Review Article

The Effectiveness of Non-surgical Therapy for Traumatic Optic Neuropathy Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

This systematic review examined non-surgical management of traumatic optic neuropathy including the use of corticosteroids, levodopa-carbidopa, mesenchymal stem cells, and erythropoietin. A thorough literature review was conducted across three databases: PubMed, Cochrane Library, and Science Direct. Clinical studies and randomized controlled trials (RCT) that were published in English and Bahasa Indonesia until June 2023 were included. The PRISMA 2020 flow diagram was utilized to guide the study selection process. Data retrieved were analyzed through random effects model to yield a comprehensive synthesis of outcomes. Eight studies were included in this review, two of which were RCTs and the other six were clinical trials. Two studies examined the use of mesenchymal stem cells, and the remaining studies examined other non-surgical approaches, including the usage of corticosteroids, erythropoietin, and levodopa-carbidopa. This review concluded that patients with traumatic optic neuropathy (TON) can be effectively treated with non-surgical therapy.

Keywords: Traumatic optic neuropathy, corticosteroids, erythropoietin, mesenchymal stem cells, levodopa-carbidopa, visual acuity, visual field.

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INTRODUCTION

Traumatic optic neuropathy (TON), a complex illness due to optic nerve damage that causes variable degrees of visual loss, has drawn attention due to its high occurrence and negative impact towards one's quality of life. Although research and therapeutic treatments exist for managing TON, there is an ongoing controversy on the efficacy of different methods, particularly non-surgical therapy.

The growing number of traumatic events, such as car accidents, sports-related injuries, and head injuries, pose a serious risk to the integrity of the optic nerve, giving rise to TON. It is a complicated illness occurring due to optic nerve injury that frequently results in visual loss.[1-3]This can ultimately lead to a substantial decline in an individual's quality of life, independence, and overall well-being. While Indonesia currently lacks specific prevalence data on TON, global statistics suggest that its incidence ranges from 0.7% to 2.5%.[4]Consequently, there is a growing need to explore and evaluate various therapeutic approaches

to mitigate the visual impairment associated with TON.

The management of TON presents a complex and intricate challenges. A significant challenge lies in the notable lack of universally recognized consensus on a standardized methodology to effectively manage TON.[5] The lack of consensus regarding this matter poses a considerable impediment to the development of definitive best practices for managing TON, resulting in a wide range of treatment options and methodologies available to healthcare professionals. Presently, there is a broad spectrum of treatment recommendations available for TON. These options encompass a conservative approach involving sole observation, surgical interventions incorporating optic canal decompression, or non-surgical therapy such as corticosteroids.[6,7] In some cases, a comprehensive approach to treat TON of ten involves a combination of these therapies, highlighting the complex nature of this treatment.

In situations of direct bone compression on the optic nerve and progress visual loss in indirect TON, surgical decompression becomes a consideration. This surgical method, however, carries significant risks, including cerebrospinal fluid leaks and meningitis, making it a controversial choice.[8,9] Non-surgical therapies have gained significant traction as a promising alternative to surgical interventions. Corticosteroids and erythropoietin are widely favored due to their anti-inflammatory and regenerative properties.[10,11] Recent research is also exploring innovative non-surgical approaches, such as stem cell therapy and the use of levodopa-carbidopa—traditionally used for Parkinson's disease—by targeting nerve healing pathways.[12,13] This growing emphasis on non-surgical treatments highlights the need to minimize invasiveness while maximizing therapeutic efficacy. Although surgical interventions remain essential in certain cases, the increasing focus on non-surgical options marks a significant advancement, offering patients effective, less invasive, and more widely accessible treatment alternatives.[5]

The limited research measuring the efficacy of non-surgical therapies has sparked ongoing debates about TON treatment. The scarcity of published data on TON complicates the development of defined guidelines for effective management, resulting in different therapeutic methods and adverse patient results. This highlights the pressing need for a systematic review and meta-analysis to assess the effectiveness and safety of non-surgical treatments.

This review was meant to investigate the efficacy of non-surgical approaches for TON patients through conducting a literature review of clinical trials that have been published across various databases.

METHODS

This study is a quantitative systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist protocol **(Figure1)**.[14] The clinical questions were formulated using the PICO framework (P: traumatic optic neuropathy patients, I: non-surgical therapy, C: placebo control or alternative treatment, O: visual acuity and visual field). This research was conducted in 2023. Study research was carried out through PubMed, Cochrane Library, and Science Direct databases for which the protocol of systematic review was performed at the author's location and corresponded to the writing suggestions of both the material advisor and the methodology advisor.

Extraction and Data Management

The data obtained from the selected studies were extracted using Microsoft Excel. The data encompasses the study title, contributor names, year of publication, study design, study subjects, study intervention, study outcomes, and DOI.

Risk of Bias

Two bias assessment instruments were used in this systematic review: the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I), and the Revised Cochrane Risk-of-bias Tool for Randomized Controlled Trials (RoB 2) 2019; This was done due to mixed studies in the analysis, which included both clinical trial studies and RCTs. The utilization of these bias assessment instruments was in accordance with the directives outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[15] The outcomes assessed using bias evaluation tools included changes in visual acuity, visual field, and adverse effects associated with non-surgical therapies for traumatic optic neuropathy.

Data Analysis

This meta-analysis was conducted by utilizing Review Manager 5.4 software, developed by the Cochrane Collaboration. The calculation of dichotomous variables was performed utilizing the Mantel-Haenszel formula employing random-effects models. The I2 statistic was employed to evaluate the heterogeneity, with values below 25%, between 26% and 50%, and above 50% indicating low, moderate, and high levels of heterogeneity, respectively. The researchers provided the effect estimate as the risk ratio (RR) for dichotomous variables, along with its corresponding 95% confidence intervals (CIs). The p-value was calculated using a two-tailed test, and the level of statistical significance was set at≤0.05.

RESULTS

After the application of inclusion and exclusion criteria to the search methodologies, a total of 182 studies were identified from PubMed, Cochrane, and Science Direct databases. From 182 studies, 24 studies were included in the initial screening, while 158 studies were excluded due to either duplication of existing literature or their classification as studies not registered as clinical trials based on automated tools. Following the screening of titles and abstracts, 9 studies were considered for further assessment regarding full-text eligibility and 15 studies were excluded due to studies not related to TON, language divergence (non-English or non-Bahasa Indonesia), study design incompatible with the research's requirements (review, case report, and other non-systematic review), and incomplete studies. Out of the9 studies initially considered, 1 study was excluded due to the unavailability of accessible full-text materials. Consequently, a total of 8 studies were incorporated into this review to investigate the effectiveness of non-surgical therapy for traumatic optic neuropathy patients.

Characteristics of the Study

Eight studies were included, comprising two RCTs and six clinical trials, involving patients aged 5 to 78 years with TON. Follow-up assessments, conducted over periods ranging from 1 to 12 months, evaluated the efficacy of non-surgical interventions such as corticosteroids, levodopa-carbidopa, erythropoietin, and mesenchymal stem cells. The studies utilized diverse control groups, including surgical, placebo,

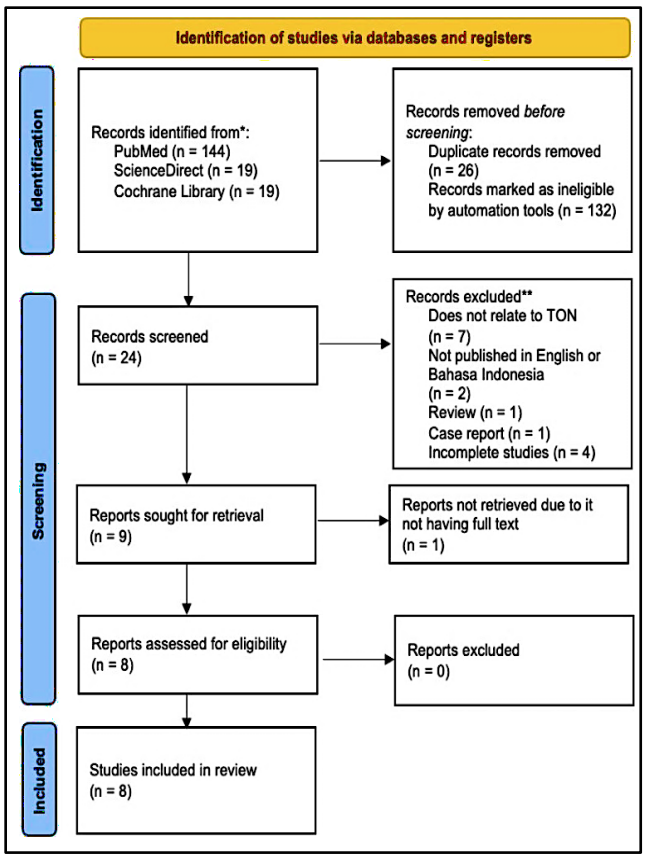

Figure 1: Flow diagram of this study illustrating the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

and non-surgical treatments, leading to intervention categorization based on comparisons between non-surgical and surgical approaches, placebo-controlled studies, and non-surgical interventions using methylprednisolone. Each intervention was analyzed separately to provide a comprehensive evaluation of its therapeutic impact.

Within the non-surgical versus surgical, placebo, and non-surgical (methylprednisolone) comparison, two articles emphasized the effectiveness of non-surgical over surgical therapy, three highlighted non-surgical over placebo, and three explored non-surgical versus non-surgical (methylprednisolone). In the separate intervention discussion, six studies focus on the steroid group, two on mesenchymal stem cells, and two covered both erythropoietin (EPO) and levodopa-carbidopa.

The study's characteristics, outlined in Table 1, include outcomes like visual acuity, visual field, and adverse effects. Among the articles, there is significant variation in outcome measures, with all studies

assessing visual acuity, one examining visual field parameters, and two studies not reporting adverse effects.

Assessment of Bias

The study rigorously assessed bias in the included literature using tailored methodologies for different study designs. Employing RoB2 for randomized controlled trials (RCTs) and ROBINS-I for clinical trials, the research categorized the eight analyzed articles into risk groups: low, moderate, and high. Two RCTs showed low bias across all domains, resulting in an overall low bias classification. However, among the six clinical trials, only one exhibited a low risk of bias, while three showed a moderate risk. Notably, two of the moderate-bias studies were in the stem cell intervention group. Conversely, the remaining two clinical trials displayed a high risk of bias in methodology and analysis. This comprehensive bias assessment provides valuable insights into the liability of the study outcomes across different interventions. In Figures 2 and 3, green indicates low risk of bias, yellow shows moderate risk of bias, and red stands for high risk of bias.

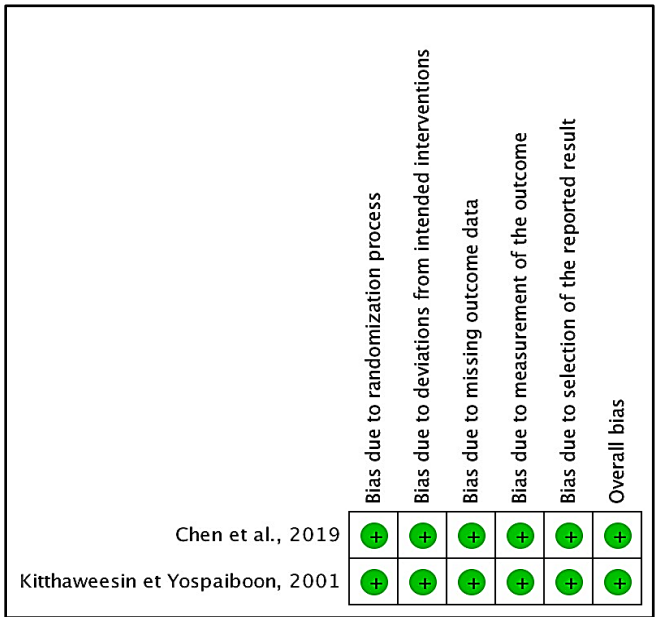

Figure2: ResultofBiasRiskAssessmentRoB2.

Effectiveness of non-surgical therapy compared to surgical therapy

1. Improvement in visual acuity

The meta-analysis, encompassing two studies using steroids as non-surgical therapy, indicated inconclusive evidence.[16,17] Chen et al., leaned towards surgical intervention (RR=0.83[95%CI0.47,1.48]), while Levin et al, favored non-surgical methods (RR=1.61[95%CI0.87, 2.99]).[16,17] The overall meta-analysis showed no significant difference in visual acuity improvement between non-surgical and surgical interventions for TON (RR=1.15[95%CI0.58,2.26],Z=0.40,p=0.69), with substantial heterogeneity (I2=61%). In individual studies, Chen et al, 2019, reported higher improvement rates in the surgical group but no significant difference in improvement degree.[16] Levin et al, initially showed worse results in the surgery group, but after adjusting for baseline visual acuity, differences were not significant.

2. Improvement in the visual field

The analysed articles lacked information on patients' visual fields, focusing solely on visual acuity. Chen et al, 2019, in addition to visual acuity, also assessed the quality of life in their study.[16]

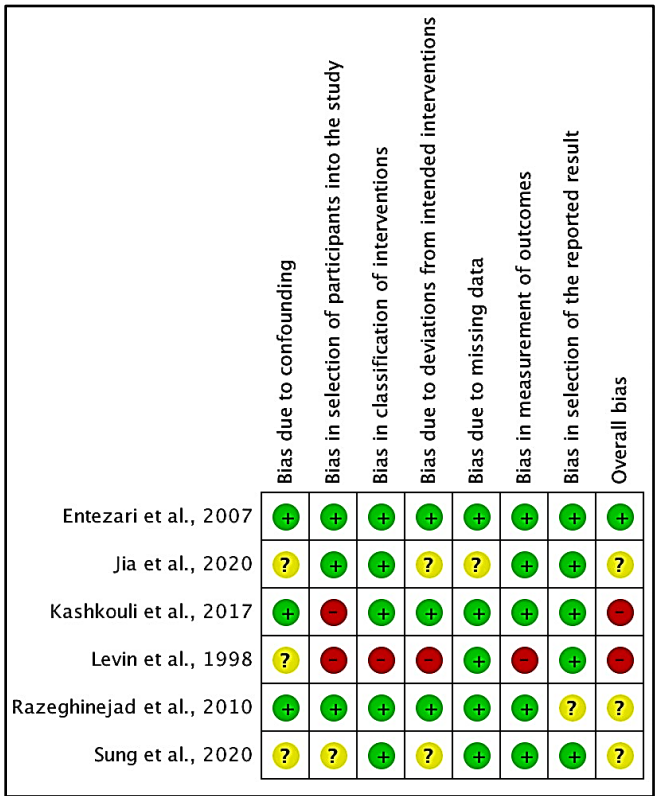

Figure 3: Result of Bias Risk Assessment ROBINS-I tool.

3. *Adverse Effect*

Chen et al., reported no adverse effects from the steroid treatment, while Levin et al., did not explicitly mention adverse effects in the article.[16]

Comparative efficacy of non-surgical treatment versus placebo

1. *Improvement in visual acuity*

The articles included in this group aimed to compare the effectiveness of non-surgical interventions against placebos in improving visual acuity, incorporating findings from three studies.[17,8,19] This meta-analysis included four studies in total, with the majority focusing on non-surgical therapy using steroids, and Kashkouli et al, exploring erythropoietin (EPO) as well. Individual studies indicated trends favoring non-surgical interventions but lacked statistical significance. The overall meta-analysis showed a slight, non-significant tendency favoring non-surgical interventions over placebos for visual acuity improvement (RR=1.31[95%CI0.93,1.86],I2:0%).

A subsequent meta-analysis focused on mean differences resulting from EPO and steroid treatments.[19] The mean differences for both interventions did not reach statistical significance, suggesting negligible differences between non-surgical and placebo groups (EPO:-0.66[95%CI -1.69,0.37];Steroid:-0.02[95%CI -1.35,1.31]). The overall meta-analysis combining data from both studies also did not exhibit statistical significance (Mean Difference: -0.42 [95% CI -1.24, 0.40], I2: 0%). In study by Entezari et al., the mean difference between placebo and treatment groups lacked statistical significance, with both showing improvement, albeit slightly more in the non-surgical group without statistical significance.

2. *Improvement in visual field*

Regarding visual field assessments, none of the three included articles reported visual field outcomes. Two studies[17,18] exclusively measured visual acuity, while Kashkouli et al, conducted a more comprehensive evaluation, including visual acuity, color vision, and Relative Afferent Pupillary Defect (RAPD)grading.

3. *Adverse Effect*

In the comparison between non-surgical and placebo interventions, two studies did not provide any specific information regarding the presence or absence of side effects in their report.[17,18] In contrast, the third study explicitly stated the absence of observed side effects within both treatment groups throughout their study.[19]

Comparative efficacy of non-surgical treatment versus surgical treatment

1. *Improvement in visual acuity:*

The meta-analysis on non-surgical versus non-surgical (methylprednisolone) treatment for improving visual acuity included three studies.[19,20,21] Kashkouli et al, reported a slight inclination towards steroid interventions (RR=1.03 [95% CI0.61, 1.74]), while Kitthaweesin et al and Razeghinejad et al, indicated a tendency favoring non-surgical treatments, although statistical significance was not reached. The overall meta-analysis yielded a combined RR of 1.68 [95% CI 0.67, 4.19], which did not show statistical significance, indicating moderate heterogeneity (I2:51%).

In Kashkouli et al., the mean difference on visual acuity was -0.64 [95% CI -1.68, 0.40], but statistical analysis did not demonstrate significance (p=0.23). Similarly, Kitthaweesin et al and Razeghinejad et al, reported no statistically significant differences in visual improvement between compared groups in their respective studies.

2. *Improvement in visual field*

None of the studies within the non-surgical interventions, specifically focusing on steroids, directly addressed visual field changes in their respective articles.

3. *Adverse Effect*

Kitthaweesin et al, reported no adverse effects for both drugs in their study. Similarly, Kashkouli et al, found no observed side effects in either treatment group. Additionally, Razeghinejad et al, studying levodopa, noted that none of the patients experienced commonly reported side effects associated with the medication.

Effectiveness of steroid therapy

1. *Improvement of Visual Acuity*

In the steroid group of 8 studies, 6 specifically

Table 1: *Characteristics of the Study*

Author, Year	Study Design	Participants	Duration of therapy	Therapy Regimen	Outcome	Visual Acuity				BCVA			Adverse
						Intervention		Comparator		Basal	End	Outcome	
						Event	Total	Event	Total				
Kittha-Weesinet Yos-Paiboon, 2001	RCT	21 participants **Age** Mean±SD 26.38±11.89	2months	**Dexamethasone**:4mg IV, continued with 3 mg/kg four times a day. **Methylprednisolone**30 mg/kg IV, continued with 15mg/kg four times a day. After72 hours→by 1 mg/kg/day of oral prednisolone, which was Discontinued within two weeks.	VA was measured in Snellen chart	6	9	2	6	There was no significant di□erence in the visual improvement between the two groups at week two or month two on the three or more lines improvement of BCVA stratified by initial BCVA.			No AE of eitherdrug was observed duringthe study.
Chenet al., 2019	RCT	30participants **Age** (Median± range) **Steroid** 24(12-44) **Surgical** 62(16-45)	9months	**Steroid**:Initialdose:30 mg/kg megadose of methylprednisolone(IV) Subsequentdose:15 mg/kgevery6hoursfor3 Days **Surgical:** ETOCD	VA was measured in logMARunit, the extent of improvement: "Improvement degree[22]") Other: QoL→ SF 36	10	18	8	12	The total improvement rate of visual acuitywas66.70%inthesurgical cohortand55.56%inthesteroid cohort. The mean improvement was 35.70% in the surgical cohort. The di□erence in improvement between the two therapy groups were statically insignificant, with a P value of 0.443			Noadverse e□ectsfrom thesteroid treatmentin thisstudy
Levin et al, 1998	CT	127 participants **Age** Mean±SD 34±18	1 month	**Steroid:** corticosteroid were given within 7 days of injury. Classified based on: -Megadosefor=5400mg -Veryhighdosefor2000 –5399mg -Highdosefor500– 1999mg -Moderatedosefor100– 499mg -Low dose for<100mg **Surgery:** Optic canal decompressionsurgery was conducted, with or without corticosteroid	VA was measured in Snellen Chart	**Steroid**: 33	**Steroid**: 64	**Surgery** : 8 **Placebo** : 4	**Surgery** : 25 **Placebo** : 7	**Steroids:** -unable to test: 3(4) -NLP:26(31) -LP:8(9) -HM:14(16) -<20/200to CF: 16(19) -<20/40to= 20/200:8(9) -=20/40:10(12) **Surgery:** -unable to test:- -NLP:22(67) -LP:5(15) HM:2(6)	**Steroids**: -NLP:15(23%) -LPorHM:3 (5%) -<20/200toCF:8 (12%) -<20/40to= 20/200:10(15%) -=20/40:30 (45%) **Surgery**: -NLP:11(44%) -LPorHM:4 (16%) -<20/200toCF:5 (20%)	

				medication. **Placebo:** corticosteroids And optic canal Decompression was not given.						-<20/200to CF: 2(6) -<20/40to= 20/200:1(3) -=20/40:1(3) **Untreated:** - Unable to test:- -NLP:3(33) - LP:0 -HM:1(11) -<20/200toCF: 2(22) -<20/40to= 20/200:2(22) =20/40:1(11)	-<20/40to= 20/200:4(16%) -=20/40:1 (4%) **Untreated**: -NLP:2(29%) -LPorHM:0 -<20/200toCF:0 - < 20/40 to = 20/200:2(29%) -=20/40:3 (43%)	
Entezari et al, 2007	CT	31participants **Age** Mean±SD 29±10.02	3months	**Steroid**: 250 mg methylprednisolone IV every6hoursfor3days, continuedwith1mg/kg prednisoloneoralfor14 days. **Placebo**:50mlnormal salineIVevery6 hours for3days,thenplacebo for 14 days.	VA was measured in logMAR unit And presented in mean differences	11	16	8	15	**Steroid group**: 1.9±0.99 **Placebo group** 2.3±0.93(P=0.27)	The mean difference between placebo and treatment groupwas0.67 [CI95%:- 1.54to 0.2]	
Kashkouli et al, 2017	CT	100participants **Age** Mean±SD 28.47±14.31	3months	**EPO**: -EPOinfusedin200mL ofnormalsalineIVover2 hours, every day for three days -10,000IU/day for patients <13 years - 20,000IU/day for patients =13 years - Aspirin (80mg):1hour before infusion **Steroid**:250mg Methylprednisolone IV, 3 0minutes, 4x/day for 3 Days	VA was measured in logMAR (SD) Other outcome: Color vision And RAPD grading	EPO:38	EPO:69	Steroid: 8 Placebo: 5	Steroid: 15 Placebo: 16	**EPO** -Mean logMAR (SD):2.84(±1.66) -(range)(SE): (0.1-4.7)(0.20) **Steroid** - Mean logMAR (SD): 3.25(1.59) - (range)(SE): (0.8-4.7)(0.41) **Placebo** -Mean logMAR (SD):3.25(1.73) -(range)(SE): (0.4 4.7)(0.43)	**EPO** -Mean logMAR (SD):1.95(1.87) -(range)(SE):(0-4.7)(0.22) -*P*value:0.000 **Steroid** -Mean logMAR (SD): 2.59(1.87) -(range)(SE):(0-4.7)(0.48) -*P*value:0.005 **Placebo** -Mean logMAR (SD):2.61(1.91)	No side effect was observed in any two treatment groups

				as out patients in the clinic for 3 days.						Total Mean logMAR(SD): 2.97(1.65)- (range)(SE):(0.1-4.7)(0.16) *P*Value: 0.52	(range)(SE): (0.1-4.7)(0.47) -*P*value:0.003	
Sung et al, 2020	CT	5participants 18<**Age**<70	1year	MSC: Application of 0.5%proparacaine Involved the instillation of 2 - 4 drops into the conjunctival sac. Subsequently, the conjunctiva was incised with scissors at the inferior-medial region of the for nix, followed by the insertion of af ine- gauge needle. A volume of 5x10^{7}hPMSCs was gently administered via subtend on injection through the needle. The incision site was subsequently scaled.	VA was assessed using the Snellen Eye Chart, and the results pertaining to early treatment of diabetic retinopathy were provided in letter score format. VF was measured HVF and VFI.	4	4	-	-	**Patient1**: -SE:8letters(FC at4feet) -FE:79letters (20/25) on a Bailey-lovie chart **Patient2**: -SE:58 letters (20/64,eccentric fixation) -FE:83letters (20/20) **Patient3**: -SE:NLP -FE:81letters (20/25) **Patient4**: - SE:NLP - FE:87letters (20/20)	**Patient1** -SE:18letters (20/500) -FE:84letters (20/20) on a Bailey-lovie chart **Patient2**(1year) -SE:73 letters (20/32) -FE:83 letters (20/20) **Patient3**: - SE:HM - FE:88 letters (20/20) **Patient4**: - SE:HM - FE:91letters (20/15)	**Patient1:** No significant AE occurred throughout 3 months after trans-plantation **Patient 2,3,** **4**: No significant AE throughout the1-year-post trans-plantation Period
Jia et al, 2020	CT	20participants **Age** Mean±SD 28.15±15.07	6months	**MSC:** EOCD, followed by covering of the operating field of the optic canal with a MSC-gelatin sponge sca_old with a cell viability of 95%forgroup1(1× 10^6 cells) **Surgery:** EOCD and only with a sterile gelatin spongesca_old for group 2 transplantation	VA was measured in mean logMAR. Other outcome: color vision and RAPD grading	10	10	10	10	**Group1:** -Mean logMAR (SD):2.82(0.41) -(range)(SE): (1.7-3.1)(0.129) **Group2:** - Mean logMAR (SD): 2.84(0.42) - (range)(SE): (1.7-3.1)(0.132) ***P*value**:0.936	**Group1**: -Mean logMAR (SD):1.77(1.11) - (range)(SE): (0.3-3.1)(0.249) - Pvalue:0.007 **Group2:** -Mean logMAR (SD): 2.36(0.81) -(range)(SE): (1-3.1)(0.181) Pvalue:0.048	No AE related to local transplantatio n was observed in The patients.

											P value:	
Razeghine Jad et al, 2010	CT	32 participants **Age** Mean±SD 23±7.63	**L-dopa group**: 6 months **Steroid group**:5 months	All patients? 250mg medrol IV for 3days? by oral prednisolone 1 mg/kg BW/dayfor11 days,&taperedover3 days. **L-dopa:** levodopa-c tablets(l-dopa100mg/ carbidopa 10 mg) at 1 tablet 3x/day for 1 month.	VA was measured in mean (logMAR)	9	16	11	10	**L-dopa Group** -logMAR:2.8± 1.8 -significance: 0.009 **Steroid Group** -logMAR:4.09± 1.01 -significance: 0.34	**L-dopa Group** -logMAR:2.1± 2.1 -significance: 0.009 **Steroid Group** -logMAR:3.92± 1.2 -significance: 0.34	No patients su□ered From the common side e□ects of levodopa in this study.

Abbreviation:AVE=average;RCT=RandomizedControlledTrial;CT=ClinicalTrial;ETOCD=Endoscopicallyassistedtransconjunctivalopticcanaldecompression;SF-36=Shortform-36;VA=VisualAcuity; QoL= Quality of Life; NLP= No Light Perception; LP= Light Perception; HM= Hand Motion; NR=Not Reported; EPO=Erythropoietin; IV=Intravenous; RAPD= Relative A□erent Pupillary Defect; MSC= Mesenchymal Stem Cell; hPMSCs= human Placental Mesenchymal Stromal Cells; VF= Visual Field; HVF=Humphrey Visual Field; MD=Mean Deviation; VFI= Visual Field Index; AE= Adverse Event; SE= Study Eye; FE= Fellow Eye; BW= Body Weight; EOCD= Endoscopic Optic Canal Decompression

[1]:Improvement degree

= ????????????(??????)?????-????????????(??????)?????? / (2.45 * -????????????(??????)??????) ;the *arteriskindicatesthat20/15(logMAR=0.12)isconsideredperfect vision

Table 2: *Visual Field Outcome.*

Author, Year	Study	Participant	Visual Field	
			Basal	End
Sung et al, 2020	Clinical Trial	5participants 18<**Age**<70	Patient 1 (loss to three months follow-up): - Large scotoma on SE (study eye) - Mean deviation (MD):-25.66dB - Visual field index (VFI):20% Patient2: - VFdefectonthesuperiortemporalquadrantinSE - Mean deviation (MD):-8.21dB - Visual field index (VFI):74% Patient 3: - Total VF defect in the SE -MD:-32.07 dB - VFI:0% Patient4: - Total VF defect in the SE -MD:-33.13 dB - VFI:0% ($p< 0.5$)	Patient1 (loss at three months follow-up): - scotomas lightly decrease in size - Mean deviation (MD):-21.88dB - Visual field index (VFI):32% Patient2: - At 6 months of followup, the VF defect size decreased - Mean deviation (MD):-6.87dB - Visual field index (VFI):76% Patient 3: - The VF defect shows minimal improvement -MD:-31.90dB - VFI:1% Patient4: - No significant di erences -MD:-33.13dB -VFI:0%($p<0.5$)

Table 3: *Summary of Systematic Reviews.*

Intervention	Visual Acuity		Visual Field	Number of Participants (Study)	Conclusion
Non-surgical versus surgical	No significant di□erences	-	119 participants (2 studies)	Non-surgical therapy may be e□ective in improving visual acuity, however no significant di□erences are observed between non-surgical and surgical interventions.	
Non-surgical versus placebo	No significant di□erences	-	218 participants (3 studies*)	Non-surgical therapy may be e□ective in improving visual acuity, however no significant di□erences are observed between non-surgical and placebo interventions.	
Non-surgical versus non-surgical (medro)	No significant di□erences	-	125 participants (3 studies)	Non-surgical therapy may be e□ective in improving visual acuity, however no significant di□erences are observed between non-surgical and non-surgical(methylprednisolone) interventions.	
Steroids versus placebo	No significant di□erences	-	155 participants (3 studies)	Steroids may be e□ective in improving visual acuity, however no significant di□erences are observed between steroids and placebo interventions.	
Mesenchymal Stem Cells	No significant di□erences	No significant di□erences	14 participants (2 studies)	The e□ect of mesenchymal stem cell therapy on improving visual acuity and visual field in TON patients is in conclusive due to both studies being Phase 1 clinical trials primarily concentrating on safety assessments for TON patients is inconclusive due to both studies being Phase 1 clinical trials primarily concentrating on safety assessments for TON.	
Erythropoietin	No significant di□erences	-	69 participants (1 study)	Erythropoietin may be e□ective in improving the visual acuity in patients with TON, however no significant di□erences are observed between erythropoietin, steroids or placebo interventions.	
Levodopa-carbidopa versus steroids	Improve	-	20 participants (1 study)	Levodopa-carbidopa combined with steroids may likely be e□ective in improving visual acuity than steroids alone.	

*)One of the three studies (Kashkouli *et al,* 2017 included in the comparison between non surgical and placebo interventions addresses two interventions, EPO (erythropoietin) and steroids.
**)Three out of the six studies (Entezari *et al,* 2007; Kashkouli *et al,* 2017 (steroids); Levin *et al,* 1998) discuss the comparison of steroid and placebo, while the remaining (Kitthaweesin*et* Yospaiboon, 2001; Chen*et al.,* 2019; Kashkouli*et al,* 2017 (EPO); Razeghinejad *et al,* 2010) will be discussed separately on the non-surgical versus non-surgical, non-surgical versus surgical, erythropoietin, and levodopa-carbidopa group respectively.

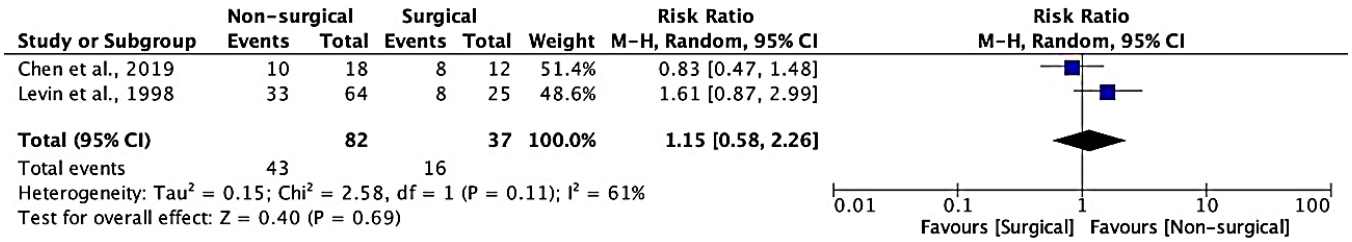

Figure 4: Meta-analysis and forest plot assessing the efficacy of non-surgical versus surgical therapies in enhancing visual acuity in individuals with traumatic optic neuropathy.

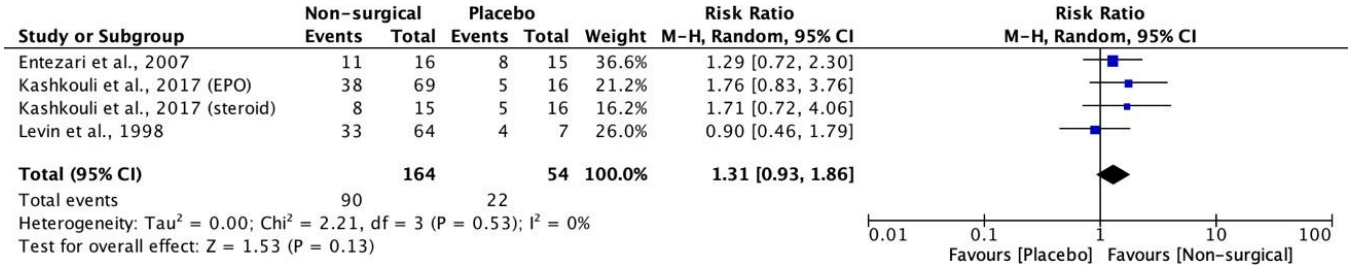

Figure 5: Meta-analysis and forest plot assessing the efficacy of non-surgical therapies compared to placebo in enhancing visual acuity in individuals with traumatic optic neuropathy.

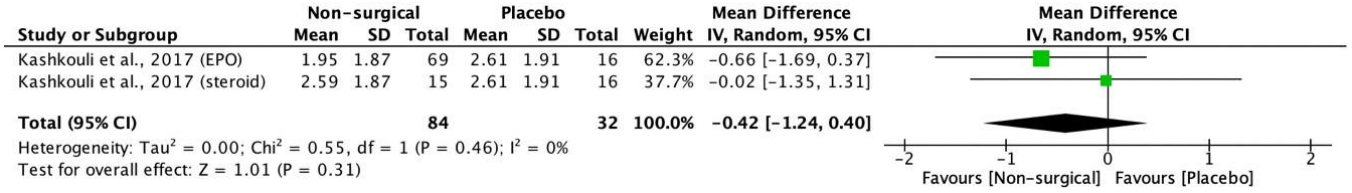

Figure 6: Meta-analysis and forest plot assessing the efficacy of non-surgical therapies compared to placebo on the mean differences in visual acuity among patients with traumatic optic neuropathy.

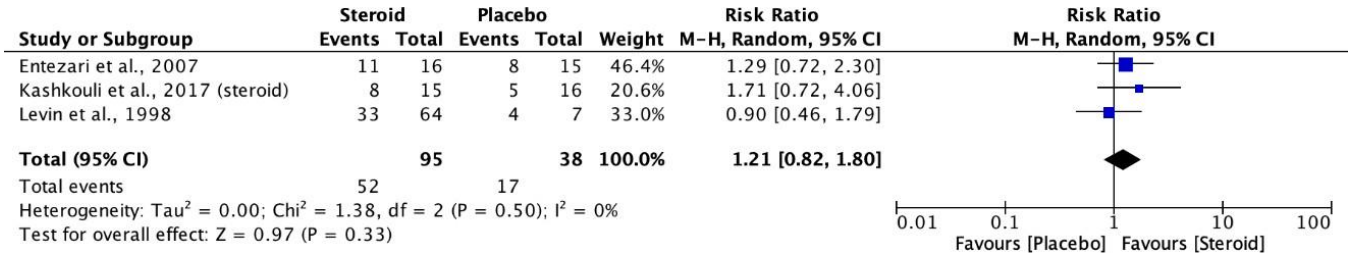

Figure 7: Meta-analysis and forest plot assessing the efficacy of steroids compared to placebo in enhancing visual acuity in patients with traumatic optic neuropathy.

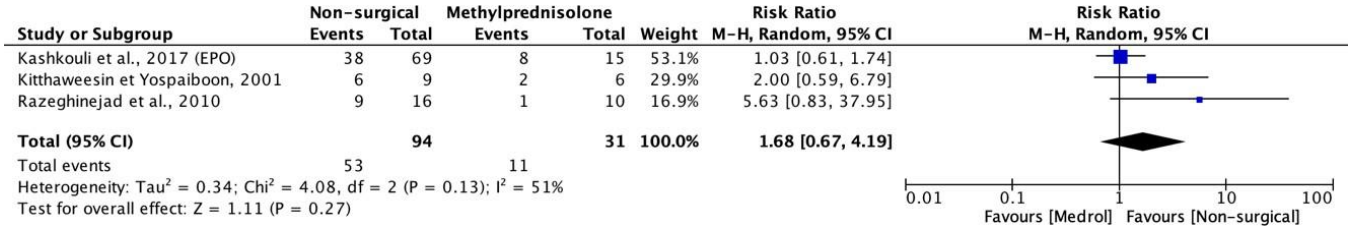

Figure 8: Meta-analysis and forest plot comparing the efficacy of non-surgical therapies, specifically methylprednisolone on the enhancement of visual acuity in patients with traumatic optic neuropathy.

discussed steroid therapy, but only 3 compared steroids with placebo alone, with the remaining studies having different comparators. The meta-analysis focused on these 3 studies, while the remaining studies comparing steroids with various interventions are discussed separately. Entezari et al., reported a non-significant RR of 1.29 [95%CI0.72,2.30], favoring steroids, similarly, Kashkouli et al, indicated a non-significant RR of 1.71 [95% CI0.72,4.06] in favor of steroids, while Levin et al, showed a non-significant RR of 0.90[95%CI0.46, 1.79], favoring placebo. The overall meta-analysis resulted in a non-significant RR of 1.21[95%CI0.82,1.8], indicating no statistically significant difference between steroids and placebo in improving visual acuity (Z=0.97, p=0.33), with homogenous outcomes across the studies (I2:0%).

Effectiveness of erythropoietin therapy

1. ***Improvement of Visual Acuity***

Ina trial involving 100 participants, 69 were assigned to the erythropoietin (EPO) group, 15 received steroid treatment, and 16 were placed under observation. The LogMAR acuity revealed that 55.1% of the EPO group, 53.3% of the steroid group, and31.3%ofthe observation group experienced a change of 0.3 in their last follow-up. After accounting for the initial visual acuity, no statistically significant difference was observed, even though the treatment groups experienced vision improvements.

In the study by Kashkouli et al, although all groups showed enhanced vision, the steroid-treated group exhibited the fastest recovery within the initial month, while the EPO-treated group demonstrated steady and sustained progress beyond the third month. Evaluation of color vision and RAPD revealed improvements across all groups, with statistically significant enhancement in color vision noted in the EPO group. However, the study cautioned about potential bias due to the higher patient count in this group. While statistically significant improvements in RAPD were observed across all groups as a categorical variable, mean RAPD improvement achieved statistical significance in the EPO and steroid groups.

The analysis emphasized the impact of trauma-to-treatment intervals exceeding three days and initial visual acuity categorized as no light perception (NLP) on poorer final visual acuity outcomes. These findings underscore the crucial role of timely intervention and initial visual acuity in determining the ultimate visual recovery for TON patients.

2. ***Improvement in Visual Field***

The primary outcome focused on BCVA, with color vision and RAPD grading as secondary measures. Although visual field assessment was initially designated as a secondary measure, practical limitations, such as compromised visual acuity and unavailability of testing resources, prevented data collection. Many patients had severely impaired vision, making them unsuitable for standard visual field testing, and logistical constraints further hindered access to the necessary tests before medication initiation. Consequently, visual field assessment was excluded from the recorded parameters of the study.

3. ***Adverse Effects***

The administration of erythropoietin and steroids to patients showed a notable absence of side effects within the treatment groups. The lack of adverse reactions may indicate a favorable safety profile for both erythropoietin and steroid therapies.

2. ***Improvement in Visual Field***

In the group of six studies on steroid treatment, none reported information on visual field outcomes, with the primary focus being on visual acuity assessment. Kashkouli et al, included measurements of color vision and Relative Afferent Pupillary Defect (RAPD) grading alongside visual acuity and explored the effects of erythropoietin as a treatment for TON. Another study measured SF-36 scores, focusing on the quality of life as a secondaryoutcome.[16]

3. ***Adverse effects***

Among the six studies in the steroid group, three reported no observed adverse effects associated with steroid administration.[16,18,19] However, the remaining two studies did not mention any adverse effects related to steroid administration.[20,21]

Effectiveness of levodopa-carbidopa therapy

1. ***Improvement of Visual Acuity***

   The research examining the effects of levodopa-carbidopa on visual outcomes in patients with indirect traumatic optic neuropathy (ITON) demonstrated encouraging results.[21] Administering levodopa-carbidopa, specifically one tablet (100/10mg) thrice daily for a month, led to improvements in visual acuity (VA) for 56.2% of the treated patients, compared to only 10% in the placebo group (p=0.02). The baseline Best-Corrected Visual Acuity (BCVA) for the levodopa-carbidopa group was 2.8±1.8 logMAR, significantly improving to 2.1 ± 2.1 at the final follow-up (p=0.009). Adjusting for the initial differences in vision, patients with comparable baseline BCVA in both groups showed significant improvement in the levodopa group (p=0.03), emphasizing the therapeutic effect of levodopa-carbidopa on vision compared to corticosteroids with a placebo.

2. ***Improvement in Visual Field***

   This study lacks information about the visual field before and after administering levodopa-carbidopa, as the main outcomes focused on visual acuity and Pattern Visual Evoked Potential (PVEP).[23] The article provides visual acuity data only at the conclusion, omitting details about PVEP due to challenges recording it caused by the poor vision of the patients.

3. ***Adverse Effects***

   No adverse events, such as a decline in visual acuity, were reported in either the levodopa-carbidopa or steroid group, suggesting a potential benefit for visual recovery through levodopa treatment. The study observed that levodopa does not produce any of the typical adverse effects that are associated with it, such as hallucinations, dyskinesia, skin rash, mood and mental changes, drowsiness, dizziness, headache, anorexia, and nausea as well as vomiting.However,theacknowledgmentthatsome patientsmightbeintolerant to these drugs could potentially hinder the completion of the treatment course.

DISCUSSION

In this study, eight studies were included, with two randomized controlled trials (RCTs) and six clinical trials. Steroid interventions were the most studied, followed by mesenchymal stem cells, erythropoietin, and levodopa-carbidopa. Visual acuity, adverse effects, and visual field were the most frequently reported outcomes across all intervention types. However, substantial differences existed in the study populations, subjects, control groups, interventions, and outcome measures, rendering statistical pooling or quantitative analysis inappropriate.

The reviewed studies exhibited varying levels of bias: three had low risk, three had moderate risk, and two had high risk. This heterogeneity highlights the need for careful interpretation of the findings, considering the methodological strengths and weaknesses.

Studies on interventions for TON show visual acuity improvements across different treatments, but no significant advantage among them. Non-surgical therapies, surgical approaches, and placebos yielded similar outcomes. Chen et al., suggested potential benefits of surgical optic nerve decompression, though statistical significance was limited by a small sample size. Levin et al., favored non-surgical approaches, emphasizing individualized treatment decisions. The findings suggest that vision restoration may occur even without specific interventions, especially in severe cases.[16,17]

Non-surgical therapy showed visual acuity improvement over placebo, though without statistical significance. Kashkouli et al, found that the steroids group experienced the fastest vision recovery within the first month, with no further significant changes.[19] The observation group showed minimal early recovery, improving after two weeks and continuing for up to 2.5 months before plateauing. The EPO group exhibited steady improvement from the beginning, maintaining progress beyond the third month.[19]

Studies comparing non-surgical therapies for TON, including EPO, dexamethasone, and levodopa with methylprednisolone, found no significant differences in visual outcomes.[24]Kashkouliet al., noted EPO's potential benefits but found no advantage over methylprednisolone, with delayed treatment and severe impairment linked to poorer outcomes.[19] Kitthaweesin et al, suggested

dexamethasone's cost-effectiveness and lower dosing benefits, though based on a single study.[20] Razeginejad et al, highlighted levodopa's potential due to its blood-brain barrier penetration, but no significant superiority among treatments was observed, and further studies on prolonged treatment effects are needed.[21]

Steroid regimens for TON varied across studies, with five using intravenous methylprednisolone or prednisolone and one using oral methylprednisolone. All regimens showed visual acuity improvement, but no significant difference in effectiveness was observed between intravenous and oral treatments.

Interpreting reports on visual improvement after optic nerve injuries is challenging due to inconsistent definitions and variations in visual acuity testing. Many studies lack standardized criteria, often classifying even minor changes as improvement. While significant gains, such as recovery from no light perception (NLP) or substantial enhancement in patients with better initial acuity, are considered credible, minor improvements in those with existing vision are viewed with skepticism.

In addition, there is also variability in the reporting of outcome measurements for visual acuity. Some studies reported visual acuity using Snellen charts,[17,20] Bailey-Lovie charts,[25] and logMAR.[6,18,19,21] This variability in measurement scales for visual acuity across studies may introduce challenges indirectly comparing and synthesizing the outcomes. Differences in measurement methods can potentially impact the interpretation and pooling of data in meta-analyses.

There is considerable variability in how visual acuity outcomes are reported, with some studies using Snellen charts,[17,20] others using Bailey-Lovie charts,[25] and some employing logMAR.[6,18,19,21] These differences in measurement scales create challenges in directly comparing and synthesizing results, potentially affecting data interpretation and the accuracy of meta-analyses.

Non-surgical therapy shows promise for improving visual acuity in TON patients, with no significant differences among treatments. Treatment choices depend on patient preferences, disease severity, risks, and resource availability, while timely intervention is crucial. The limited studies on TON highlight the need for larger clinical trials with standardized reporting to enhance transparency and accuracy.

This study has limitations, including a small number of studies, limited data on visual field assessments, reliance on clinical trials, and diverse outcome measurements.

CONCLUSION

This research underlines the potential efficacy of non-surgical approaches in enhancing visual acuity and visual field in patients with TON, but no significant differences were found compared to other interventions. Despite a safe profile, the overall efficacy of non-surgical therapy remains inconclusive. Initial visual acuity at diagnosis is a crucial factor in TON prognosis. The study notes significant flaws, including a scarcity of human clinical trials on TON and reliance on animal models, revealing a gap in human population studies. In adequate reporting of missing data and varied outcome reporting in human studies pose challenges for quantitative analysis.

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