EXTENDED REPORT

Surgical induction of chorioretinal venous anastomosis in ischaemic central retinal vein occlusion: a non-randomised controlled clinical trial

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Aim: To evaluate the safety and efficacy of surgical induction of chorioretinal venous anastomosis in the management of ischaemic central retinal vein occlusion (CRVO).

Methods: In a comparative clinical trial, 28 patients with ischaemic CRVO were included, of whom 18 who declined surgery were considered as controls. The 10 surgical cases underwent standard vitrectomy with incisions into the choroids adjacent to the partially cut major retinal veins. Mersilene suture insertion was done to induce chorioretinal venous shunt. Mild endolaser was applied. Patients were followed up for 6–18 (mean 10) months.

Results: Clinical success in shunt development was 90%. Surgical cases had a significantly better visual acuity improvement compared with controls (mean difference: 1.5 logMAR, p = 0.001) with 80% of them showing improvement (compared with 28% of the controls, p = 0.016). Neovascularisation developed in 39% of the control group compared with 0% of the surgical cases (p = 0.03). In multivariate analysis, surgery remained the sole significant predictor of visual improvement. There were three re-operations for vitreous cavity haemorrhage, cataract, and retinal detachment.

Conclusions: Surgical induction of chorioretinal venous anastomosis may result in visual acuity improvement and prevent neovascularisation in ischaemic CRVO. Randomised studies are needed to compare the current study modality with the natural course of CRVO and emerging procedures, such as optic neurotomy, in the management of ischaemic CRVO.

Central retinal vein occlusion (CRVO) is a relatively common cause of visual loss; after diabetic retinopathy, it is the most frequent vascular accident. The prevalence and five year incidence of CRVO were estimated to be 0.1–0.4% and 0.2%, respectively. The two most frequent complications of CRVO are persistent macular oedema and neovascular glaucoma.

There are two types of CRVO— ischaemic and non-ischaemic. Almost 20% of the cases are of ischaemic type at presentation, with some 10% of the non-ischaemics eventually converting to ischaemic type. In the non-ischaemic category, 48% of the patients go on to complete resolution and anterior segment neovascularisation is rare. But in the ischaemic group visual outcome is poor and only 10% of patients gain a visual acuity (VA) better than 20/400, and there is a high incidence of iris neovascularisation (up to 60%).

Several reports have suggested restoring the venous outflow by: (1) creating a laser or surgically induced chorioretinal anastomosis; (2) administering recombinant tissue plasminogen activators; (3) cannulating the retinal vein transvitreally; (4) transecting the posterior scleral ring, and (5) radial optic neurotomy. These modalities are largely advocated for the non-ischaemic subtype and limited studies have been done so far on the ischaemic types.

A variety of procedures have been proposed for the iatrogenic induction of chorioretinal venous anastomosis in non-ischaemic types, including diathermy (Verhoeff, 1948) and Argon laser photocoagulation (McAllister et al, 1995). Vitrectomy combined with intentional interruption of retinal vein in a group of intermediate CRVO cases also reported by Koizumi et al in 2002.

In 1999, Fekrat et al performed venipuncture to induce the venous shunt in a case of ischaemic CRVO. In the same year, Peyman et al reported surgical chorioretinal venous anastomosis for the ischaemic subtype in which, following standard vitrectomy, they inserted Mersilene suture beneath the retina, adjacent to the major retinal veins. The surgical approach was modified by Quiroz-Mercado et al in 2001 in which, following vitrectomy, they applied Erbium:YAG laser to induce shunt formation. All groups reported their findings in a non-comparative fashion and concluded that the procedures might improve prognosis in some of the eyes affected with ischaemic CRVO.

The purpose of the current study is to evaluate the success of the surgical induction of venous chorioretinal shunt formation and its efficacy in terms of visual improvement and prevention of neovascularisation in a comparative trial.

MATERIAL AND METHODS

Setting

This is a non-randomised controlled trial on patients with ischaemic CRVO referred to Farabi Eye Hospital. The study was approved by the Hospital Review Committee. The criteria for diagnosis were: a VA of less than 20/200, the presence of a relative afferent pupillary defect of 2+ or more, extensive retinal haemorrhage and 10 or more disc areas of capillary non-perfusion (fig 1), and the absence of neovascularisation. Twenty eight of the 32 referred cases in the period of March 2001 to October 2003 were included. The risks and benefits of the surgical modality were fully explained to all patients and written informed consent was obtained. The patients who declined the surgery were considered as the controls.

Abbreviations: CRVO, central retinal vein occlusion; VA, visual acuity
Examinations and the procedure
The baseline VA, relative afferent pupillary defects, slit lamp exam, intraocular pressure, funduscopic, and gonioscopic findings were recorded. Fundus photography and fluorescein angiography were also performed. Following surgery, patients were examined weekly in the first month, monthly for six months, and every other month thereafter. Fundus photographs and retinal fluorescein angiography were repeated at months 1 and 3 and at the last follow up to evaluate shunt development and patency.

The surgical procedure was a standard three port vitrectomy followed by creation of posterior hyaloid separation and removal of the posterior cortical vitreous; then slit-like incisions were made with a microvitreoretinal blade through Bruch's membrane, adjacent to the major branch of retinal vein in each quadrant (a total of 1–4 shunts were attempted). After that, the subjacent vein was partially cut off and small pieces of 5–0 Mersilene suture were inserted in the incised sites (to maintain its patency and to promote formation of collateral channels) (fig 2). Endolaser treatment was applied around the incision sites followed by mild peripheral retinal photocoagulation. The parameters were: a power of 200–500 mW and duration of 200 ms for 300–800 spots.

Shunt patency evaluation
A combination of fundus photographic and angiographic criteria were applied to evaluate the functionality of the shunts.\(^{10,14}\) Criteria to evaluate shunt function; fundus photographic and fluorescein angiographic clues:

1. Thinning of the venous segment proximal to the anastomosis (fig 2) or asymmetric vein diameter at the disc.
2. Reverse tapering sign (increasing venous diameter further from disc).
3. Trilaminar flow.
4. Retrograde venous flow between the disc and the anastomosis.
5. Sharp change in hyperfluorescence at the anastomosis (this sign suggests a relative discontinuation in the thickness of fluorescein column at an anastomosis site).
6. Disappearance of the vein at the anastomosis (fig 2).

Figure 1 Baseline fundus photograph (A) of case number 4 and fluorescein angiography (B) of case number 10, showing extensive retinal haemorrhage and capillary non-perfusion characteristic of ischaemic central retinal vein occlusion.

Figure 2 (A) Case number 1: eight week post-surgical fundus photograph depicting three attempted shunts (retinal haemorrhage and oedema have resolved). (B) Case number 5: thinning of the venous segment proximal to the anastomosis site. (C) Case number 3: disappearance of the vein at the anastomosis sites. (D) Case number 4: development of collaterals without leakage at the attempted shunt site.
Analysis
By “presentation time” we mean the time period from the onset of vein occlusion to the time of referral and the expression “month 8 post-event VA” refers to the visual acuity eight months after the occurrence of vein occlusion. The VA data were converted into logMAR equivalents and all the statistical analyses of VA were based on this notation. The Mann-Whitney U and the Wilcoxon ranked tests were used to compare the VA data of the two study groups and to compare baseline with month 8 post-event VA of the surgical cases respectively. The $\chi^2$ test was used to compare VA improvement between early and late presentation times in the surgical cases, to compare VA improvement between the two groups, and to compare the occurrence of neovascularisation.

To evaluate the effect of (potential) confounders, the two groups were compared for age, sex, ocular and systemic associations, presentation time, and presentation VA with $\chi^2$ and Mann-Whitney U tests. Multinomial logistic regression analysis was used to evaluate the association of the three outcomes of month 8 post-event VA, VA improvement, and neovascularisation with three baseline covariates of presentation time, presentation VA, and the study group.

RESULTS
Of the 32 referred patients, 28 met the inclusion criteria. Ten of the participants consented to surgery. The age range was 33–80 years (mean 60 (SD 13) years). Fifteen cases were male. The range of presentation time was 1–6 months (mean 33 (SD 13) months). Median VA at presentation was counting fingers at 1.5 m equivalent to 20/800 (range: HM to 20/240).

For details of the cases see table 1.

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Control group

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F, female; M, male; L, left eye; R, right eye; HTN, hypertension; HCH, hypercholesterolaemia; DM, diabetes mellitus; VA, visual acuity; HM, hand motion; LP, light perception; RD, retinal detachment.

All of the surgical patients developed at least one active shunt and the surgical success rate (patent/attempted) was 47% (as stated in the methods section, 1–4 shunts were made for every eye) (see fig 2). The course of case number 9 was complicated by retinal detachment, so we calculated our clinical success (defined as uneventful postoperative course and developing at least one active, inferiorly placed shunt) as 90% (9/10).

The patients were followed for 6–18 months (mean 10 months). Three patients needed further operations for cataract, vitreous cavity haemorrhage, and retinal detachment (as stated)—cases number 4, 10, and 9, respectively (see table 1). No other significant complications occurred. Collaterals at the shunt site (without leakage) were observed in two of the patients (fig 2).

The visual acuity improvement (month 8 post-event VA minus presentation VA) was 1.5 logMAR units more in the surgical group (p = 0.001; actually control subjects lost 0.57 logMAR and the surgical patients achieved 0.94 logMAR units). The means of logMAR month 8 post-event VA were equivalent to counting fingers at 2 m and 0.5 m for the surgical and control cases, respectively. When presentation VA was compared with the month 8 post-event VA, in a paired fashion for the surgical group, again the improvement in VA (0.94 logMAR units) was significant (p = 0.044). Overall, 80% of the surgical cases showed visual acuity improvement compared with 28% of the controls (p = 0.016). In the surgical group, those with presentation times less than 3 months had 1 logMAR unit more improvement in their vision (p = 0.134).

Seven of the controls (39%) developed neovascularisation compared with none in the surgical group (p = 0.03). Four
cases of neovascular glaucoma, two of disc neovascularisation, and one of iris neovascularisation occurred.

The two groups were not significantly different in the distribution of age, sex, hypertension, diabetes mellitus, and glaucoma (p values were 0.584, 0.433, 1.0, 0.357, and 1.0, respectively). However, mean presentation time for the surgical group was nine weeks later than that of the controls and mean logMAR of presentation VA were 2.5 and 1.5 for surgical and control groups, respectively (p<0.001). Hypercholesterolemia was significantly more common in the surgical groups (60% v 17%, p = 0.035).

In multivariate analysis, surgery was shown to be the sole significant predictor of the visual improvement and the prevention of neovascularisation (table 2).

**DISCUSSION**

The current treatment modalities for retinal vein occlusion, such as laser or surgical induction of chorioretinal anastomosis, administering tissue plasminogen activators, transvitreal cannulation of the retinal vein, transecting the posterior scleral ring, and radial neurotomy, aim at restoring venous flow by bypassing the occlusion. These are in opposition to the classic approach in the management of retinal vein occlusions in which the consequences of the retinal vein occlusion are treated, such as macular oedema and neovascularisation.

Histological studies have shown that the central retinal vein may become permanently narrowed by the thickened walls after an intraluminal thrombus has recanalised and perhaps alternative pathways for venous blood to exit the impeded retinal circulation should be considered. Such pathways may occur naturally in CRVO with the so-called opticociliary anastomosis. It was thought that performing a retinal vein bypass in eyes with an ischaemic vein occlusion was not likely to lead to either reperfusion of the areas of retinal capillary dropout or improved VA. However, it has been hypothesised that if the parafoveal and perifoveal areas remain non-ischaemic in an eye with an otherwise largely ischaemic CRVO, there may be some visual benefit from improved venous outflow and lessened macular oedema. In addition, the iatrogenic shunt induction may reduce the likelihood of the development of neovascularisation.

Our study showed that surgical shunt induction can result in VA improvement (80% of our cases had some improvement). Peyman et al also reported 60% VA improvement in a similar cohort of ischaemic CRVO cases. Additionally, the shunts seemed to prevent the development of neovascularisations in the operated cases. One may argue that the patients in the surgical category presented when the risk of developing neovascularisation had been largely eliminated. In fact the risk of the development of neovascularisation persists for at least eight months after retinal vein occlusion. However, we believe that the argument is relevant but cannot fully explain such a difference in the magnitude of the occurrence of neovascularisation between the two groups and, as stated, occurrence of neovascularisation was best predicted by the study group (table 2).

Central retinal vein occlusion occurs at the level of the lamina cribrosa. The bifurcation of the superior and inferior central retinal veins occurs anterior to the lamina cribrosa; so the entire retina could be drained with a single inferior anastomosis. Although our surgical success (defined as patent/induced shunts) was 47% and less than that of Peyman's report (62.5%), the clinical success (defined as uneventful postoperative course and development of at least one inferiorly placed active shunt) was 90% (Koizumi et al reported a clinical success of 70% for fibrous shunt induction in a group of intermediate CRVO subjects).

It seemed that those who referred to us early in their course had less of a desire for operation (mean presentation time difference of nine weeks for the surgical v control groups; p<0.0004). Conforming to the expected natural course of CRVO in the early post-event months, those who presented late had worse vision. The later the patients presented, the worse their vision (in our study the Pearson coefficient for the presentation time and presentation VA was 0.433, p = 0.021). This might have made these cases more receptive for the surgical choice. As stated, in multivariate analysis, surgery was shown to be the sole significant predictor of the visual improvement (table 2).

In statistical terms, some of the improvements and deteriorations of VA—respectively, in the surgical cases and the controls—could be attributed to the regression-towards-mean phenomenon and this may invalidate the inference of the effect of the surgery. This phenomenon may explain part or all of the observation on the control cases—that is, the VA deterioration. But in the case of VA improvement in surgical cases, studies on the natural course of ischaemic CRVO have shown that only 10% of these cases gain or maintain a VA of 20/400 or better (in our study 60% of the surgical cases achieved a VA of 20/400 or better).

Three (30%) of our patients needed further surgery—for retinal detachment, vitreous cavity haemorrhage, and cataract. Three of the five patients in Peyman's study needed further surgery for retinal detachment, vitreous cavity haemorrhage, and cataract. One of the patients in Koizumi et al's study needed further operation for recurrent fibrous proliferation and vitreous cavity haemorrhage. Hence, the safety profile seems quite acceptable compared with other modalities (see below).

The possibility of selective creation of retinal-choroidal vein anastomosis by high energy laser photocoagulation has been demonstrated, but this is difficult to achieve in patients with significant media opacities, with a reported clinical success rate of 33–54%. A grossly swollen retina may prevent target tissue disruption and there are certain complications such as subretinal and vitreous haemorrhages, ruberosis, neovascular membrane formation, and preretinal and subretinal fibrosis in eyes with intact posterior cortical vitreous; another complication noted was the occlusion of the distal portion of the venous tributary. This can induce ischaemia to a level that makes neovascularisation very likely. McAllister et al reported a complication rate of 29% for neovascular proliferation and vitreous haemorrhage. A grossly swollen retina may prevent target tissue disruption and there are certain complications such as subretinal and vitreous haemorrhages, ruberosis, neovascular membrane formation, and preretinal and subretinal fibrosis in eyes with intact posterior cortical vitreous; another complication noted was the occlusion of the distal portion of the venous tributary. This can induce ischaemia to a level that makes neovascularisation very likely. McAllister et al reported a complication rate of 29% for neovascular proliferation and vitreous haemorrhage. Theoretically, reperfusion of the remaining retinal capillaries resulting from surgical shunt induction and controlled creation of the shunts must lessen the risk of such complications—in our study none of these complications was observed in the follow ups.

Anticoagulants, both parenterally and intravitreally, may ease the passage of blood past the site of obstruction or dissolve the thrombus. Hattenbach et al reported VA improvement in 44% of their ischaemic cases, but as thrombus...
organisation and endothelial cell proliferation seem to occur early, the potential benefit should be limited. Additionally, parental injection could be associated with systemic bleeding complications and even death. On the other hand, intravitreal injection could just be considered in acute management of non-ischaemic CRVO (presentation earlier than seven days). Transvitreal cannulation of retinal veins has been reported in animal models and is currently under investigation.  

Radial optic neurotomy has been studied recently for the management of ischaemic and/or severe CRVO cases. Preliminary data showed that it could result in VA improvement or stabilisation in the majority of cases. Moreover, the procedure has been reported to induce opticullary shunt development. The clinical efficacy of the procedure has to be evaluated in a comparative manner.  

Following the vascular insult in ischaemic CRVO—during the ensuing months—the inner retina undergoes progressive degenerative changes and the architecture of fovea is disrupted. In our study, the patients operated on earlier gained a better final VA. This finding failed to achieve statistical significance (p = 0.134); however, we attributed it to the relatively small sample size of the study. So it could be well advised that surgical intervention—if chosen—be applied at the earliest time before irreversible changes develop in the macula.  

It seems that the very development of shunt, regardless of the method of induction (whether laser induced (Argon or Erbium:YAG) or surgically induced) is associated with VA improvement. It is argued that vitreotomy itself may also contribute to VA improvement and prevention of complications. Some intrinsic metabolic agents seem to be responsible for ischaemia and the development of cystoid macular oedema and, in eyes with vitreous macular attachment, the oedema persists because the metabolic agents remains in contact with macula. Complete posterior vitreous detachment seems to protect against retinal or optic disc neovascularisation.  

Centripetal traction transmitted to the Muller cells by vitreous fibres inserted into the macula in an eye with intact vitreous macula interface is another explanatory mechanism. So, vitrectomy may eliminate the retina access to metabolic agents present in the vitreous as well as the mechanical traction on the macula; this way it might result in better perfusion and prevent retinal and optic disc neovascularisation. In our study, none of the surgical patients developed anterior or posterior segment neovascularisation. Similar to the previous reports, we performed peripheral retinal photocoagulation for our patients. It could be argued that photocoagulation actually prevented neovascularisation. Vitrectomy generally may increase the likelihood of anterior segment neovascularisation because it facilitates the access of angiogenic factors into the anterior chamber (although as stated it may decrease the likelihood of posterior neovascularisation); in order to counteract this untoward effect, mild peripheral retinal photocoagulation was applied. Our total dose of photocoagulation was far less than the dosage applied in the Central Vein Occlusion Study and the study did not recommend prophylactic retinal photocoagulation as it could not eliminate the risk of neovascularisation (despite prophylactic photocoagulation, some 20% developed neovascularisation; although it was less than the 35% occurrence in the control group, the difference was not statistically significant). Although the prevention of neovascularisation may be in part or wholly explained by photocoagulation, this does not seem to explain VA improvement.  

In conclusion, surgically induced chorioretinal venous anastomosis may be considered as a viable therapeutic option for the management of ischaemic CRVOs. Future studies should aim at evaluation of the selective role of vitrectomy, posterior vitreous detachment induction, photocoagulation, and the shunt formation itself. Because of the non-randomised nature of the study and small size of the sample, stricter designs such as randomised controlled trials are needed to control the effects of potential confounders to better estimate the true clinical efficacy and safety. Furthermore, the role of this modality should be placed in the context of other emerging approaches in the management of retinal vein occlusion, such as radial optic neurotomy, which has shown preliminary success.  

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Ischaemic CRVO and chorioretinal anastomosis


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