Predictors for choroidal neovascular membrane formation and visual outcome following blunt ocular trauma

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Abstract

Aim: The aim of this study was to determine the predictors for choroidal neovascular membrane formation and visual outcome after blunt ocular trauma.

Methods: Retrospective review of electronic medical records of patients with blunt ocular trauma from January 2013 to December 2016 at Narayana Nethralaya Super Speciality Eye Hospital (Bangalore, India) was done. Cases with positive macular findings were enrolled. Data such as age, sex, laterality, mode of injury, presenting and final vision, follow-up duration and retinal findings were noted.

Results: A total of 853 cases were referred to the retina clinic with history of blunt ocular trauma. Of which, 37 cases with positive macular findings were identified. Trauma with ball (18/37, 49%) was the most common mode of injury. Choroidal rupture was seen in 33 (89%) eyes. Other retinal findings noted were as follows: retinal haemorrhages (11%), commotio retinae (22%), submacular haemorrhage (43%), macular hole (11%), epiretinal membrane (3%), macular scar (8%) and vitreous haemorrhage (4%). Choroidal neovascular membrane was noted in 6 (16%) out of 37 eyes. No retinal findings showed any positive association with choroidal neovascular membrane formation. Using Pearson’s correlation test, independent variables such as presenting visual acuity ($r = 0.601$, $p = 0.000$) and choroidal neovascular membrane formation ($r = -0.356$, $p = 0.031$) showed a strong correlation with final visual acuity.

Conclusion: The occurrence rate of post-traumatic choroidal neovascular membranes is about 12% in eyes with choroidal rupture. Most choroidal neovascular membranes occur within 1 year of trauma. Eyes with poor presenting vision and choroidal rupture or subretinal haemorrhage warrant regular and shorter follow-up intervals for long periods to identify the choroidal neovascular membrane. Treatment with intravitreal anti-vascular endothelial growth factor therapy is useful.

Keywords: choroidal neovascular membrane, choroidal rupture, ocular trauma, visual outcome
detachment. The scarring and atrophy that follow may cause irreversible visual morbidity. One of the common risk factors identified for the development of CNV following ocular trauma is choroidal rupture (CR).\textsuperscript{1} Approximately 5–10% of eyes with CR develop CNV that may cause delayed visual loss.\textsuperscript{2–4} As of date, the largest series of 111 eyes with traumatic CR was published by Ament and colleagues.\textsuperscript{5} In 111 eyes of patients having blunt ocular trauma and CR, they found the rupture location and poor presenting visual acuity (VA) were independently associated with visual outcome. Of the 12 patients diagnosed with CNV, 5 were not treated, 4 were treated with argon laser photocoagulation, 1 was treated with surgery, 1 was treated with argon laser photocoagulation followed by surgery and 1 was treated with verteporfin photodynamic therapy (PDT). Secretan and colleagues\textsuperscript{6} reviewed 79 eyes of 79 patients diagnosed with indirect CR at one tertiary referral centre. Of which, 16 (20%) eyes developed CNV. Secretan and colleagues\textsuperscript{6} observed that ruptures located closer to fovea were significantly more likely to develop neovascularisation than ruptures located peripherally (1500 μm from the foveal avascular zone). Also, longer ruptures (4000 μm), independent of location, predisposed to the development of neovascularisation. The rupture width was not found to be significant. Initial VA found no relation with final visual outcome. In 82% of the patients, neovascular lesions developed during the first year. Based on the findings, it was recommended that extrafoveal membranes be treated with photocoagulation and that subfoveal membranes be observed. Secretan and colleagues\textsuperscript{6} stated that patients with subfoveal neovascular membranes had an average final VA of 0.18 (20/111). They quoted two published series\textsuperscript{3,7} in which lesions regressed spontaneously. Previous published literature regarding the treatment of post-traumatic CNV had taught that they could be observed because of a higher likelihood to regress spontaneously. Of 17 untreated cases reported in 7 case series,\textsuperscript{2,3,8–12} only 5 patients (29%) recovered VA to better than 20/50.

The last big series of CNV in ocular trauma was published more than a decade ago. Treatment of CNV following ocular trauma has evolved in the last few years with few reports of treatment for post-traumatic CNVs with intravitreal anti-vascular endothelial growth factor (VEGF) therapy being published.\textsuperscript{13,14} The purpose of our study was to evaluate the possible risk factors for post-traumatic CNV development, to look at the treatment outcomes and also to describe the potential predictors for final visual outcome independent of CNV formation.

**Methods**

After obtaining the permission from the Institutional Review Board (IRB) of the Narayana Nethralaya Super Speciality Eye Hospital (Bangalore, India; ECR/187/Inst/Kar/2013/RR-16), patients diagnosed with blunt ocular trauma were identified using a computerised diagnosis code search. Only patients with positive retinal findings at the macula were included in the study. These patients presented to the retina clinic between January 2013 and December 2016. Blunt ocular injuries were classified as external, anterior segment or posterior segment based on the classification devised by Pieramici and colleagues.\textsuperscript{15} Intraocular foreign body cases were excluded from the study. The location of the CNV or CR was classified into four groups: (1) extrafoveal – located >200μm from the centre of the fovea; (2) juxtafoveal – located 1–199 μm from the centre of the fovea; (3) subfoveal – located underneath the fovea; and (4) peripapillary – surrounding the optic nerve head.

A total of 853 patients of blunt ocular trauma were evaluated during the study period; 37 eyes of 37 patients with positive macular findings were identified and further analysed. Medical records and fundus photographs, and fluorescein angiography and optical coherence tomography (OCT) in select cases were reviewed. The following data were extracted from each case record: (1) age, (2) sex, (3) mode of injury, (4) presenting and final visual acuities, (5) presence and location of CR and (6) presence of other retinal findings such as intraretinal haemorrhage, commotio retinae, subretinal bleed, epiretinal membrane, macular hole, scar, CNV formation, vitreous haemorrhage and optic disc pallor. CRs were classified into type 1 or 2 as described by Nair and colleagues.\textsuperscript{16}

Since CNV was a rare outcome (N=6), multivariate analysis was judged to be inappropriate. Instead chi-square test was used to identify factors that may be associated with CNV formation. Pearson’s correlation test was used to identify factors showing significant correlation with final VA. A $p$-value less than 0.05 was considered to be statistically significant.
Results
In this retrospective study, 853 eyes with prior history of blunt ocular trauma were identified during the study period. Of which, 37 eyes of 37 patients with positive macular findings were further evaluated. CR and subretinal haemorrhage (SRH) were seen in 33 and 16 eyes, respectively. Other retinal findings noted at the macula were commotio retinae in eight eyes, CNV in six eyes, intraretinal haemorrhage and macular hole in four eyes each, and epiretinal membrane and optic disc pallor in 1 eye each. The segregation of eyes with blunt ocular trauma and retinal findings is depicted in Figure 1. Demographic, VA and incidence of different retinal findings of these cases are mentioned in Table 1. Table 2 depicts the differences in eyes with and without traumatic CNV. Eyes with CNV had a poorer presenting VA compared with eyes with no CNV. None of the retinal findings showed any association with CNV development. CR was noted in four eyes with traumatic CNV. Pearson’s correlation test was used to study the correlation of final VA in eyes with CNV following blunt ocular trauma with individual retinal findings. It was noted that independent variables such as presenting VA ($r=0.601$, $p=0.000$) and presence of CNV ($r=-0.356$, $p=0.031$) showed a strong and statistically significant correlation with the final visual outcome (Table 3). Description of individual cases with traumatic CNV is given in Table 4, and Figure 2 shows the case of post-traumatic CNV in a 23-year-old boy (Case 2).

Discussion
Our study was designed to identify the prevalence, clinical profile and risk factors which could lead to CNV formation in patients with blunt ocular trauma. In addition, we aimed to look at the risk factors which would predict the final visual outcome in such patients.

In our study, CR was the most common retinal macular finding noted occurring in 33 of the 37 eyes in patients with blunt ocular trauma. CRs were commonly seen at location <200 µm from the centre of the fovea (22, 66%) in comparison with ≥200 µm from the centre of the fovea (4, 12%). Eleven (33%) of the CRs were peripapillary in location. CNV formation was noted in 4 of the 33 (12%) eyes with CR. The CRs in these eyes were juxta- or subfoveal in location. On OCT, 11 (33%) eyes had type 1 CRs and 7 (21%) eyes had type 2 rupture. In 15 (45%) eyes, the scans were not passing through the area of CR.
### Table 1. Clinical findings of patients with blunt ocular trauma.

| Variable               | No. of eyes (%) |
|------------------------|-----------------|
| Age in years (mean)    | 24.05 (6–49)    |
| Sex                    |                 |
| Male                   | 33 (89)         |
| Female                 | 4 (11)          |
| Laterality             |                 |
| Right eye              | 24 (65)         |
| Left eye               | 13 (35)         |
| Mode of injury         |                 |
| Ball                   | 18 (49)         |
| Stick                  | 7 (19)          |
| Nail                   | 2 (5)           |
| Shuttle cock           | 1 (3)           |
| Rope                   | 3 (8)           |
| Fist                   | 1 (3)           |
| Hair dryer             | 1 (3)           |
| Table hit              | 2 (5)           |
| Plastic bottle         | 1 (3)           |
| Stone                  | 1 (3)           |
| Type of injury         |                 |
| Open globe injury      | 3 (8)           |
| Closed globe injury    | 34 (92)         |
| Presenting VA Logmar – median (range) | 2.0 (0.0–3.0) |

### Table 1. (Continued)

| Variable                                   | No. of eyes (%) |
|--------------------------------------------|-----------------|
| Choroidal neovascular membrane            | 6 (16)          |
| Optic disc pallor                         | 1 (3)           |
| Location of CR                            |                 |
| Extrafoveal                                | 4               |
| Juxtafoveal                                | 10              |
| Subfoveal                                  | 11              |
| Peripapillary                              | 11              |

| Location of CNV                           |                 |
| Extrafoveal                                | 1               |
| Juxtafoveal                                | 2               |
| Subfoveal                                  | 3               |
| Peripapillary                              | 0               |

| Final VA Logmar – median (range)           | 1.0 (0.0–3.0)   |
| Follow-up duration in days – mean (range)  | 60 [2–1095]     |

CNVs were noted in three eyes and one eye with type 1 and 2 CR, respectively. Traumatic CR can be a devastating ocular injury. Risk factors for the development of CNV after CR are debated. The largest series published to date is by Ament and colleagues (111 eyes) and Secretan and colleagues (79 eyes); other published reports are smaller case series. Both the groups concluded that ruptures which were closer to the fovea have a higher likelihood for CNV development compared with eyes with ruptures away from the fovea. Our results support a similar finding where CNV formation occur more commonly in eyes with CRs <200 µm from the centre of the fovea. Secretan and colleagues also found a shorter median rupture length in eyes that did not develop CNV (median rupture length = 3054 µm) as compared with those that did (median rupture length = 4504 µm) (P < .03). In our study, we did not find CNV formation to be associated with the presence of CR (Pearson’s chi-square value = 3.768, P = 0.052). However, the likelihood of
### Table 2. Risk factors for CNV development.

| Variable                           | Eyes without CNV (N) | Eyes with CNV (N) | \( p \)-value using chi-square test |
|------------------------------------|----------------------|-------------------|-------------------------------------|
| Age (mean)                         | 24.67 ± 9.66         | 20.83 ± 9.47      | 0.481                               |
| Presenting VA                      | 1.81 ± 1.07          | 0.73 ± 0.28       | 0.035                               |
| CR                                 | 29                   | 4                 | 0.052                               |
| Commotio retinae                   | 7                    | 1                 | 1.000                               |
| Intraretinal haemorrhage           | 4                    | 0                 | 1.000                               |
| Subretinal haemorrhage             | 15                   | 1                 | 0.206                               |
| Macular hole                       | 3                    | 1                 | 0.524                               |
| Scar                               | 3                    | 0                 | 1.000                               |
| Epiretinal membrane                | 1                    | 0                 | 1.000                               |
| Optic disc pallor                  | 1                    | 0                 | 1.000                               |
| Follow-up duration in days (mean)  | 173.58               | 515.00            | 0.009                               |

CNV, choroidal neovascular membrane; CR, choroidal rupture; VA, visual acuity.

### Table 3. Correlation of independent risk factors with visual outcome using Pearson’s correlation test.

| Variable                           | Pearson’s factor | \( p \)-value (two-tailed) |
|------------------------------------|------------------|---------------------------|
| Age                                | -0.135           | 0.424                     |
| Sex                                | 0.222            | 0.187                     |
| Laterality                         | -0.022           | 0.895                     |
| Presenting VA                      | 0.601            | 0.000                     |
| Mode of injury                     | 0.173            | 0.306                     |
| CR                                 | -0.042           | 0.805                     |
| Commotio retinae                   | -0.254           | 0.130                     |
| Intraretinal haemorrhage           | 0.092            | 0.588                     |
| Subretinal haemorrhage             | 0.287            | 0.085                     |
| Macular hole                       | -0.098           | 0.563                     |
| Scar                               | 0.192            | 0.254                     |
| Epiretinal membrane                | -0.071           | 0.616                     |
| CNV                                | -0.356           | 0.031                     |
| Optic disc pallor                  | -0.071           | 0.616                     |
| CR location                        | -0.003           | 0.987                     |
| Duration of follow-up              | -0.336           | 0.042                     |

CNV, choroidal neovascular membrane; CR, choroidal rupture; VA, visual acuity.
developing CNV was nearly three times more in eyes with CRs compared with eyes without CR (likelihood ratio = 2.878). We did not do morphometric analysis of the CRs in our study. The remaining two eyes with CNV were noted in eyes following ocular trauma having associated ocular morbidities such as myopia and chorioretinal scar, respectively.

Traumatic CNVs commonly occur in the central retina. The physiologic basis of the increased susceptibility of the central retina for traumatic CNV compared with the peripheral retina is a subject of research. There are many factors that might explain the physiologic basis of this observation. Angiogenesis is thought to be a result of an imbalance between the proangiogenic and antiangiogenic cytokines that are secreted in response to cellular injury. Other significant differences between the central and peripheral retina are hydrostatic and oncotic pressure gradients, blood flow, and retinal pigment epithelial and neural architecture which may contribute to the proangiogenic features of the macula. In eyes with CRs, retinal breaks and retinal detachment are commonly noted with peripheral CRs compared with macular ruptures. This may explain the overall poor visual outcome following ocular trauma.

Subretinal haemorrhage (16/37) was the second most common retinal macular finding noted in patients with ocular trauma. All eyes with SRH had associated CR. However, CNV was identified in only one eye with SRH. It is possible that the presence of CNV was masked by the overlying SRH. Therefore, it is important to wait for resolution of SRH to identify the underlying CNV or CR. One case with SRH underwent pneumatic displacement with 0.3cc of 100% SF6 (sulphur hexafluoride) following which underlying CNV was noted. Other positive retinal findings noted in the study were presence of commotio retinae (8, 22%), intraretinal haemorrhages (4, 11%), macular hole (4, 11%), epiretinal membrane (1, 3%), scar (3, 8%), and optic disc pallor (1, 3%). None of these retinal findings showed any causative association with CNV formation.

In our study, we found eyes with traumatic CNV formation had a poorer presenting VA ($p=0.035$) and longer follow-up ($p=0.009$). The poor presenting VA in our cases of CNV was mainly due to the sub- or juxtafoveal location of the CR. Most CNV formation occurs in less than 1 year following ocular trauma (mean = 230 days). The

| Table 4. Cases with CNV. |
|-------------------------|
| No. | Age/sex | Eye | Presenting VA | CR location | Associated ocular morbidity | Treatment of CNV | No. of injections | Time to CNV | Location of CNV | Final VA | Location of CNV | Treatment of CNV | No. of injections | Time to CNV | Location of CNV | Final VA |
|----|---------|-----|---------------|-------------|----------------------------|----------------|----------------|-------------|-------------|----------|---------------|----------------|----------------|-------------|-------------|----------|
| 1 | 20/M    | RE  | 6/60          | FTMH        | Y                          | SF IVB          | 1              | 120         | SF          | 6/18     | FTMH         | SF IVB         | 1              | 120         | SF          | 6/18     |
| 2 | 23/M    | RE  | 6/36          | Commotio retinae, | Y              | SF IVB          | 3              | 365         | JF          | 6/18     | JF           | IVB            | 1              | 365         | JF          | 6/18     |
| 3 | 16/M    | RE  | 6/12          | Scar        | N                          | SF EF          | 1              | 540         | JF          | 90       | EF           | SF IVB         | 1              | 540         | JF          | 90       |
| 4 | 34/F    | LE  | 6/60          | Myopia      | N                          | SF IVB          | 3              | 90          | SF          | 6/18     | SF IVB       | SF EF          | 3              | 90          | SF          | 6/18     |
| 5 | 26/F    | RE  | 6/36          | Optic disc pallor | Y                       | JF IVB          | 1              | 90          | EF          | 6/18     | EF           | SF EF          | 1              | 90          | EF          | 6/18     |
| 6 | 6/M     | RE  | 6/60          | None        | Y                          | JF IVB          | 2              | 180         | JF          | 6/6      | JF           | SF IVB         | 2              | 180         | JF          | 6/6      |

CNV, choroidal neovascular membrane; CR, choroidal rupture; EF, extrafoveal; FTMH, full-thickness macular hole; IVB, intravitreal bevacizumab; JF, juxtafoveal; LE, left eye; RE, right eye; SF, subfoveal; SRH, subretinal haemorrhage; VA, visual acuity.
average follow-up duration in eyes without CNV formation was 173 days compared with eyes with CNV formation which was 515 days. Thus, we recommend regular and shorter follow-up intervals at least for a minimum 1 year period following trauma to identify the CNV early.

Choroidal neovascular membranes may be treated with observation, pharmacotherapy, surgery, photocoagulation or PDT. According to our analysis of published pooled case series, the natural history of untreated CNV is poor. In a study by Ament and colleagues, none of the 5 untreated eyes regained VA of better than 20/100. No patients in our series underwent treatment with laser photocoagulation, PDT or submacular surgery. We treated all our cases with intravitreal anti-VEGF (bevacizumab) therapy. The mean number of intravitreal injections required was 1.5 (range = 1–3). Five of the six eyes with CNV regained >2-line vision following anti-VEGF therapy. One eye with no improvement in VA following treatment had optic disc pallor (case 5).

Guidelines for treatment with photocoagulation are extrapolated from the Macular Photocoagulation Study Group data. Extrafoveal lesions that fit the Macular Photocoagulation Study Group criteria should be treated with laser photocoagulation. However, the majority of post-traumatic membranes were subfoveal, making laser photocoagulation a less attractive treatment option. Other treatment modalities which could be considered for subfoveal CNVs are use of submacular surgery or PDT. Guidelines for treatment with submacular surgery may be extrapolated from the studies published by Bressler and Hawkins and colleagues. However, their results were not very encouraging. PDT is an accepted form of treatment for subfoveal CNV other than age-related macular degeneration. Mennel and colleagues reported a case of post-traumatic CNV successfully treated with PDT and indocyanine green feeder vessel laser photocoagulation. In our series, none of the eyes were treated with PDT or submacular surgery.

Our study had the advantage of being one of the largest series of ocular blunt trauma cases being evaluated for macular retinal findings and CNV formation. Though there were a few anecdotal case reports describing the utility of intravitreal anti-VEGF injections for traumatic CNVs, this study was the largest case series in the current

Figure 2. Case 2 with post-traumatic CNV: 23-year-old boy with history of right eye ocular trauma with cricket ball. (a) Colour fundus photo of the right eye (RE). (b–d) RE fluorescein angiography showing focal area of hyperfluoroscence increasing in size and intensity in the progressive phases of the angiogram suggestive of classic subfoveal choroidal neovascular membrane. Choroidal rupture with overlying retinal pigment epithelial damage is noted inferior to the fovea. (e) Optical coherence tomography (OCT) image of the RE at presentation showing a subfoveal choroidal rupture (yellow star). Subretinal haemorrhage is noted inferior to the macula just within the inferior arcade. (f) One-year post presentation, RE-OCT image showing a type II subfoveal choroidal neovascular membrane (red arrow) with presence of overlying intraretinal cystic spaces (blue arrow). (g) After three intravitreal injections with bevacizumab, RE-OCT image showing scarring of the choroidal neovascular complex with resolution of the intraretinal fluid. Written informed consent was obtained from the patient to utilise the images in the article.
decade describing the treatment outcomes with intravitreal anti-VEGF therapy. However, this study also had a few limitations. Ours was a retrospective study; therefore, complete records and relevant photographs were not available for all of the patients at all visits. We included all cases with ocular trauma with no minimum follow-up duration. The study was underpowered to identify risk factors for CNV and retinal detachment using regression analysis. Morphometric analysis of CR was not performed in our study.

To conclude, the prevalence of CNVs following ocular trauma in eyes with positive macular findings is 16% and about 12% in eyes with CR. Eyes with poor presenting VA and presence of macular CR or SRH are at a high risk of CNV development. Most post-traumatic CNVs occur within 1 year of the injury. Hence, regular follow-up at shorter intervals for longer durations is necessary to identify post-traumatic CNVs early. Pharmacotherapy with intravitreal anti-VEGF therapy seems to be an effective treatment option for post-traumatic CNVs.

Author contributions
RV was responsible for drafting and analysing the scientific content of the manuscript. NKY was responsible for reviewing the manuscript. BB was responsible for data acquisition. The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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