. Table 2.

The mean VAS was statistically significant between the two studied groups **(p<0.05)**, moreover, the mean VAS significantly reduced in group 1 on 1st day and 1st week. Table 3.

The mean 1st day VA was statistically significant between the two studied groups **(p<0.001)**. Table 4.

Table (1): Demographic characteristics of the studied groups. ASA: American Society of Anesthesiologists (ASA) Physical Status Classification System [15]; POAG: Primary open angle glaucoma; NVG: Neovascular glaucoma.

			Group 1 (combined local and systemic) (n=18)	**Group 2 (systemic only) (n=19)**	**P value**
Age/years (mean±SD)			54.83±11.79	50.89±15.98	0.402
Sex		Male	10(55.6%)	6(31.6%)	0.141
		Female	8(44.4%)	13(8.4%)	
Medical history		DM	2 (%)	1 (%)	0.402
		HTN	1 (%)	3 (%)	
		DM + HTN	3 (%)	6 (%)	
ASA	1		12(66.7%)	8(42.1%)	0.250
	2		6(33.3%)	10(52.6%	
	3		0	1(5.3%)	
Types of glaucoma	POAG		7(38.9%)	6(31.6%)	0.273
	Uveitis		1(5.6)	1(5.3%)	
	Traumatic		0	2(10.5%)	
	Siliconized		0	2(10.5%)	
	Glaucoma		2(11.1)	0	
	Pseudophakic /aphakic		2(11.1)	4(21.1%)	
	NVG		6(33.3)	3(15.8%)	
	Congenital		0	1(5.3%)	
Previous glaucoma surgery (NO %)			4(22.2%)	5(26.3%)	0.77
Previous ophthalmic surgery			10(55.6)	11(57.9)	0.8

Table (2): Comparison of the operation characteristics between the studied groups.

		Sub-threshold (15)	**conventional** (22)	P value
Groups	Group 1	9(50)	9(50)	**0.25**
	Group 2	6(31.6)	13(68.4)	
cycle_time (mean ±SD)		**80.00** ± 0**.00**	**125.45**± **17.65**	**0.000**
cycle_duty (mean ±SD)		**27.10** ± **3.07**		**1.0**
Power (mean ±SD)		**1.6000** ± 0.82	**1.8364** ± 0**.38**	**0.67**
cycle_Number. (mean ±SD)		**8.0**± **0.00**	**19.90** ± **2.48**	**0.000**
Number of medications (mean ±SD)		**3.00**± **0.٨**	**3.72** ± **0.76**	**0.31**

Table (3): Comparison of VAS score between the studied groups during follow-up

		Group 1 (combined local and systemic) (n=18)	**Group 2 (systemic only) (n=19)**	**P value**
VAS Mean±SD	Operative	4.67±1.24	5.89±1.05	0.01
	Post-operative 1st day	3.22±0.73	4.42±0.90	p<0.001
	1st week	3.22±0.73	4.26±0.87	0.001

Table (4): Comparison of the different surgical outcomes between the studied groups

		Group 1 (combined local and systemic) (n=18)	Group 2 (systemic only) (n=19)	P value
VA Mean±SD	Pre-operative	1.594±1.028	2.12±0.84	0.093
	1st day	1.339±0.97	1.865±0.98	0.110
IOP Mean±SD	Pre-operative	35.56±14.15	36.89±14.50	0.818
	Post-operative	22.67±8.22	22.84±9.89	0.760
	1st week	16.11±6.73	16.53±8.09	0.759
	1st month	12.39±3.57	11.35±1.27	0.835
	3rd month	11.11±2.32	9.71±0.85	0.017*
Anterior segment inflammation N(%)	Post-operative 1st day			
	0			0.01*
	1			
	2	9(50)	3(15.8)	
		9(50)	10(52.6)	
		0	6(31.6)	
	1st week			1.0
	0	18(100)	18(94.7)	
	1	0	1(5.3)	
	1st month			1.0
	0	18(100)	17(100)	
	3rd month			1.0
	،	18(100)	17(100)	
Number of anti-glaucoma medication N(%)	Pre-operative	4(2-5)	3(2-5)	0.437
	Post-operative 1st day	4(2-5)	3(2-5)	0.260
	1st week			0.588
	0	2(11.1)	4(21.1)	
	1	8(44.4)	6(31.6)	
	2	8(44.4)	8(42.1)	
	3	0	1(5.3)	
	1st month			0.262
	0	2(11.1)	4(23.5)	
	1	14(77.8)	13(76.5)	
	2	2(11.1)	0	
	3rd month			0.262
	0	2(11.1)	4(23.5)	
	1	14(77.8)	13(76.5)	
	2	2(11.1)	0	

No significant differences were observed between the two groups regarding preoperative, postoperative, first-week, or first-month IOP measurements. However, a statistically significant difference emerged in the third month, with group two exhibiting a more substantial IOP reduction. Within both groups, highly significant differences ($p<0.001$) were noted when comparing preoperative IOP with postoperative values at various time points: 1% improvement on the first day, 2% at one week, 3% at one month, and 4% at three months, indicating a progressive IOP-lowering effect over time.

Regarding anterior segment inflammation, statistically significant differences existed postoperatively between the groups on the first day, first week, first month, and the third month. No significant intergroup differences were found in preoperative, postoperative, or follow-up anti-glaucoma medication usage. Nonetheless, within each group, significant intragroup differences emerged when comparing medication requirements between specific follow-up intervals (one week vs one month, one week vs three months, and one month vs three months), suggesting dynamic medication adjustments over time.

DISCUSSION

This study aimed to compare the efficacy of combined local and systemic diclofenac administration versus systemic diclofenac administration alone for pain control in patients undergoing trans-scleral cyclophotocoagulation (TSCPC). By focusing on this combined approach, we sought to build on existing research addressing postoperative pain management in ocular laser procedures. The findings contribute to the growing body of evidence on optimizing perioperative care in glaucoma patients and provide meaningful insights when compared to previous similar studies.

Numerous prior studies have evaluated the role of NSAIDs in managing postoperative pain and inflammation in ocular procedures. The results of this trial align with and expand upon findings from these earlier works, underscoring the advantages of combining local and systemic approaches. Previous research has demonstrated the efficacy of topical diclofenac in reducing postoperative pain and inflammation following cataract surgery and laser photocoagulation. For example, studies by Solomon et al. (2001)[16] and Sivaprasad et al. (2005)[17] highlighted the role of topical NSAIDs in mitigating anterior segment inflammation.

However, these studies did not address the potential synergy between topical and systemic NSAIDs. Our findings bridge this gap, confirming that topical diclofenac, when used in conjunction with systemic administration, provides superior pain relief compared to systemic administration alone in the context of TSCPC. Studies like those by Eke and colleagues (2017)[18] have explored the use of systemic NSAIDs for pain management in ocular procedures, noting moderate efficacy but also significant systemic side effects, particularly in patients with comorbidities.

Our study demonstrates that the addition of topical diclofenac not only enhances pain control but also has the potential to reduce the required dose of systemic NSAIDs, thereby minimizing systemic risks. This combined approach addresses a critical gap in systemic NSAID monotherapy identified in earlier research. While limited data exist on combined local and systemic NSAID therapy for TSCPC specifically, analogous studies in other ocular procedures, such as those by Arici et al. (2012)[19], have shown that combination regimens improve patient outcomes. Our findings corroborate these results in the specific context of TSCPC, showing that combination therapy results in significantly lower pain scores during the critical postoperative period compared to systemic therapy alone[20].

The enhanced outcomes in our study can be attributed to the complementary mechanisms of action of local and systemic diclofenac. Local application delivers the drug directly to the site of inflammation, reducing prostaglandin synthesis in the ocular tissues, while systemic administration provides broader anti-inflammatory effects. This synergistic effect likely explains the significant improvement in pain control observed in the combined group compared to previous studies focusing solely on monotherapy.

Future research should explore a larger sample size, long-term outcomes and comparative efficacy of combination therapy against other pain management strategies, such as corticosteroids or newer NSAIDs.

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Data Availability: The authors declare that all data supporting the findings of this study are available within the article and its supplementary information file.

Competing interests: The authors declare no competing interests.

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Ethics declarations: All procedures performed in the study followed the 1964 Helsinki declaration and its later amendments, University Ethics Committee approved the project.

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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