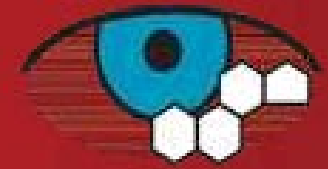


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Optic Disk Haemorrhages: a Clinical Model for Testing Neuroprotective Agents. Effects of Intramuscular Cytidine-5' diphosphocholine

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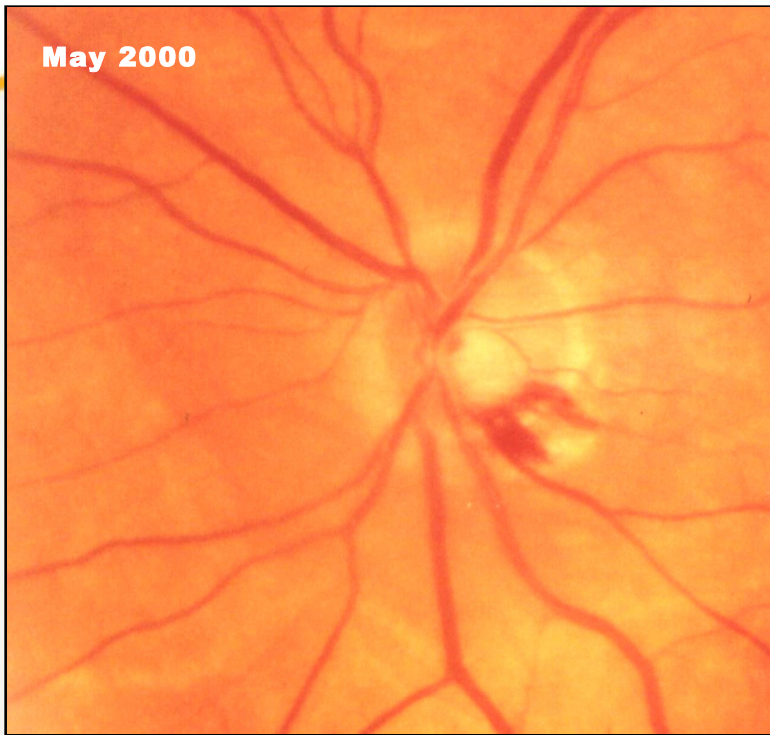
BACKGROUND

Optic disk haemorrhages (DH) are a negative prognostic sign in glaucoma and are considered a risk factor for optic neuropathy progression (*Rasker, Arch Ophthalmol 1997; Shihab, Ophthalmology 1982*)

Ocular hypotensive therapy does not reduce progression after DH (*Bengtsson, 2008*).

The onset or progression of VF defects is not immediate, as mean time to observe it is approximately 1.5 years (*Siegner et al. Ophthalmology 1996*)

May 2000



**Splinter haemorrhages
are a signal of
progressive optic
neuropathy**

Heidelberg Retina Tomograph II
Follow-Up Report

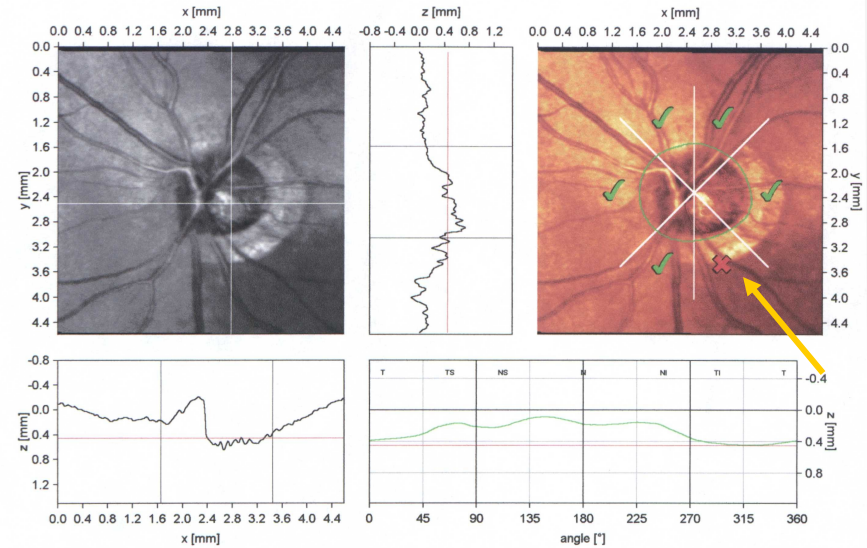
Patient: [REDACTED]

Sex: female DOB: 5/feb/1926 Pat-ID: ---

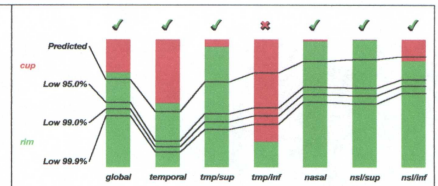
Examination: Baseline: 9/nov/2001 FollowUp: 9/nov/2001 Time elapsed: 0 months

OS

Scan: Focus: -4.00 dpt Depth: 3.00 mm Operator: ---



| Stereometric Analysis ONH | Change |
|---------------------------|------------------------------|
| Disk Area | 2.254 0.000 mm ² |
| Cup Area | 0.576 0.110 mm ² |
| Rim Area | 1.678 -0.111 mm ² |
| Cup Volume | 0.063 0.013 cmm |
| Rim Volume | 0.527 0.016 cmm |
| Cup/Disk Area Ratio | 0.256 0.049 |
| Linear Cup/Disk Ratio | 0.505 0.051 |
| Mean Cup Depth | 0.158 0.016 mm |
| Maximum Cup Depth | 0.412 -0.008 mm |
| Cup Shape Measure | -0.101 0.016 |
| Height Variation Contour | 0.358 0.008 mm |
| Mean RNFL Thickness | 0.188 0.006 mm |
| RNFL Cross Sectional Area | 1.002 0.034 mm ² |
| Reference Height | 0.454 -0.016 mm |
| Topography Std Dev. | 21 μm |



Comments:

Date: 9/nov/2001 Signature:

Classification: Outside normal limits (*)

(*) Moorfields regression classification (Ophthalmology 1986;105:1557-1563).
Classification based on statistics. Diagnosis is physician's responsibility.

PATHOGENESIS

The pathogenetic mechanism of neuropathy following DH is not clear.

Among pathogenetic ipothesis, there is the ***apoptosis activation due to phopsholipid synthesis depression***, typical event in course of ischemic diseases and/or disturbances to axoplasmic flow that might be ***induced by microfibrotic lesion (microscar)*** produced by DH, with a mechanism similar to that occurring after cerebral infarction.

The latency and the great likelihood to observe progression offer the opportunity to interfere pharmacologically with this process.

Therefore, DH might represent a good model for testing clinically neuroprotectants

PURPOSE

Since patients presenting DH are at high risk to develop visual field (VF) defects in a short/medium period, the purpose of this study was to investigate on the clinical efficacy of CDP-choline (citicoline) as a neuroprotective agent in glaucoma, evaluating whether it is capable to prevent VF from the deterioration that typically follows the occurrence of a DH.

METHODS

EXPERIMENTAL DESIGN:

Retrospective case-control study

INCLUSION CRITERIA

- Patients suffering from primary open angle glaucoma (POAG) who presented at least one DH during their clinical history
- IOP pharmacologically normalized (never >19 mmHg)
- At least 6-month follow-up
- Complete clinical documentation including ophthalmoscopy, VF test, laser polarimetry (GDx) and tonometry.

METHODS

Clinical documentation was considered complete when were available for the analysis:

- accurate description and localisation of DH
- accurate medical history, including detailed description of concomitant treatments
- accurate description of ophthalmoscopy during time performed at least every 6 months
- minimum of 3 Humphrey (30-2) VF test during observation time

(Patients with incomplete polarimetry (GDx) documentation were included in the study)

EXCLUSION CRITERIA

- IOP > 20mmHg
- therapy with miotics
- concomitant treatment with any neuroprotective substance, apart from CDP-choline
- patients who modified previous systemic treatment (antiaggregant, hypotensive, cardiovascular) throughout the observation period
- secondary glaucoma
- narrow angle
- cataract (any opacity superior to N2-Ctr-P0 according to LOCS II)
- corneal opacifications
- non glaucomatous neuropathies and/or optic disk malformations
- myopia (>5 diopters)
- hyperopia (> 3.5 diopters)
- astigmatisms (> 2.5 diopters)
- age related macular degeneration
- diabetes

METHODS

The patients recruited (n=32) were divided into two groups:

- TREATED: patient (n=10) who received i.m. CDP-choline (1 g daily per 15 days every 3-4 months)
- CONTROLS: patients (n=22) who never received any neuroprotectants

PRIMARY OUTCOME: frequency of progressors (*)

SECONDARY OUTCOMES: changes in MD, PSD, retinal nerve fiber layer thickness, and “the number” (GDx).

(*) Definition of “progressor”: Patient presenting a sensitivity loss ≥ 5 dB in at least 2 adjacent points in the visual field area corresponding to the DH quadrant

EXAMPLE OF A CLINICAL CASE

Initials: AP
 Age: 66
 Gender: male

Group: controls
 Diagnosis: POAG
 DH localisation: IT quadrant (LE)

| | | | | | |
|----|----|----|----|----|----|
| -7 | -4 | 1 | | | |
| -1 | -2 | -5 | 1 | | |
| 0 | -5 | -3 | -2 | -2 | |
| -3 | -1 | -3 | -1 | -3 | -2 |
| -3 | -1 | -1 | -1 | -2 | -3 |
| -3 | 1 | -2 | -5 | 0 | -3 |

Before DH

| | | | | | |
|----|----|----|----|----|----|
| -4 | 3 | 1 | | | |
| -8 | -5 | 1 | -2 | | |
| -1 | -1 | -1 | -2 | 1 | |
| -1 | -1 | -3 | -4 | -6 | -2 |
| 1 | -1 | -1 | -1 | -2 | 0 |
| -1 | -1 | -3 | 0 | -4 | -4 |

After 8 months

| | | | | | |
|----|----|----|----|----|----|
| 0 | -3 | -3 | | | |
| -3 | 0 | -7 | -3 | | |
| -5 | -3 | -3 | -4 | -2 | |
| -2 | 0 | -5 | -6 | -8 | -4 |
| 0 | -3 | -2 | -3 | -7 | -4 |
| -1 | 0 | -1 | -1 | -2 | 0 |

After 13 months

| | | | | | |
|---|----|----|----|-----|-----|
| 1 | -1 | -1 | | | |
| 4 | -2 | -4 | -9 | | |
| 5 | -3 | -1 | -6 | -3 | |
| 5 | 0 | -2 | -5 | -10 | -11 |
| 3 | 3 | 0 | -6 | -3 | -4 |
| 0 | -2 | 0 | 0 | -1 | 2 |

After 18 months

STATISTICS

Inferential statistics:

- Contingency tables with chi-square test and survival analysis were applied to evaluate the frequency of progressors.
- ANOVA was used to test parametric data.

Power of the study $(1-\beta) = 0.8$

Able to detect as significant ($P < 0.05$) a reduction $\geq 50\%$ in frequency of progressors

DEMOGRAPHICS

| | TREATED | CONTROLS | P |
|----------------------|----------------------------|----------------------------|------|
| n. | 10 | 22 | - |
| Age (years) | 75 (sd 9.2) | 68 (sd 10.9) | 0.1 |
| Gender (M/F) | 5/5 | 7/15 | 0.4 |
| IOP (mmHg) | 16.5 (sd 3.3) | 15.7 (sd 2.9) | 0.49 |
| MD (dB) | -2.28 (sd 3.60) | -3.36 (sd 3.62) | 0.43 |
| GDX (the n°) | 23 (sd 21) | 34 (sd 22) | 0.19 |
| NFL thickness (µm) | 61.5 (sd 7.2) | 66.9 (sd 88) | 0.1 |
| Recurrent DH | 5 (50%) | 9 (41%) | 0.7 |
| Bilateral DH | 2 (20%) | 5 (23%) | 0.8 |
| Diagnosis (POAG/NTG) | 8/2 | 19/3 | 0.63 |
| Follow-up (months) | 14 (sd 6.7) range: 6-24 | 18 (sd 7.1) range: 6-24 | 0.14 |

RESULTS: Frequency of progressors

| | PROGRESSORS | | NON-PROGRESSORS | |
|----------|----------------------------|--------------------------------|---------------------------|--------------------------------|
| CONTROLS | 77% (17/22) (*) | | 23% (5/22) (*) | |
| | recurrent DH 100% (9/9) | w/o recurrent DH 62% (8/13) | recurrent DH 0% (0/9) | w/o recurrent DH 38% (5/13) |
| TREATED | 30% (3/10) (*) | | 70% (7/10) (*) | |
| | recurrent DH 60% (3/5) | w/o recurrent DH 0% (0/5) | recurrent DH 40% (2/5) | w/o recurrent DH 100% (5/5) |

$$\chi^2 = 13.7 \quad P = 0.004$$

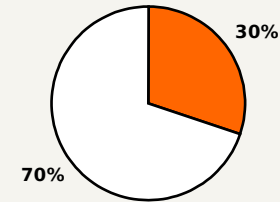
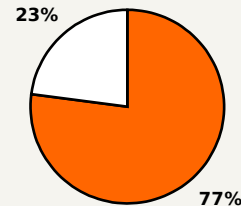
$$(*) \chi^2 = 4.7 \quad P = 0.03$$

RESULTS: Frequency of progressors

CONTROLS

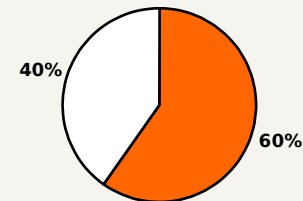
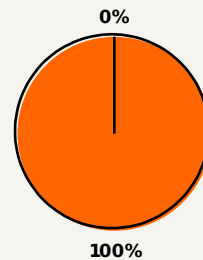
TREATED

all patients



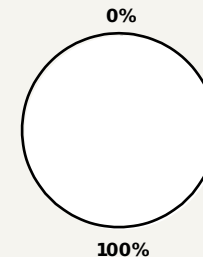
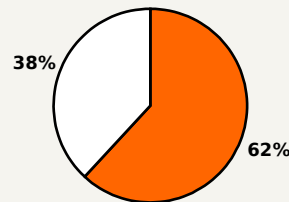
$P=0.030$

recurrent DH



$P=0.11$

w/o recurrent DH

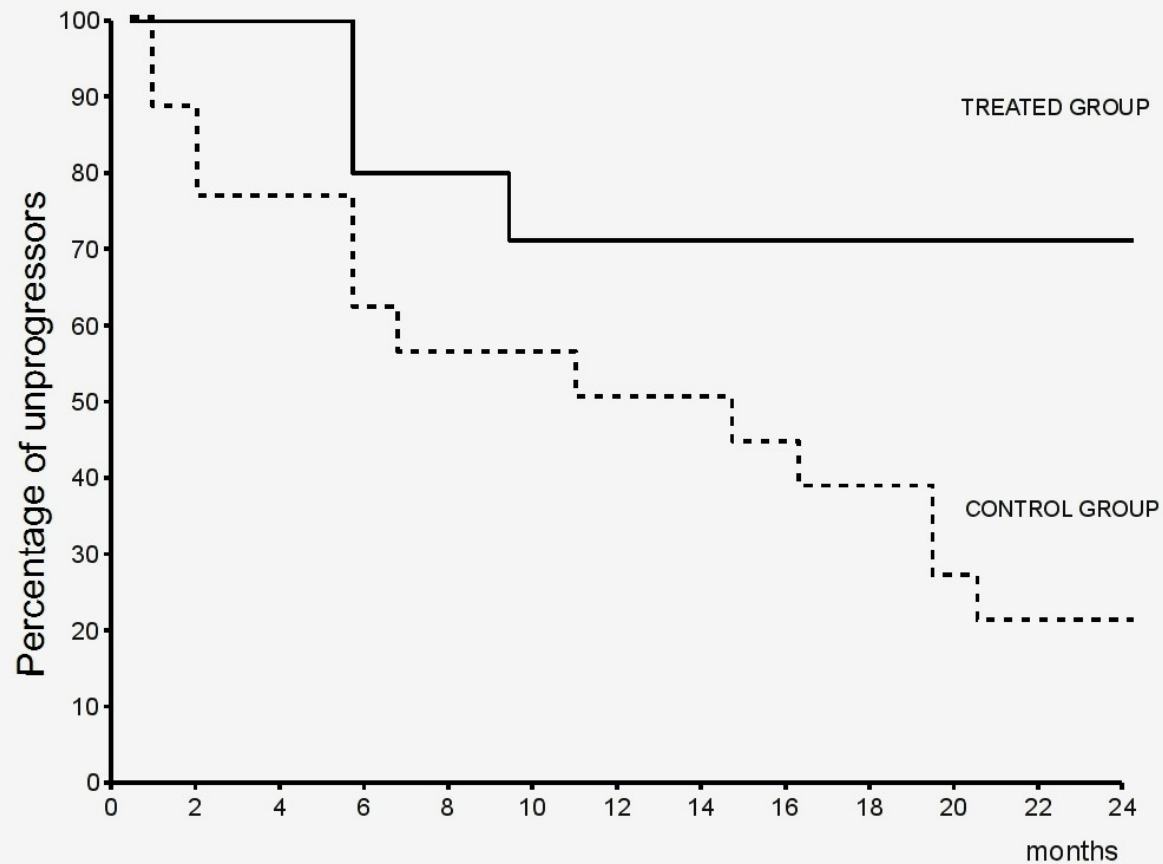


$P=0.036$

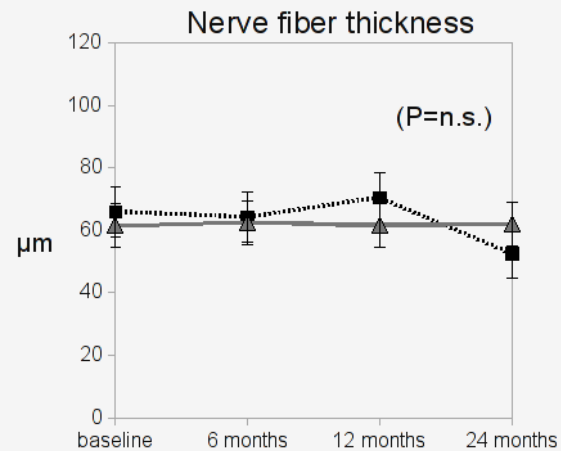
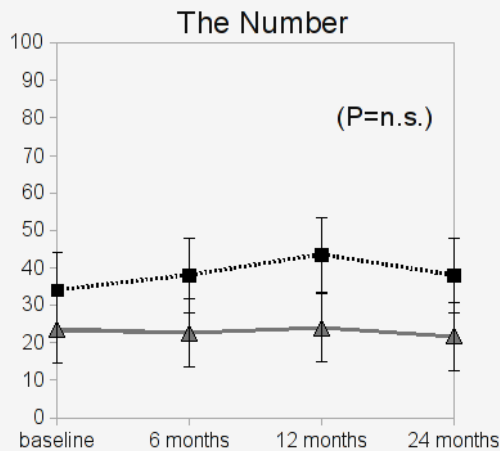
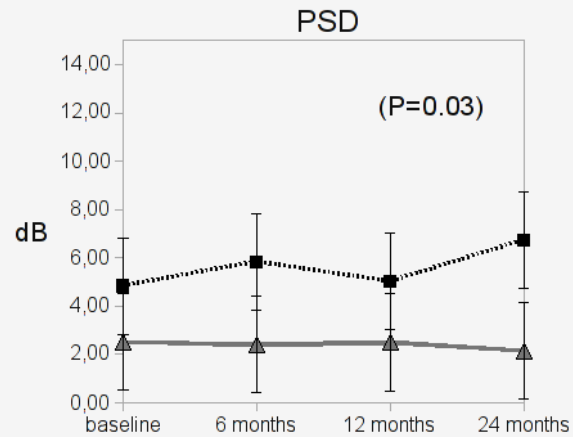
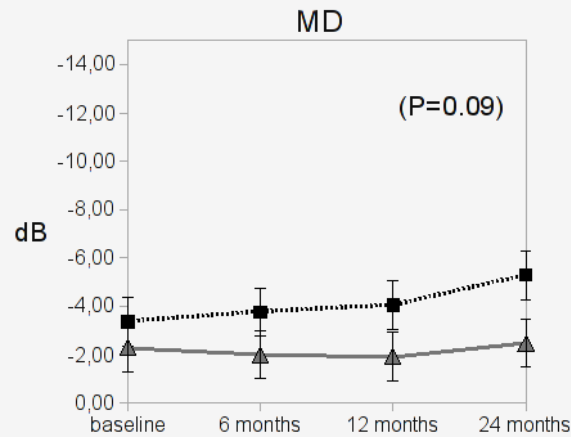
■ = progressors
□ = non-progressors

RESULTS: Kaplan-Meier curve

Log rank test $P=0.08$



RESULTS: secondary outcomes



■ controls
▲ treated

CONCLUSIONS

- As VF defects follow DH in a very high percentage of subjects (77%), DH may represent a good clinical model for testing efficacy of neuroprotective agents in glaucoma
- The present study represents an additional support to the clinical benefits of citicoline when administered as a complement to ocular hypotensive agents.
- It also showed that pulses of treatment protect a significantly high percentage of glaucomatous patients from optic neuropathy progression consequent to DH.

CONCLUSIONS: mode of action

Among putative neuroprotectants, citicoline is, perhaps, the drug with the widest scientific documentation.

Massive degradation of phospholipids following various insults is detrimental to the cells.

Phosphatidylcholine catabolism is enhanced by ischemia and/or traumas. That is attributed mainly to the activation of phospholipase-A2 ([Farooqui, 1997](#)). Accumulation of arachidonic acid and other free fatty acids, inner mitochondrial membrane dysfunction, release of proapoptotic factors like ceramide, and calcium overload are possible mechanisms that lead to cell death ([Kristan, 1998](#)). Similar events can occur in retinal ganglion cells in course of glaucoma ([Tatton, 2001](#)). Inhibition of phosphatidylcholine breakdown and/or stimulation of its synthesis may spare cells from apoptosis (Bladergroen, 1999).

Citicoline stimulates the formation of phosphatidylcholine in brain ([Lopez Coviella, 1995](#); [Wang, 2000](#)), **inhibits activation of phospholipase A2** and ([Rao, 2001](#)) and **prevents accumulation of free fatty acids**. Citicoline **also attenuates glutamate excitotoxicity in vitro** ([Mir, 2003](#))

Moreover, citicoline is also known to increase the levels of acetylcholine, norepinephrine, dopamine and serotonin in some brain areas. In particular, the dopamine stimulating effect, whose mechanism remains unclear, seems responsible for the beneficial neurological responses observed in patients with Parkinson's disease ([Agnoli, 1982](#); [Eberhardt, 1990](#)) and for the improvement in visual acuity observed in amblyopic patients ([Fresina, 2008](#)).

Hence, ***citicoline seems to protect retinal ganglion cells from degeneration and might represent a valuable option for attempting a neuroprotective therapy in glaucoma.***