

## Research

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# Posterior Sub-Tenon Triamcinolone Injection for Chronic Macular Oedema Associated With Non-Ischemic Branch or Central Retinal Vein Occlusion

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## ABSTRACT

**Aims:** To evaluate the effectiveness and safety of Posterior Sub-Tenon (PST) Triamcinolone Acetonide (TA) injection for persistent macular oedema associated with non-ischemic Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO) in non-vitrectomized eye.

**Methods:** Fourteen consecutive eyes of 14 patients characterized by macular oedema lasting more than 3 months and with a visual acuity of less than 20/40 were enrolled. Six eyes presented with BRVO, 8 eyes with CRVO. PST injection of 40 mg TA was performed in topical anaesthesia. All patients were phakic, and followed for at least 6 months. Snellen visual acuity converted to LogMAR units and anatomic responses were evaluated before, and at 1, 3, 6, and 12 (if required) months after injections and re-injection considered.

**Results:** In the BRVO group, mean foveal thickness was  $548.2 \pm 49.50$   $\mu\text{m}$  preoperatively, and  $452.8 \pm 56.2$   $\mu\text{m}$  and  $280.8 \pm 62.5$   $\mu\text{m}$  at 1 and 12 month follow-up, respectively. Statistical analysis showed significant differences between preoperative and postoperative measurements ( $p < .05$ , paired  $t$  test) 3 months after injections. Improvement of visual acuity by at least 0.2 LogMAR was seen in 3(50%) of the 6 eyes. No re-injection was needed. In the CRVO group, mean foveal thickness was  $543.7 \pm 34.4$   $\mu\text{m}$  preoperatively, and  $283.0 \pm 29.0$   $\mu\text{m}$  and  $234.8 \pm 23.6$   $\mu\text{m}$  at 1 and 12 month follow-up, respectively. Statistical analysis showed significant differences between preoperative and postoperative measurements ( $p < .05$ , paired  $t$  test). Improvement of visual acuity by at least 0.2 LogMAR was seen in 7 eyes (88%). Mean number of re-injection was of  $2.1 \pm 0.3$ . Intraocular pressure elevation of 22 mm Hg or higher was found in 2/14 eyes (14%). Cataract progression was noted in 5/14 eyes (36%).

**Conclusions:** PST injection of TA appears to be as safe and effective treatment for chronic macular oedema associated due to both non-ischemic BRVO or CRVO, with a better efficacy in BRVO.

**KEYWORDS:** Branch/Central retinal vein occlusion; Chronic macular oedema; Triamcinolone; Posterior sub-Tenon injection.

**ABBREVIATIONS:** PST: Posterior sub-Tenon; TA: Triamcinolone Acetonide; CRVO: Central Retinal Vein Occlusion; BRVO: Branch Retinal Vein Occlusion; Anti-VEGF: Anti-Vascular Endothelial Growth Factor; IOP: Intraocular pressure; SEM: Standard Error of the Mean; ILM: Internal Limiting Membrane; LOCS II: Lens Opacities Classification System, version II.

## INTRODUCTION

Macular oedema is the most common cause of visual loss among patients with Retinal Vein Occlusion (RVO).<sup>1,2</sup> The only proven treatment before the Anti-Vascular Endothelial Growth Factor (Anti-VEGF) intravitreal injection era consisted of grid pattern laser photoco-

agulation which is based on the results of Branch Vein Occlusion Study (BVOS).<sup>2</sup> In the BVOS, patients received laser treatment when vision had been lower than 20/40 for at least 3 months and if there was no macular ischemia. The rationale for this waiting period was that one third of patients with retinal vein occlusion may have spontaneous resolution of macular oedema within this time span.<sup>1-3</sup> Grid laser treatment has also been advocated for macular edema in Central Retinal Vein Occlusion (CRVO). This therapy only had a positive effect on the edema, however not on visual acuity.<sup>1</sup>

Anti-VEGF intravitreal injection is nowadays widely considered as the first choice for retinal vein occlusion macular edema management with effective subsequent visual acuity improvement.<sup>4,5</sup> However the need of frequent administration, the risk of potential local and systemic complication and their high cost, unravelled the search of alternative treatment.<sup>6</sup>

Triamcinolone Acetonide (TA) is a corticosteroid that has been reported to be efficacious in the treatment of retinal vein occlusion induced macular edema when administrated intravitreally.<sup>7,8</sup> Nevertheless, intravitreal procedures may be associated with endophthalmitis, vitreous haemorrhage, retinal detachment, and high intraocular pressure. In some studies less invasive procedures such as Posterior sub-Tenon (PST) TA infusion<sup>9</sup> or TA injection in vitrectomized eyes<sup>10</sup> have been evaluated as a treatment for macular oedema associated with retinal vein occlusion.

In the present study we have evaluated the efficacy and safety of PST injection of TA in primarily non-vitrectomised eyes with severe macular oedema secondary to non-ischemic branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

## MATERIALS AND METHODS

The study adhered to the tenets of Helsinki. We included 14 consecutive eyes of 14 patients, who had severe macular oedema secondary to non-ischemic branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) lasting more than 3 months after onset, with a visual acuity of less than 20/40 and without prior treatment. The patients were evaluated on the basis of central retinal thickness using a horizontal 5 mm Optical Coherence Tomography (OCT) scan through the macula (Stratus system, OCT Model 3000, software version 3.0; Carl Zeiss-Meditec, Dublin, CA, USA), Best Corrected Visual Acuity (BCVA), Intraocular pressure (IOP) and cataract progression as Lens Opacities Classification System, version II (LOCS II) classification system.<sup>11</sup> BCVA was obtained using Snellen charts and converted to LogMAR units. PST injection of TA injection (Kenacort A40, Dermapharm AG, Hünenberg, Switzerland) was performed in an outpatient setting. None of our patients had previous vitrectomy. After topical oxybuprocaine hydrochloride 4% had been instilled, a cotton tip soaked in 4% tetracaine was

placed over the superotemporal quadrant for 1 minute as the patient was asked to look inferonasally. The upper eyelid was elevated manually and a 25 G needle was then passed through the conjunctiva and Tenon's capsule into the PST space, and 40 µg of TA was injected. Ofloxacin 3 mg/ml was instilled three times daily for 1 week. BCVA, central retinal thickness and IOP were assessed at 1, 3, 6, and 12 months after the injection or prior to these dates if the patient re-attended the clinic due to visual loss. Criteria for re-injections included worsening of macular oedema thickness on OCT defined as an increase of 100 microns or more coupled with worsening of the BCVA defined as a decrease of 2 or more lines after initial improvement following the first injection. These patients were then seen again after the second injection at the intervals described above to ascertain improvement both clinically and on OCT.

Third injections were performed if both BCVA and OCT worsened again during follow-up after the second injection. If patients showed no improvement after the first injection they continued to receive the standard treatment including anti-VEGF intravitreal injection and/or macular grid laser for BRVO patients *versus* clinical follow-up for CRVO patients.

Changes overtime in LogMAR visual acuity, central retinal thickness and IOP were compared using the *paired t test*. The differences between BRVO and CRVO groups in LogMAR visual acuity, central retinal thickness, IOP and other continuous variables were compared using the *Mann-Whitney U test*. Linear correlation between the number of required PST injections and cataract progression or IOP elevation, as well as with macular thickness and BCVA, was tested with the *Pearson correlation co-efficient*. Data were expressed with Standard Error of the Mean (SEM).

## RESULTS

The patient characteristics of both groups are shown in Tables 1 and 2. Six patients were included in the BRVO group. The mean patient age was 64.3±4.2 years (range: 52 to 80 years) and the mean duration of the symptoms, according to patient history before TA injection, was 13.7±5.0 months (range: 3 to 24 months). Eight patients were part in the CRVO group. Mean age was 70.3±2.9 years (range: 59 to 81 years) and the mean duration of the disease was 7.6±2.6 months (range: 3 to 24 months). No statistically significant differences were found between groups regarding age ( $P=0.15$ , *Mann-Whitney test*), or duration of the occlusion ( $P=0.09$ , *Mann-Whitney test*).

### BRVO Group

Data are summarized in Table 3. Patient 5 stopped attending our clinic 6 months after injection for personal reason. The mean follow-up period after injection was 9.0±3.3 months (range: 6 to 12 months). Mean foveal thickness was 548.2±49.0 µm preoperatively, 452.8±56.2 µm at 1 month follow-up,

Patient	Age (years)	Duration (months)	Pre-VA (LogMAR)	Final VA (LogMAR)	Pre-OCT thickness (µm)	Final-OCT thickness (µm)	Follow-up (months)	Recurrence and date of re-injection
1	60	7	0.8	0.7	660	400	12	-
2	60	6	1.0	0.7	672	340	6	-
3	74	24	0.4	0.1	439	250	12	-
4	52	3	1.3	0.1	630	190	12	-
5	60	24	0.5	0.5	400	232	6	-
6	80	18	0.6	0.5	488	583	6	-

**Table 1:** Baseline and follow-up data for BRVO patients treated with posterior sub-tenon triamcinolone injection. Duration from onset of visual impairment to injection. VA: Visual acuity.

Patient	Age (years)	Duration (months)	Pre-VA (LogMAR)	Final VA (LogMAR)	Pre-OCT thickness (µm)	Final-OCT thickness (µm)	Follow-up (months)	Recurrence and date of re-injection
1	64	3	0.8	0.2	630	150	12	2 and 4 months
3	81	7	0.4	0.1	550	175	12	-
4	72	24	0.4	0.1	431	275	12	6 months
5	59	3	0.7	0.1	670	340	12	-
6	81	3	1.0	0.5	500	265	12	3 and 6 months
6	63	9	0.6	0.4	691	224	12	6 months
7	68	4	0.9	0.2	484	200	12	6 and 11 months
8	74	3	0.4	0.5	480	300	12	1 and 3 months

**Table 2.** Baseline and follow-up data for CRVO patients treated with posterior sub-tenon triamcinolone injection. Duration from onset of visual impairment to injection. VA: Visual acuity.

Time point	Foveal Thickness (µm)		Visual Acuity (LogMAR)		Pearson correlation		IOP (mm Hg)	
	Mean±SEM	P value	Mean±SEM	P value	R <sup>2</sup>	P Value	Mean±SEM	P value
Baseline (n = 6)	548.2±49.0 NA		0.77±0.14 NA		0.66 0.05		16.2±1.3 NA	
1 month (n = 6)	452.8±56.2 0.07		0.48±0.11 0.07		0.40 0.18		15.8±0.7 0.82	
3 month (n =6)	340.0±5.8 0.01		0.42±0.13 0.05		0.25 0.67		20.0±5.1 0.44	
6 month (n=3)	390.3±105.3 0.01		0.33±0.18 0.05		0.89 0.21		18.0±1.1 0.63	
12 month (n = 3)	280.8±62.5 0.01		0.30±0.20 0.04		0.92 0.18		18.0±2.0 0.50	

**Table 3:** Summary of changes in foveal thickness, visual acuity and intraocular pressure (IOP) for BRVO. Differences were analyzed with the paired *t* test and considered significant when *P*<0.05. Foveal thickness and visual acuity was correlated by the Pearson R<sup>2</sup> correlation test and considered significant when *P*<0.05.

340.0±5.8 µm at 3 month follow-up, 390.3±105.3 µm at 6 month and 280.8±62.5 µm at 12 month follow-up. Statistical analysis showed significant and sustained decreased in foveal thickness between preoperative and postoperative measurements from the third months after PST injection (*p*>.05, at 1, 3, 6 and 12 months, paired *t* test) without need of further injection. Visu-

al acuity improved also significantly 3 months after injections from preoperative 0.77±0.14 LogMAR (range: 1.3 to 0.4) to 0.30±0.20 LogMAR (range: 0.7 to 0.1; *p*=0.04, paired *t* test) at 12 month follow-up. Improvement of visual acuity by at least 0.2 LogMAR was seen in 3(50.0 %) of the 6 eyes. Time of injection (duration of the disease) did not influence final visual acuity

(Pearson correlation co-efficient,  $r^2=0.01$ ,  $p=0.84$ ).

### CRVO Group

Data are summarized in Table 4. The mean follow-up period after injection was of 12 months. Average re-injection number was  $2.1\pm 0.3$ . Mean foveal thickness was  $543.7\pm 34.4$   $\mu\text{m}$  preoperatively,  $283.0\pm 29.0$   $\mu\text{m}$  at 1 month follow-up,  $372.0\pm 60.1$   $\mu\text{m}$  at 3 month follow-up,  $255.0\pm 22.4$   $\mu\text{m}$  at 6 month and  $234.8\pm 23.6$   $\mu\text{m}$  at 12 month follow-up. Statistical analysis showed significant differences between preoperative and post-operative foveal thickness measurements ( $p<0.01$ , at 1, 3, 6 and 12 months, paired  $t$  test). Visual acuity improved significantly from preoperative  $0.65\pm 0.08$  LogMAR (range: 1.0 to 0.4) to  $0.26\pm 0.06$  LogMAR (range: 0.5 to 0.1;  $p<0.01$ , paired  $t$  test) after 12 months of follow-up with a non-significant value at 3 months which correspond to the mean interval  $4.0\pm 2.0$  months before a second re-injection was needed. Improvement of visual acuity by at least 0.2 LogMAR was seen in 7(87.5%) of the 8 eyes.

Duration of the disease did not influence final visual acuity (Pearson correlation co-efficient,  $r^2=0.14$ ,  $p=0.18$ ).

No statistically significant differences were found between BRVO and CRVO groups regarding foveal thickness before and after treatment ( $p=1.0$ ,  $p=0.13$ , respectively, Mann-Whitney test), or visual acuity before and after treatment ( $p=0.55$ ,  $p=0.16$ , respectively, Mann-Whitney test). In 6(0.75%) eyes of the CRVO group, additional injections were performed because of recurrent macular edema, and 4(50%) of those eyes required a third injection. Intraocular pressure elevation of 22 mm Hg or higher was found in 2/14 eyes (14%, CRVO group) but were not associated with the number of injections (Pearson correlation co-efficient,  $r^2<0.01$ ,  $p>0.97$ ). The IOP in those eyes could be controlled with topical low-pressure medication. All eyes were phakic and cataract progression was noted in 5 eyes (1 eye BRVO and 4 eyes CRVO), of which patient 3 of the CRVO group had cataract extraction 6 months after the injection. Cataract progression was not correlated with the number of injections (Pearson correlation co-efficient,  $r^2=0.04$ ,  $p=0.48$ ).

### DISCUSSION

Several studies have suggested various invasive options to treat CRVO and BRVO including intravitreal tissue plasminogen activator,<sup>12,13</sup> radial optic neurotomy,<sup>14</sup> sheathotomy,<sup>15</sup> macular decompression using vitrectomy and Internal Limiting Membrane (ILM) peeling,<sup>16</sup> and laser induced chorioretinal anastomosis.<sup>17</sup> Intravitreal TA has been shown to be effective in treating macular oedema due to CRVO and BRVO.<sup>8,9,18</sup> However, intravitreal injections carry considerable risks, including acute infectious endophthalmitis<sup>19</sup> and pseudophthalmitis.<sup>20</sup>

PST injection seems to be less effective than intravitreal TA or grid laser photocoagulation for treatment of macular edema in BRVO.<sup>21</sup> However, PST of TA on the other hand may give rise to intravitreal TA concentrations comparable to the level achieved by intravitreal injection<sup>22</sup> without incurring the same risks. TA delivered *via* the posterior sub-tenon route has previously been widely used for treating macular edema due to Irvine-Gass Syndrome,<sup>23</sup> diabetes,<sup>24</sup> and uveitis.<sup>25</sup> Lin, et al. reported the clinical outcome of PST of TA in the early treatment of macular edema in CRVO lasting for not more than 15 days prior to the injection.<sup>26</sup> It was concluded that early injections are effective in reversing macular edema and improving visual acuity. However, since one third of patients with retinal vein occlusion may have spontaneous resolution of macular edema within the first 3 to 4 months,<sup>1-3</sup> we performed the sub-tenon injection of TA only after 3 months in the present study.

Our results showed that this form of treatment is effective in reversing macular oedema and improving visual acuity in retinal vein occlusion even after the presence of macular edema for several months. Those findings are in keeping with some recent reports.<sup>27,28</sup> However our study is the first one to compare PST injection between BRVO and CRVO patient. This treatment might be more effective in BRVO than CRVO patient, as only one injection was required in BRVO patients. In the CRVO group, while OCT and visual acuity values improved during the first months, patients often necessitated a second or a third injection after the transient effect of a PST. Compared to the CVOS data, where only 20% of the eyes with an initial VA ranging from

Time point	Foveal Thickness( $\mu\text{m}$ )		Visual Acuity (LogMAR)		Pearson correlation		IOP	
	Mean $\pm$ SEM	P value	Mean $\pm$ SEM	P value	R <sup>2</sup>	P value	Mean $\pm$ SEM	P value
Baseline (n = 8)	543.7 $\pm$ 34.4 NA		0.65 $\pm$ 0.08 NA		0.02 0.36		15.8 $\pm$ 0.7 NA	
1 month (n = 8)	283.0 $\pm$ 29.0<.01		0.38 $\pm$ 0.03<.01		0.23 0.11		18.9 $\pm$ 1.5 0.11	
3 month (n = 8)	372.0 $\pm$ 60.1<.01		0.43 $\pm$ 0.15 0.11		0.34 0.06		17.6 $\pm$ 1.5 0.40	
6 month (n = 8)	255.0 $\pm$ 22.4<.01		0.34 $\pm$ 0.07<.01		0.27 0.12		15.3 $\pm$ 1.0 0.69	
12 month (n = 8)	234.8 $\pm$ 23.6<.01		0.26 $\pm$ 0.06<.01		0.25 0.16		17.9 $\pm$ 1.3 0.27	

**Table 4:** Summary of changes in foveal thickness, visual acuity and intraocular pressure (IOP) for CRVO. Differences were analyzed by the paired  $t$  test and considered significant when  $P<0.05$ .

0.4 to 1.0 LogMAR improve to 0.4 or better, our results showed that 75% of the eyes (6/8) improved to that level.

Although the IOP rise in our study (2 eyes, 14%) is better compared to the IOP after intravitreal injections (20-33%),<sup>3,7,18,24</sup> it could be still argued that the incidence of intraocular pressure elevation is very high, and that TA injections should thus only be used in exceptional circumstances. However, in view of the devastating long-term effects of retinal vein occlusions on visual acuity we believe that these side effects can be managed either medically or surgically, and that this form of treatment should be evaluated further given the ease of injection, the low costs as well as the low risks of its application in an outpatient setting.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

#### DISCLOSURE

The authors have no financial interest in the materials or methods used in this study.

#### CONSENT

The patient has provided written permission for publication of the manuscript.

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