Exudative Diabetic Maculopathy Treated By Frequancy Doubled Nd: Yag Laser (532nm)

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Summary:

Background: *Diabetic maculopathy means involvement of the macula by edema and exudates or ischemia which is the most common cause of visual impairment in diabetic patients, particularly those with type 2diabetes.*
Objective: *The literatures are rich in publications of these regards, nevertheless the works in general were not systematic, not enough details regarding procedures and dose parameters in using laser for treatment are mentioned. "In the present work, an attempt to build a systematic procedure regarding dose parameters, application parameters and laser safety."*
Methods: *A frequency doubled Nd: YAG laser was used to treat all eyes included in this study with diabetic maculopathy. Forty eyes of twenty five non insulin dependent diabetic Iraqi patients were evaluated, sixteen males and nine females. Their ages were 42- 76 years, all of them from patients attending ophthalmic out-patient department in the medical city.*
Results: *Maculopathy regressed in 38/40 of the treated eyes, unchanged in 2/40 eyes and no one was deteriorated. Visual acuity improved in 6/40 of the treated eyes by at least two lines of Snellen's chart while it stabilized in other 34/40.*
Conclusion: *Exudative diabetic maculopathy is responsible for reduction in vision and even legal blindness in many patients. Close regular follow up and early laser treatment of eyes with maculopathy is significant in stabilization of vision and reducing the rate of visual loss.*
Key wards: *Diabetic maculopathy, exudative maculopathy, clinically significant macular edema.*

Introduction:

Aim of the study:

1-To evaluate the effect of frequency doubled Nd: YAG laser in treatment of diabetic maculopathy.
2- The literatures are rich in publications of these regards, nevertheless the works in general were not systematic, not enough details regarding procedures and dose parameters in using laser for treatment are mentioned. "In the present work, an attempt to build a systematic procedure regarding dose parameters, application parameters and laser safety."

Clinically significant macular edema:

Clinically significant macular edema (CSME) has the following characteristics:
a- Retinal edema within 500 gm of the center of the fovea. b- Hard exudates within 500µm of the center of the fovea.
c- Retinal edema one disc area (1500 µm) or larger, any part of which is
within one disc diameter of the center of the fovea.
CSME requires laser photocoagulation irrespective of the level of visual acuity because treatment reduces the risk of visual loss by 50%. Improvement of visual function is infrequent, rendering such treatment prophylactic. Pretreatment FA is useful to delineate the area and extent of leakage and also to detect capillary non-perfusion at the fovea (ischemic maculopathy) which carries a poor prognosis and is a contraindication to treatment

Laser tissue interaction:

The interactions between laser radiation and biological tissue depend on the parameters of laser light as well as on the optical and thermal tissue properties. **The laser parameters** includes wavelength, power, time of exposure, the size of focusing spot measured by half diameter of laser beam at l/e (maximum energy), power density (irradiance) which means power/area, energy density (fluence) which means energy/area. **The optical tissue properties** include, absorption coefficient, scattering coefficient, and albedo which is the ratio of scattering coefficient/ absorption coefficient +scattering coefficient. **The thermal properties** refer to the significant change in absorption coefficient, minor change of scattering coefficient, and
(g) associated with an increase temperature [(2)].
An increase in temperature is the significant local parameter, the non specific thermal effect of laser light illustrated in different form on the tissue depending upon duration and peak value of tissue temperature achieved i.e. each one related to certain temperature. The changes are shown in the table1-1 (Z):

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Table 1-1 Thermal effects of laser radiation

Temperature	Biological effect
37°c	Normal--
45°c	Hyperthermia
50°c	Reduction in enzymatic activity and cell immobility
60°c	Denaturation of protein and collagen (coagulation)
80°c	Increase membrane permeability
100 °c	Vaporization, Thermal decomposition
>150^{0}c	Carbonization
>300°c	Melting

Laser safety:

Safety measures for laser room starting from outside to inside as follow' 3.4):

a- Outside laser room; warning labels on walls or doors of the laser room with audible alarm when person accidentally pass to the room. **b- Safety interlocks** for the doors.

c- Inside the room; include the energy extent inside the room which is called maximum permissible exposure (MPE). MPE is the level of laser to which a person may be exposed without hazardous effects or biological changes in the eye or skin. MPE is determined as a function of laser wavelength, exposure time, and pulse repetition rate. MPE is usually expressed either in terms of energy density in J/cmZ or as irradiance in W/cmZ for a given wavelength and exposure duration. Exposure to laser energy above MPE can result in tissue damage.

d- Type of room; (Avoid specular reflecting surfaces) and (The beam direction must be not in the direction of the eye level, doors, or other entrances).

e- **Eye protection:** The main eye protection is eyewear.

f- Key switch for the laser system to avoid misuse.

g- Safe shut off within the system.

h- Labels of the laser.

i- Visual and audible warning with invisible beam. **j- Filter in the slit lamp** for the surgeon.

Patients And Methods :

Patients:

This prospective study was done during a period of nine months, from the first of September 2004, till the end of April 2005. During this period, forty eyes of twenty five non insulin dependent diabetic Iraqi patients were evaluated, sixteen males and nine females. Their age were 42-76 years, all of them from patients attending ophthalmic out-patient department in the medical city. Duration of the disease ranges from 5-22 years, and all of our patients who have been included in this study having best corrected visual acuity 6/36 or better. The eyes with exudative maculopathy were classi lied into:

a- Maculopathy with background diabetic retinopathy (M + BDR).

b- Maculopathy with pre-proliferative diabetic retinopathy (M + PPDR). c- Maculopathy with proliferative diabetic retinopathy (M + PDR) (only those with NVD or NVE were selected).

By using questionnaires and meticulous examination, any patient with vitreous hemorrhage or gliosis, significant media opacities, glaucoma, ocular trauma or previous intraocular surgery was eliminated. Known cases of systemic medical disorders like hypertension and renal failure were eliminated too. All statistical tests and analyses were based on eyes rather than subjects so that the result could be correlated with those reported by many other investigators.

Methods:

Criteria of treatment:

a- Thickening of the retina closer than 500 µm to the center of the macula.

b- Hard exudates closer than 500 pin to the center of the macula associated with adjacent areas of retinal thickening.

c- Areas of retinal thickening larger than one disc diameter, any part of which is within one disc diameter of the center of the macula

Explanation to the patient:

The patient must be reminded that the procedure generally is painless or associated with very slight burning sensation, and have to tell the patient to expect laser flashes. The patient has to be told not to talk or move during the laser firing period. Detailed explanation of diabetic maculopathy, way of treatment, expected results and the schedules of follow up was done for all patients.

Pretreatment ocular examination:

The pretreatment ocular examination included the following:

a- Best corrected visual acuity (Snellen's test).

b- Slit lamp biomicroscopical examination of the anterior segment.

c- Goldmann applanation tonometry to measure the intraocular pressure. d- Examination of the vitreous and retina with slit lamp biornicroscopy using non contact condensing lens (+ 90 and +78) and Goldmann triple mirror contact lens.

e- Fundus color photographs for some patients which are using in showing the patient his or her macular problem, the follow up by comparison pre and post treatment photographs and for medico-legal purposes.

Laser dose parameters:

-Spot size: 50-100 µm. (52.5 µm -105 µm on retinal tissue) **-Pulse duration:** 0.1-0.2 second.

-Power: initially we start at 100 Milliwatt and adjust

as necessary (150, 200, 250, 300, 350 Milliwatt) to achieve a light to moderate intensity burn to produce a relatively burn without spreading of the spot. Before operation, all the personnel inside laser room should discharged out except one assistant who should wear goggle specific for frequency doubled Nd- YAG laser (we have only one goggle with our laser system), and even with goggle should not gaze to the laser beam directly.

-Pulse repetition rate: 1 Hz
-Energy: 10 mJ,15 mJ, 20 mJ, 25 mJ, 30 mJ, 35 mJ respectively to the power 100 mW, 150 mW, 200 mW, 250 mW, 300 mW, 350 mW with duration of 0.1 second.

Post operative follow up:
Follow up examination were performed two weeks after treatment and monthly for four months and then after two months. These steps of examinations were identical to pre treatment assessment. Evaluation of the treatment was based on its effect on visual acuity, retinal edema and exudation.
Changes in vision by at least two lines was required to be considered better or worse, while visual acuity that remained the same or change by _: one line was considered stable.
Retreat any focal areas of leakage if clinically significant macular edema persists on the last follow up visit (approximately six months post operatively).

Laser safety in work:
-The laser system is placed in place where it is not exposed to the direct sunlight in the specified temperature and humidity and protected from excessive dust.
-Labels for our laser system include the warning logotype (Danger), and description information about the laser (type, class, wave length). -Laser system must always be in stand by mode except during actual treatment, it prevents accidental exposure if the foot pedal is in advertently. -As we mention previously, we start coagulation with low out put first and gradually increase the out put in order to avoid unintentionally intense burn which may be produced.
-Before operation, all the personnel inside laser room should discharged out except one assistant who should wear goggle specific for frequency doubled Nd- YAG laser (we have only one goggle with our laser system), and even with goggle should not gaze to the laser beam directly.
-To protect the physician's eyes from any kind of hazardous radiation reflected from target tissue, the delivery unit has protective filter. If this filter is not set in observation path, the coagulation beam cannot be emitted through the foot pedal.
-In the case that trouble occurs in the laser system, the safety shutter automatically shuts down the optical path of coagulation beam and the laser system is stopped.
-Back reflection and scattering of laser beam prevented by black painting of the wall behind the patient.
-We put special local air conditioner inside the laser room in addition to central one to avoid harmful effect of rising temperature above 30 °c. -Registration and maintenance done by specialist engineer regularly every three months.

Statistical tests:
All statistical tests and analyses were based on eyes rather than subjects so that the result could be correlated with those reported by many other investigators. Students t-test was used to check statistical significant of' regression in maculopathy and stabilization of visual acuity and we regarded a p value of less than 0.05 as a significant indicator.

Results:
In the period of study, Forty eyes of twenty five non insulin dependent diabetic patients were evaluated, sixteen males and nine females. Their age was 42-76 years as shown in table 3-1.
Table 3-2 shows the distribution of the eyes with exudative maculopathy according to the type of associated diabetic retinopathy:
a- Maculopathy with background diabetic retinopathy (M+BDR).
b- Maculopathy with pre-proliferative diabetic retinopathy (M+PPDR). c- Maculopathy with proliferative diabetic retinopathy (M+PDR) [only
those with NVD or NVE were selected].
Table 3-3 shows the distribution of the eyes according to duration of diabetes mellitus, this table shows increase in the incidence of diabetic retinopathy associated with long duration of the disease.
A statistically significant regression in Maculopathy was occur in 38 out of 40 treated eyes ($p<0.05$), unchanged in 2/40 (including only eyes of M+PDR) and no eye was deteriorated as it shown in table 3-4.
Visual acuity improved in 6/40 (all related to the eyes with M+BDR and their initial VA 6/18 or better) of the treated eyes by at least two lines of Snellen's chart while it significantly stabilized in other 34/40 ($p<0.05$), those who has either no change in visual acuity or changed by ± only one line of Snellen's chart as it shown in table 3-5.

Table 3-1: The a e sex and number of e es distribution

Age group	40-49 years No. of eyes	50-59 years No. of eyes	>60 years No. of eyes	Total No. of eyes
Male	4	18	4	26
Female	2	10	2	14
Total	6(15%)	28(70%)	6(15%)	40(100%)

Table 3-2: The distribution of e es accordin to the sta e of D.R.

Stage of Diabetic retinopathy	Number of eyes	Percentage
Maculopathy + background	27	67.5%
Maculopathy + pre-jroliferative	10	25%
Maculo~athy + proliferative	3	7.5%
Total	40	100%

Table 3-3: Number of eyes and its percentage per duration of diabetes

Duration of D.M.	Number of eyes	Percentage
<5 years	5	12.5%
5-10 years	13	32.5%
>10 years	22	55%
total	40	100%

Table 3-4: Changes in maculopathy after focal laser treatment

Changes in maculopathy after treatment	M+ BDR N0. of eyes	M + PPDR N0. of eyes	M+ PDR N0. of eyes	TOTAL N0. of eyes
Regressed maculopathy	27	10	1	38(95%)
Stabilized maculopathy	0	0	2	2(5%)
Progressed maculopathy	0	0	0	Zero

Table 3-5: Changes in visual acuity after focal laser treatment

Changes in VA after treatment	M+ BDR N0. of eyes	M + PPDR N0. of eyes	M+ PDR N0. of eyes	TOTAL N0. of eyes
Improved VA	6	0	0	6(15%)
Stabilized VA	21	10	3	34(85%)
Deteriorated VA	0	0	0	0
Total No. of eyes	27	10	3	40(100%)

Discussion:

All patients have type 2 Diabetes and this occurs accidentally without excluding type I Diabetic patients. This finding can be explained by the following facts:

A- Maculopathy is more prevalent in type 2 diabetes and this result is in agreement with the result of (Bodansky et al 1982) s and (Ronald klein et al 1995) 6.

B- Patients with type I diabetes usually presented with proliferative changes (i.e. vitreous hemorrhage and gliosis) rather than maculopathy "° and such patients were eliminated from this study.

C-Type 2 diabetes is commoner (95%) than type Idiabetes (5%) in general population 7

From the results of table 3-1, we found an increase in the percentage of diabetic maculopathy among patients with increasing age, so the majority of' eyes with maculopathy were among the age group 50-59 year (70%) instead of (15%) among the age group 40-49 year.

Maculopathy decreased again to (15%) among old age group (>60 year) duo to an increase the incidence of morbidity and mortality among such group with diabetic retinopathy.

Table 3-3 shows the duration of diabetes as an important risk factor for the development of diabetic maculopathy. There is a highest percentage (55%) among those patients with duration more than 10 years and a lowest (12.5%) percentage in those having duration less than 5 years. This result is in a good agreement with the results of (Masaki Ishihata et al 1983) (9, (Marshall G. et al 1993) (10', (Yanko and associates) (' '), (Qasim K. F. 1997) (12)

Tables 3-4 and 3-5 show that the frequency doubled Nd: YAG laser is statistically significant ($P<0.05$) in regression of maculopathy (95%) and also there was significant ($P<0.05$) stabilization of VA (85%) or even improvement of it (15%) with minimal or no complications.

There are many clinical trials of photocoagulation for treatment of maculopathy compared to our study and some of them are listed in table 3-6.

Although the treatment protocols and case selections of each study differ, the conclusions are similar "laser treatment tends to reduce the rate of vision loss in eyes with macular edema" but relatively few eyes show substantial vision improvement.

Table 3-6: Trials of hotocoa ulation for CSME

Trials	Laser technique	Follow->a treatment -_
Qasim k. F. (1997) (12)	**Argon laser 100-200 µm spot**	**Follow up monthly for 4 months and then after** 2 **months. Re treatment if any leakage.**
Ok(1986) (13)	**Argon laser Focal 100 lam spot**	**F.A. every 4 months and treatment if any leakage.**
E.T.D.R.S. (1987) (13)	**Argon laser Focal 50-200 µm spot**	**Follow up every 4 months and treatment if any leakage.**
M. Khairallah. et al (1996) (14)	**Krypton laser 50-100 pi spot**	**F.A. every 4 months and treatment if any leakage.**
Nagam Al-Zubadi 2004 (15	**Frequency doubled Nd- YAG laser 50-100 m spot**	**Examination of macula** 2-3 **months post laser and re treatment any ersist CSME**

By observing again the results of clinical trials listed in table 3-7, there is no significant difference between the results of studies that used fluorescein angiography (F.A.) and others that didn't use it prior to laser treatment. An angiogram is particularly useful when it is suspected that these leaking lesions are very close to the fovea or in eyes that show worsening of vision after laser treatment to explain the cause of visual deterioration which is usually due to associated ischemic maculopathy (16)

Table 3-7: Chan es of VA after hotocoa ulation treatment for CSME

Trials	Vision improved by 2 or more lines No.	%	Vision unchanged Or change by f I line No.	%	Vision worse by 2 or more lines I No.	'%	Total
Qasim k. F. (1997) (12)	19	18%	79	76%	6	6%	104
Ok(1986) 113)	19	45%	19	45%		10%	42
E.T.D.R.S. (1987) (13)	65	16%	321	77%	30	7%	416
M. Khairallah. et a (1996) (14)	13	18%	55	75%	5	7%	73
Nagam Al-Zubadi (2004) (15	8	19.5%	31	75.5%	2	5%	41
Our study	6	15%	34 34	85%	0	0	40

There are, however two complementary techniques for photocoagulation
in patients with focal exudative macular edema (16):
a- Direct blanching of the vascular lesion (microaneurysms).
b- Treatment of the retinal pigment epithelium underneath the vascular
lesion (indirect).

The intensity of the reaction should be sufficient to produce a visible change in the microaneurysm. The microaneurysm will either darken or blanch (2). It is known that laser photocoagulation of the microaneurysms is not directly influenced because the laser power is far too low to occlude
them directly (17).

More recent studies have shown that blanching of the microaneurysm through the use of a laser that directly absorbed within hemoglobin, is not mandatory to cause subsequent closure of the retinal vascular lesions. Alternatively, mild treatment of the retinal pigment epithelium underlying a retinal microaneurysm using just a single burn causes regression of the retinal microaneurysm and stops the leakage within weeks. This is a very gentle mode of treatment which causes less damage to the sensory retina, and it is extremely helpful when treating in close proximity to the fovea. The mechanism of action of this new technique is not as yet completely understood. There is a hypothesis that there are vasoinhibitory factors released from the retinal pigment epithelium which mediate closure the retinal microaneurysms 16).

Conclusions:

a- Diabetic maculopathy is responsible for reduction in vision and even legal blindness in many patients.
b- Close regular follow up is essential for patients with diabetic maculopathy.
c- Early laser treatment of eyes with exudative diabetic maculopathy is significant in reducing the rate of visual loss.

Future work:

a- Articles about diabetes and its complications in newspapers, radio, and TV, these are useful for increasing the awareness of people towards diabetes and its complications.
b- Primary care physician should inform the patients at the time of diagnosis of diabetes that ocular complications are associated with diabetes and may threaten vision. They should know that early detection and treatment nay reduce the risk of visual loss.
c- Education of primary car physician on principles of ophthalmological examination and early detection of abnormalities or referring diabetic patients to the ophthalmologist.
d- Diabetic clinics: ideally should have an ophthalmologist, an ophthalmic trained nurse and the use of non dilating fundus camera to detect early diabetes.
e- Similar work can be done in sheep, rats, and rabbits to facilitate performing post laser histological and pathological examination. Also we can use different power and different exposure time in order to calculate the absorption coefficient and penetration depth for this type and other types of laser.
f- Optical Coherence Tomography (OCT) is a

promising diagnostic imaging technique which can be used in future similar studies to get more accurate results.

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