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# Chettinad Health City

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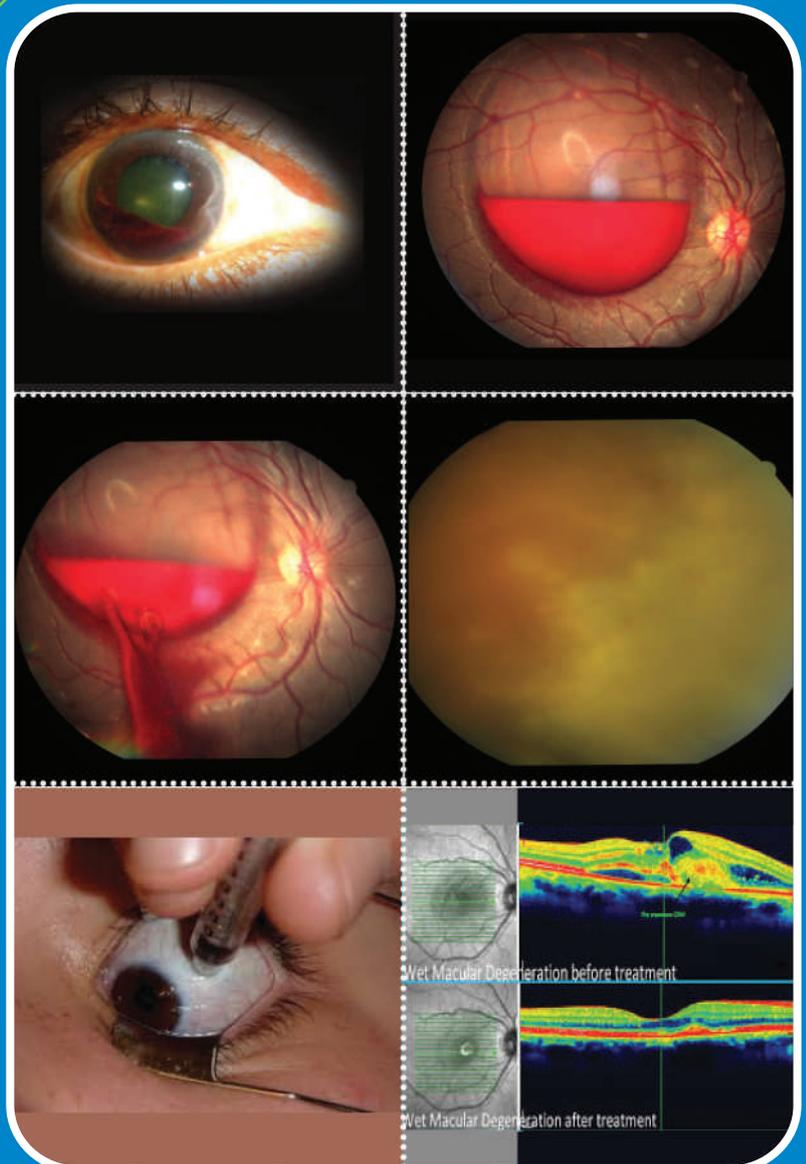
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- What is Anti - VEGF?





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## Editorial

Greetings from Chettinad Health City Medical Journal!

It gives me immense pleasure and privilege in writing the editorial for this issue of the journal which focuses on the field of Ophthalmology.

The perspective article on Bayesian medicine enlists the importance of scientific diagnosis based on notion of probability and evidence based approach. The other perspective article on glaucoma screening focuses on various modalities and importance of glaucoma screening from community level to advanced hospital based investigations for early glaucoma diagnosis.

The original article on glaucoma awareness among medical doctors focuses the importance of continuing medical education as a tool for updating the knowledge. The article on endometrial thickness highlights the embryo quality rather than the endometrial thickness on successful implantation. The article on argon laser hyaloidotomy in management of premacular subhyaloid haemorrhage is interesting. The article on low responders in assisted reproductive technology gives the information regarding demographical profile of the patients.

The review article on acute and chronic otitis media highlights the importance of early treatment and its complications. The article on Calcium hydroxide reviews the applications, advantages and disadvantages of the same in the field of Endodontics. The other review article on dentistry gives a valuable information about the association between oxidative stress and oral malignancies.

Two of International Case reports on Vascular disorders i.e. Aortic dissection in young male body builder and spontaneous recanalization of occluded internal carotid artery is highly interesting and informative.

There are interesting case reports on acute retinal necrosis, Bisphosphonates induced uveitis, atypical unilateral Ocular Myasthenia from Ophthalmology Speciality.

Classroom on Anti-VEGF and its indications in ophthalmology is informative. The article from the pages of history highlights the invention and development of Intraocular lenses a major breakthrough in Cataract surgery.

In conclusion this edition of the journal highlights the ophthalmology subspecialty from history to recent advances with other medical and dental specialities. I hope it would be an academic feast for all the readers

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# Perspective Article

## Bayesian Medicine: An Approach to Systematic Diagnosis

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### Abstract

Faulty diagnosis is often at the heart of medical treatment gone wrong. The root cause of this is that the medical practitioner is averse to a lengthy diagnosis process and relies exclusively on intuition and prior experience to arrive rapidly at a diagnosis. The purpose of this article is to advance a method of scientific diagnosis that would yield the highest probability of success. The method relies on a notion of probability that was introduced a few centuries ago. Using this method, it is possible to quantitate the degree of confidence in one diagnosis relative to the degree of confidence in another differential diagnosis. The method provides an objective metric to differentiate between two competing diagnoses and select the correct diagnosis based on the strength of the evidence and findings. Adoption of the method would potentially improve the standards of medical treatment available in our country.

**Key Words:** Clinical diagnosis, Evidence-based medicine, Differential diagnosis, Bayes' theorem, Conditional probability, Likelihood ratios

### Introduction

Thomas Bayes was an 18th century English theologian who laid down the foundations for an alternative, possibly authentic, interpretation of probability. Through the famous theorem that bears his name, he established a method for probability inference which factors the history of occurrence of the event in predicting the chances of its future occurrence. Using this interpretation, it is possible to update prior beliefs in the light of new relevant evidence in a precise manner. The Bayesian approach facilitates the quantitative integration of new sample information with old data to assess and refine our understanding of the states of nature.

Bayes' theorem is an elementary formula for calculating conditional probabilities, i.e, the probability of something given something else that has happened. For example, let us postulate a certain hypothesis H to explain some phenomena. Let the prior probability (before any measurement or observation has been made) of H being the true explanation be  $p(H)$ . What is the posterior probability of the validity of hypothesis H in the light of acquisition of some new data D for the same phenomena? Following Bayes' theorem, this is given by:

$$p(H|D) = \frac{p(D|H)p(H)}{p(D)} \quad (1)$$

where  $p(H|D)$  is the required posterior probability,  $p(D|H)$  is the likelihood of the data D given the hypothesis H, and  $p(D)$  is the overall likelihood of the data D under any hypothesis. From this, the theorem's key insight emerges, namely that a hypothesis is strengthened by unbiased data that its truth renders objectively

probable. This idea is the foundation of Bayesian inference, which is applied to estimate the posterior probability of a given hypothesis in the context of new evidence. In the following, we will see that the heart of evidence-based medicine follows Bayesian tenets.

### Diagnostic Reasoning

The diagnostic process is based on the clinical interview between the doctor and the patient. The clinical interview is subject to the same difficulties that bedevil any dialogue, even with an empowered patient. When we communicate our thoughts to others, we use descriptive terms with shared meanings. It is this notion of shared meanings that makes possible the idea of human communication. A diagnosis is the title we attach to a portrait of affliction. This might be pictured with varying degrees of meaning by different medical professionals, depending on the interpretation of the available evidence recorded in a particular patient. There will be substantial variation between what medical professionals imagine when a diagnosis is discussed. This in turn depends on what they have read, their personal experience, and research experience. As a matter of convention, the label for a given disease is used to connote the essence of the disease as generally understood. This motivates the need to delineate diagnostic envelopes specific to each disease. In developing diagnostic labels, we translate the 'particular' evidence from a specific patient and generalise the findings to evidence for a generic diagnosis. The sum of evidence would be adding of the probability of a diagnosis. Arguably (or inarguably) medicine is a probabilistic art, the aim being to maximise the probability of cure. As William Osler remarked, "Variability is the law of life, and as no two faces are the

same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease."

## Intuitive Approach to Diagnosis

Most doctors use a non-transparent reasoning process. The diagnostic process need not involve conscious reasoning, it could be entirely intuitive. This seems to involve recognising combinations of signs and patterns of findings subconsciously and which suggest or confirm a diagnosis. When analysing the thought processes of doctors with long years of experience, it becomes evident that choosing a diagnostic lead (called a 'pivot') was key to the explanations of senior physicians in making a diagnosis. In a team setting, the team's consensus opinion might have been recorded. The way that one's own mind (or a colleague's) worked to reach the diagnosis might be impossible to explain. The intuitive approach to diagnosis emphasizes the subconscious aspect of the diagnostic method. It is a skill that could be trained and improved by experience. Practice confers a degree of automaticity to rapidly recognise the constellation of signs, symptoms and findings as suggesting a diagnosis. Over time, this could become second nature just like recognising someone's face. However attractive this approach, it has its limitations, namely that it tends to calcify with time and fails to keep pace with the advances in medical knowledge. Over-reliance on this approach would subject the diagnostic process to unintentional, sometimes grave, slips. These considerations motivate the need for a 'transparent' reasoning process.

## Evidence-Based Approach

If a few or handful of differential diagnoses do not spring to mind readily, it is a paramount ethical obligation to employ a 'transparent' reasoning process. At the end of it, one might examine the outcomes of the non-transparent and transparent thought processes and see if they agree or not. If they are at variance, the doctor might wish to revise his/her opinion of the possible diagnoses. Unfamiliar situations frequently arise however experienced one becomes, which means that the transparent approach will be of permanent value. Transparent reasoning is a directed approach to solving diagnostic problems. It involves identifying an aggregate of specific which could be matched with a certain diagnosis. This could be initiated by selecting one diagnostic lead but not necessarily be the presenting complaint or the first finding the doctor sees. Multiple diagnoses would be consistent with the lead. All the diagnoses consistent with a lead are called differential diagnoses. The key duty of the physician's art is to arrive at the correct diagnosis from the set of several competing differential diagnoses. By practising evidence-based medicine, the doctor would be validating the proposed diagnosis with an orthogonal mental procedure, just as we would double-check a calculation by permuting the symbols in an allowed manner. The transparent evidence-based approach verifies the clinical diagnosis and could take either the passive form or the stronger active diagnosis.

## Evidence-Based Passive Diagnosis

Evidence-based passive approach involves thinking about each of the patient's findings in turn and to consider if there is only one diagnosis that is common to each list of differential diagnoses<sup>1</sup>. If there is only a single diagnosis common to a number of findings, it follows that the diagnosis will be probable, i.e it will occur very frequently in a group of patients with those findings. Zeroing in on the diagnosis involves the identification of evidence confirmatory of a single diagnosis. A diagnosis could be confirmed in different ways. Here it is useful to distinguish between necessary and sufficient criteria. To illustrate with an example, in order to make a diagnosis of ectopic pregnancy, it is obvious that the subject is female and not male. If the patient is not female, then the patient lies outside the diagnostic envelope. Such an invariable diagnostic finding is termed a 'necessary' criterion. But the finding of necessary criteria may not be sufficient for confirming a diagnosis. If at least one sufficient criteria of a diagnosis is present, then the diagnosis becomes a candidate diagnosis. A confirmatory finding delineates the envelope of patients with the diagnosis. The multiple confirming findings present the 'definitive criteria' of the diagnosis, which are both sensitive and specific to those with the diagnosis. In other words, they are necessary as well as sufficient for the diagnosis. The evidence-based approach to diagnostic confirmation requires us to choose the 'confirmatory' test which could be shown superior to rival tests based on the balance of responder patients and those not responding to the treatments directed at the diagnosis. Essentially we would like to optimize the response rates in patients, the critical component of which is the determination of the correct diagnosis.

The best findings are those that maximise the frequency of successful diagnosis. The balance of probability of the finding modifies the likelihood of the diagnosis. If the finding is indicative of the pursued diagnosis but less so of another competing diagnosis, the pursued diagnosis becomes more probable relative to the competing, alternative diagnosis. In tandem with the earlier findings, the combined set of evidence would adduce correspondingly more weight to the pursued diagnosis. The same arguments hold for the finding that is not very representative of the pursued diagnosis. In this case, one of the competing diagnoses might gain in favour, and eventually replace the earlier pursued diagnosis.

## Evidence-Based Active Diagnosis

Diagnoses could be actively pursued by searching for findings that would gradually confirm the pursued diagnosis. Absent such confirming findings, the tentative diagnosis could be progressively discounted, and another candidate diagnosis could take its place. The process is initiated by looking at the chart of findings and selecting one lead with the minimal list of consistent differential diagnoses accounting for the maximum fraction of patients with the lead finding. The other findings from the total evidence are used in the process of refining the diagnosis. If a finding has been shown to have a small number of differential diagnoses and these diagnoses account for a very high proportion of patients with that finding, then this would be evidence

of its ability to act as a good lead during the differential diagnostic process. In order to differentiate between the diagnostic categories, the physician has to choose a diagnosis to chase, which is called the postulated diagnosis. This should be the most probable diagnosis or dangerous diagnosis (to avoid delay). To put this framework on a precise footing, a mathematical treatment is necessary. We seek a measure of the ability of a test/finding to function as a differentiator of a pair of competing diagnoses. If a finding increases the likelihood of one diagnosis while simultaneously decreasing the likelihood of a competing diagnosis, then intuitively that finding would help to discriminate between the diagnostic pair.

The evidence-based method is a quantitative approach to differentiate between the competing diagnoses so that some become more probable and others less probable. The index of this ability to discriminate between two diagnoses is measured as simply the ratio of the conditional likelihoods of the two diagnoses given the finding. This ratio is different from the plain 'likelihood ratio' which is defined as simply the frequency of a finding in patients with a confirmed diagnosis divided by the frequency of the same finding in all those confirmed not to have that diagnosis. This ratio refers to a specific pair of differential diagnoses, and is thus termed a 'differential likelihood ratio.' If this differential likelihood ratio (R) is significantly greater than one, then the finding could be said to improve the odds of the differential diagnosis under question. In general, if R is significantly different from one, then the finding favours one diagnosis over the other whereas if  $R \approx 1$  the finding is neutral with respect to the two diagnoses. The relationship between empirical observations and the theoretical diagnosis is quantified using Bayes' theorem. Let  $p(H_1)$  be the prior probability of the diagnosis (given the lead finding  $F_1$ ), and  $p(H_2)$  the prior probability of the differential diagnosis. Given another finding  $F_2$ , the corresponding posterior probabilities are calculated using Bayes' theorem:

$$p(H_1|F_2) = \frac{p(F_2|H_1)p(H_1)}{p(F_2)} \quad (2)$$

$$p(H_2|F_2) = \frac{p(F_2|H_2)p(H_2)}{p(F_2)} \quad (3)$$

The net effect of this procedure is to update the evidence for the diagnoses under consideration and identify those whose evidence has weakened in the light of the finding  $F_2$  and the estimates of the prior probabilities of the diagnoses given the diagnostic lead. The differential likelihood ratio between the competing diagnoses is given by the ratio of equations (2) & (3):

$$\text{Diff. Likelihood ratio} = \frac{p(H_1|F_2)}{p(H_2|F_2)} \quad (4)$$

The differential likelihood ratio obtained above is an objective indicator of the fitness of the diagnosis being chased relative to the competing differential diagnoses in the context of a specific finding and certain prior findings. A single diagnosis would be a final diagnosis if it could explain all the patient's findings, otherwise

at least two diagnoses would be needed, for example in comorbid conditions. A strong differential likelihood ratio provides general evidence of a finding's ability to perform well as a differentiator during the diagnostic process. Given this background, we could objectively characterise the diagnostic lead as that finding with the maximal differential likelihood ratio. Auxiliary findings used in the diagnostic process provide further confirmatory differential likelihood ratios (or progressively discount the putative diagnosis in favour of some competing diagnosis). Bayesian estimation provides an objective method to revise the confidence in a particular diagnosis, eventually resulting in treatment decisions with better outcomes.

## Conclusions

It is clear that scientific methods of diagnosis are the best answer to the plague of misdiagnosis that dominates medicine today. In the current scenario where new diseases are emerging, chances are even greater for the physician to fall into a diagnostic trap. Scant attention paid to the diagnostic process could equate to medical negligence and malpractice, and would lead to harm to the patient. The evidence-based approach with its solid foundation in Bayesian analysis is the way forward to resolving the diagnosis in difficult cases. The art of diagnostic detection could nearly match forensic criminology in its complexity, a fact attested by the popular fictional detective whose character was modelled on the diagnostic prowess of the physician Joseph Bell<sup>2</sup>. Bayesian medicine holds the key to systematic diagnosis and captures the soul of evidence-based detection. It is the necessary criterion for the advancement of precision medicine.

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# Perspective Article

## Glaucoma Screening

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### Introduction

Glaucoma is one of the leading causes of preventable blindness. Due to the asymptomatic nature in early stages, the diagnosis is missed quite often. This leads to irreversible loss of vision, thereby reduction in quality of life. As per estimation there are more than 60 million cases of glaucoma worldwide and 20 million more are expected to get added by 2020<sup>1</sup>. Approximately 12% of total blindness is due to glaucoma<sup>2</sup>. Around 50% of glaucoma cases are undetected<sup>3</sup>. Chennai glaucoma study has observed that more than 90 % of the cases are unidentified. As of now glaucoma has no cure. Hence early detection and treatment is the main stay in management of glaucoma and prevention of blindness.

### Objective

The objective of screening is to pick the disease early and to prevent the potential blindness by appropriate management. Effective and economically beneficial approach is needed for early detection and further management. From the patient's point of view, regular eye checkup is the mainstay of early detection.

### Modes of screening

Screening can be done either at community level or at institutes.

#### Community screening

People can be screened at the community level by conducting regular eye camps. Torch light examination with intra-ocular pressure (IOP) measurement by non-contact tonometer or rebound tonometer and ophthalmoscopy can pick most of the cases. Those with high IOP and/or findings suggestive of glaucoma should be referred to hospitals for further management. Combined ophthalmoscopy and tonometry for all persons and perimetry for high risk persons has a sensitivity of 80%<sup>4</sup>.

#### Screening at hospitals

Govt of India has recommended opportunistic screening for people aged above 40 yrs visiting outpatient department. Other means of screening include intra-ocular pressure measurement for all patients at first visit and conducting regular glaucoma screening programs etc. Family members of glaucoma patients need to be screened regularly. Glaucoma suspects will undergo detailed examination and investigations to quantify the damage and commencement of treatment.

### Screening tests

All tests are focused on the optic nerve head to detect the presence of either structural damage or functional damage.

#### Tests to detect functional damages

Tonometry and perimetry are used to detect functional damage of the optic nerve. Goldmann Applanation Tonometry (GAT) is the gold standard to measure the intra ocular pressure. Standard Automated Perimetry (SAP) is used to detect the visual field defects whereas Frequency Doubling Perimetry (FDT) which requires lesser time can be used mainly for screening purpose.

#### Tests to detect structural damages

Optic Disc Photography, Heidelberg Retinal Tomography, Optical Coherence Tomography, Retinal Nerve Fiber Layer (RNFL) Analysis and Scanning Laser Polarimetry (SLP) are used to quantify the structural damage.

The sensitivity and specificity of each test individually is not promising. As no single test is conclusive, diagnosis and management cannot be finalized on a single test result. Combination of multiple methods somewhat aid in effective screening. Sight savers study combined IOP, FDT and a questionnaire (three tests) and the sensitivity and specificity were found to be 88.6%, and 57.1% respectively<sup>6</sup>. The ultimate aim is to find out effective and cheap methods for screening.

### Challenges

There is no definite method or combination of methods for effective screening<sup>7</sup>. Further studies are needed to customize the optimal combination of screening tests to detect glaucoma at a much earlier stage. Till then we should target the high risk individuals. Following people are at high risk for glaucoma:<sup>8</sup>

- Aged 40 years and above.
- With family history of glaucoma.
- High intraocular pressure.
- African Americans (for open-angle glaucoma).
- East Asians and people with East Asian ancestry (for closed-angle glaucoma).
- Myopes (greater risk for developing open-angle glaucoma)

Hypermetropes (greater risk for developing closed-angle glaucoma).  
Those taking corticosteroid in any form.  
With diabetes/hypertension.

## Conclusion

Screening for glaucoma not only prevents avoidable blindness but also improves the medical quality of the patient and the economic quality of the society. Though glaucoma screening is tough, the result i.e. early detection and management to prevent blindness is rewarding. Regular eye examination is proved to be the effective way of screening glaucoma as recommended by various studies. Greater focus should be on the family members as there is 10-fold increase in the risk of glaucoma among the relatives<sup>9</sup>. Better education and awareness about glaucoma go a long way in the detection of the dreaded disease<sup>10</sup>.

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# Original Article

## Oxidative Stress a Link to Periodontal Disease and Oral Cancer

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### Abstract

The oral cavity is an entry of other systems of the body; it should not be viewed as an isolated area. Diseases that it lays down can have systemic impact and significantly affect the quality of life of individuals who suffer them. Periodontal disease is one of the oral health problems that most often affect the global population, lack of treatment leads to loss of tooth organs and consequently alters the digestion and nutrition, without considering other relevant aspects as phonation, aesthetics and social or emotional impact. The importance of periodontal disease has raised possible bidirectional relationships with systemic diseases such as diabetes, metabolic syndrome and cardiovascular disease. We address herein the role of oxidative stress in the pathogenicity of periodontal disease. In the same context, another disease that has become relevant in our days is the oral cancer. Detection of the reactive oxygen species in the periodontitis patients and oral cancer patients reveal the relationship between the oxidative stress in periodontitis and oral cancer patients.

**Key Words:** Oxidative stress, Periodontal disease, Oral cancer

### Introduction

Oxidative stress is the systemic disturbance caused by the increased Reactive oxygen species a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g. O<sub>2</sub><sup>-</sup> (superoxide radical), OH (hydroxyl radical) and H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide)<sup>1</sup>. In humans, oxidative stress is thought to be involved in the development of Asperger syndrome<sup>2</sup>, ADHD<sup>3</sup>, cancer<sup>4</sup>, Parkinson's disease<sup>5</sup>, Lafora disease<sup>6</sup>, Alzheimer's disease<sup>7,8</sup> atherosclerosis<sup>9</sup>, heart failure<sup>10</sup>, myocardial infarction<sup>11,12</sup>, fragile X syndrome<sup>13</sup>, Sickle Cell Disease<sup>14</sup>, lichen planus<sup>15</sup>, vitiligo<sup>16</sup>, autism<sup>17</sup>, infection<sup>18</sup>, chronic fatigue syndrome<sup>19</sup>. Periodontitis<sup>20</sup>. Epidemiological data show that the incidence of this neoplasm has been increasing in several countries. The impact of oral cancer on patients, who suffer it, is devastating. The role of oxidative stress in the development of this disease and some alternatives for its treatment, are topics addressed in this brief. Periodontitis and oral cancer are two oral diseases and a sample of the plethora of effects that oxidative stress may have at local and systemic level. So this study analyses the reactive oxygen species in saliva samples there by proving their role in periodontitis and oral cancer.

### Objectives

The study has following objectives

1. To detect the oxidative stress in periodontitis

patients and oral cancer patients

2. To compare the oxidative stress between oral cancer patients and periodontitis

### Study groups

The case control study was done in department of periodontology under the ethical clearance from Dr. MGR UNIVERSITY And Research Institute three groups n=25 was selected

1. Group of periodontitis (n=25)
2. Group of oral cancer (n=25)
3. Group of healthy controls (n=25)

### Materials and methods

The saliva samples were collected from the three groups and stored in the plastic bottles, and the study done in regenix laboratory, Chennai. Oxidative stress status was assessed by measuring the total antioxidant capacity (TAOC) and biomarkers of oxidative stress 8-hydroxy-2-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) in saliva and the activity of some of the main antioxidant enzymes glutathione peroxidase (GPx) and superoxide dismutase (SOD).

GPx and SOD activities and TAOC levels were determined using a competitive ELISA kit (Cayman Chemical Company; Item numbers 703102, 706002, and 709001, resp.) according to the manufacturer's instructions. MDA levels were measured with NWLSS Malondialdehyde Assay (Northwest Life Science Specialities; Catalog number NWK-MDA01) following the manufacturer's instructions. 8-hydroxy-2-deoxyguanosine (8-OHdG) levels were measured with NWLSS High Sensitivity 8-OHdG ELISA (Northwest Life Science Specialities; Catalog number NWK-MDA01) following manufacturer's instructions.

## Statistical Analysis

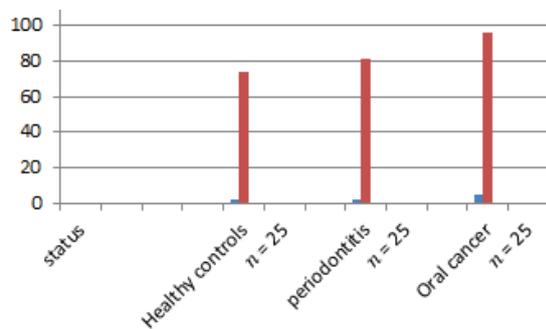
All results shown are expressed as mean and 95% confidence interval. Statistical comparisons between groups were assessed by Mann-Whitney or Kruskal-Wallis tests. The linear trend between groups was analyzed by the Jonckheere-Terpstra test. Multivariate linear regression predictive models were made with the different oxidative stress parameters as the dependent variable. The independent variables were age, gender, smoker (as confounding variables).

## Results

We obtained a highly significant elevation of all oxidative stress marker levels except for that of SOD. Periodontitis group and oral cancer denoted increased oxidative stress level. Therefore, the presence of oxidative stress in periodontitis and oral cancer is significant compared to healthy group.

status	Oxidative stress parameters				
	8-OHdG <sup>1,2</sup> (ng/ml)	GPx <sup>1,2</sup> (U/L)	TAOC <sup>1,2</sup> (mM)	SOD <sup>1,2</sup> (U/ml)	MDA <sup>1,2</sup> (nM)
Healthy controls	2.20	75.04	0.91	3.24	4.43
n = 25	(1.88-2.52)	(72.35-77.72)	(0.80-1.01)	(3.16-3.31)	(3.61-5.24)
periodontitis	2.33	80.99	1.03	3.62	4.51
n = 25	(1.84-2.82)	(76.83-85.15)	(0.89-1.17)	(3.37-3.86)	(3.35-5.68)
Oral cancer	5.54	95.58	1.09	4.17	5.94
n = 25	(4.96-6.12)	(93.12-98.04)	(1.01-1.17)	(3.91-4.42)	(5.04-6.84)

**Table 1:** Oxidative stress parameters and periodontal status



**Table 2:** Comparison between the three groups

## Discussion

The pathological events which lead to the destruction of the periodontium during inflammatory periodontal disease have been related to the effect of the imbalance between oxidants and antioxidants in patients with periodontal disease<sup>20</sup>.

ROS are generated predominantly by PMN during an inflammatory response<sup>21</sup> It has been suggested that the bacterial species in subgingival plaques and the PMN response are important factors in the changes in periodontal disease status. An increase in ROS leads to the destruction of periodontal tissue, and it is one of the most important causes of periodontal disease. The present study has demonstrated significant changes in oxidative stress by measuring different oxidative stress

markers (8-OHdG, MDA, GPx, SOD, and TAOC) that increased with worsened periodontal status.

The involvement of free radicals in cancer development has been studied for 3 decades, and there is sufficient evidence that implicates theirs in the multistage theory of carcinogenesis Free radicals are products of the oxidation-reduction systems of the cell and its participation in cellular metabolic functions is essential for cell survival. A classic example is the electron transport chain in mitochondria. However, in what pathological conditions, free radicals can become deleterious?

In fact, what are the results of its harmful effects. They are proposed to cause diverse DNA alterations like: punctual mutations, DNA base oxidations, strand breaks, mutation of tumor suppressor genes and can induce overexpression of proto-oncogenes<sup>22</sup>. Several works explore the levels of oxidative stress in patients with oral cancer<sup>23</sup> most of them quantified the products of lipid-peroxidation (mainly malonaldehyde) and contrast them with the activity of antioxidant enzymes or exogenous antioxidants levels in blood or even saliva. The results agree that there is an imbalance between the high amount of free radicals and insufficient antioxidant system activity. Added to this, some researchers have observed that high levels of lipid-peroxidation combined with low levels of thiols and antioxidant status, correlate with poor survival rate in patients with oral cancer<sup>24</sup>. It should be added that oxidative protein damage participates in facilitating the development of cancer. The present study has demonstrated significant changes in oxidative stress by measuring different oxidative stress markers (8-OHdG, MDA, GPx, SOD, and TAOC) that increased in oral cancer.

Our results agree partly with Canakci et al.<sup>25</sup>. In salivary samples from 30 patients with chronic periodontitis and 30 periodontally healthy controls, these authors obtained higher salivary 8-OHdG and MDA levels and lower salivary antioxidant activities that seem to reflect increased oxygen radical activity during periodontal inflammation.

## Conclusion

Certainly, the main limitation of the study has been the small sample size, but the study could confirm the possible linear correlation between markers of oxidative stress and the periodontitis and oral cancer. Further studies with larger sample size should continue this line of research. In conclusion, the determination of oxidative stress levels could be a potent tool in controlling the development of periodontitis and tool in detection of oral cancer.

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## Original Article

# Survey of Awareness about Glaucoma Among Medical Doctors of A Medical College and Tertiary Care Hospital in South India

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### Abstract

**Purpose:** Glaucoma is one of the leading causes of blindness. Various studies have highlighted the lack of awareness among general population which leads to non-diagnosis or late diagnosis of glaucoma. Very few studies have been done among medical professionals. The present study was conducted to evaluate the level of awareness and knowledge about glaucoma among the doctors in a medical college and tertiary care hospital. **Methods:** A structured questionnaire-based survey was conducted among 350 doctors of a tertiary health care institution to evaluate the level of awareness and knowledge about glaucoma. **Results:** Of the 350 doctors enrolled for the survey, responses from 319 (91.14%) participants were evaluated. 110 (34.48%) were specialists and 209 (65.52%) were non-specialists. 18% of the participants think that glaucoma is always symptomatic and 12.7 % think it is painful always. Surprisingly 23.1% (n=70) of medical doctors think that central vision is affected first. 20.7% think that lost vision can be restored by treatment. 35.1% think that glaucoma is directly related to blood pressure and 18.4 % think that diabetes is not a risk factor. **Conclusion:** Knowledge about glaucoma among doctors is poor. Doctors of a medical college are instrumental in propagating the information of the irreversible blindness that could arise from delay in glaucoma diagnosis and treatment. Hence there is a dire need to update their knowledge on glaucoma.

**Key Words:** Glaucoma, Awareness, Medical doctors

### Introduction

The general public believe that doctors are aware about all diseases and rely on them for medical related issues. Most often non-ophthalmic doctors are the first point of contact for many patients with eye related issues. Hence it is imperative that all doctors are made aware about certain ocular diseases particularly those which are asymptomatic in early stages, like glaucoma. Glaucoma is a progressive optic neuropathy characterized by optic nerve head damage and visual field damage with or without increased intra ocular pressure (IOP). The disease with prevalence varying from 2.6%<sup>1</sup> to 4.1%<sup>2</sup> invariably results in blindness if left untreated. Glaucoma related blindness is preventable only with early detection and regular treatment. This study is conducted to evaluate the level of awareness and knowledge about glaucoma among doctors of a medical college and tertiary care hospital in South India. No studies have been reported so far from this part of the country.

### Materials and Methods

This study was conducted in Chettinad Hospital and Research Institute and Chettinad super specialty hospital which is a tertiary care medical college hospital located in South India. This cross sectional study included 350 medical doctors including interns from various specialties. Study was conducted after obtaining the approval from the institutional ethics

committee. After obtaining an informed consent, all participants were given a structured questionnaire and asked to complete the presence of one of the investigators. As all the participants were educated, the questionnaire was printed in English. We initially validated first 10 questionnaires to look for any potential changes and proceeded with other participants. 350 doctors filled the questionnaire out of which 319 responses were valid. Incomplete questionnaires were excluded from evaluation. All the data were entered and analyzed with SPSS. Categorical variables were analyzed with the independent t-test and Pearson's chi-square test. A P value of less than 0.05 was considered statistically significant.

**Inclusion criteria:** All doctors including the interns of Chettinad Hospital and Research Institute and Chettinad Super Specialty Hospital who are volunteered for the survey.

**Exclusion criteria:** Ophthalmologists, Residents and interns working in the Dept of Ophthalmology, CHRI.

### Results

Responses from 319 participants were analyzed. The mean age of participants was 38.24± 8.54. 110 (34.48%) were specialists and 209 (65.52%) were non-specialists.

**Table: 1 Have you heard about glaucoma?**

Yes	No	Total
316	3	319

It was surprising that 03 participants had not heard about glaucoma (Table 1). Most of the doctors were aware that glaucoma is associated with increase in intra-ocular pressure that damages optic nerve head. 4.7 % of doctors thought otherwise (Table 2).

**Table: 2 If yes, what is glaucoma?**

Increase in IOP that damages optic nerve head	301
Age-related problem	11
Others	4
Total	316

**Table:3**

	YES	%	NO	%	Don't know	%
Patients with glaucoma always have symptoms	57	18.0	255	80.7	4	1.3
Glaucoma is always painful	40	12.7	271	85.8	5	1.6
Glaucoma can affect vision	303	95.9	7	2.2	6	1.9
Type of vision affected in glaucoma	214	70.6	70	23.1	19	6.3
Is there any treatment for glaucoma?	306	96.8	7	2.2	3	0.9
Without treatment glaucoma will cause blindness	297	94.0	15	4.7	4	1.3
Lost vision can be restored by treatment	66	20.9	236	74.7	14	4.4
Glaucoma is directly related to blood pressure	111	35.1	193	61.1	12	3.8
Is DM a risk factor for glaucoma?	246	77.8	58	18.4	12	3.8

18% of the participants think that glaucoma is always symptomatic and 12.7 % think it is painful always. Out of 303 participants who think that glaucoma can affect vision, 23.1% think that central vision is affected first. 2.2% think that there is no treatment for the disease. 20.9% think that lost vision due to glaucoma can be restored. 35.1% think that glaucoma is directly related to blood pressure and 18.4 % think that diabetes is not a risk factor (Table 3).

55.38% of participants rightly thought that family history is the strong risk factor for glaucoma whereas 20.89 % thought it is an age-related problem. Around 12% thought refractive error is the strong risk factor (Table 4). All the values were statistically significant.

Majority (97.8%) rightly thought that regular check-up is the best measure to prevent glaucoma (Table 5).

Irregular treatment is the main culprit which would make glaucoma worse and potentially lead to blindness. Only 74.4% of the participants rightly thought so. Respectively 13.3% and 10.4% think that stress and exercise and prolonged computer viewing will worsen glaucoma which is contrary to the fact (Table 6).

## Discussion

Various studies have been conducted among patients and general public<sup>3-6</sup>, but very few among health care personnel<sup>7, 8</sup>. Probably there are no studies conducted among medical doctors in this part of the country. In a study conducted among workers in a Nigerian tertiary health care institution, awareness and knowledge were compared among clinical and administrative staff (n=120 each). No statistically significant difference about the knowledge of the aspect of vision that is first affected by glaucoma, the painless nature of glaucoma among most Africans and the irreversible nature of glaucoma-related blindness, were found<sup>8</sup>.

**Table:4 Strong risk factors for glaucoma**

Family history	175 (55.38%)
Age	66 (20.89%)
Refractive error	36 (11.39%)
Don't know	39 (12.34%)

**Table:5 Measures for prevention of glaucoma**

Regular check-up	309 (97.8%)
Healthy nutrition	3 (0.9%)
Don't know	4 (1.3%)

**Table: 6 Which will make glaucoma worse?**

Stress and exercise	42 (13.3%)
Prolonged computer viewing	33 (10.4%)
Reading	2 (0.6%)
Irregular treatment	235 (74.4%)
Don't know	4 (1.3%)

Parul et al, had surveyed physicians and nurses of a medical college in North India (n=119). Our study has been conducted among medical staff including interns and a larger number of participants were included (n=319). The results are comparable to that study.

Surprising facts that have surfaced with regards to knowledge of doctors in this study are as follows:-

16% of the medical doctors have not undergone an eye check-up till date. Though they are working at a place with easy access to health care, there is barrier to

undergo eye examination. 18% think that glaucoma is always symptomatic. 23% think that glaucoma affects central vision first. 20% think that lost vision due to glaucoma is reversible. Respectively 20% and 16% think that age and refractive errors are the strong risk factors for developing glaucoma.

Even though the medical doctors are working in a tertiary care hospital, their knowledge about glaucoma is disheartening. These findings expose the lacuna in our medical curriculum in terms of preventive medicine. In addition to the fact that all medical doctors are expected to update their medical knowledge, the state should also organize education programmes to promote awareness and refresh knowledge about all common diseases particularly of those which are asymptomatic at earlier stages.

## Conclusion

Among medical doctors, though the awareness is good, the knowledge about glaucoma needs up-gradation. Loss of touch with the subject among specialists of non-ophthalmic specialties is known to be the major issue. Periodical Continuing medical education programmes and lectures should be conducted in health care institutions to sensitize the doctors.

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## Original Article

# Does the endometrial thickness really matter in Assisted Reproductive Technology Cycles - A Retrospective analysis

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### Abstract

**Aim:** The objective of the study was to observe the thickness of endometrium on HCG trigger day during Assisted Reproductive Technology (ART) cycles and correlating it with pregnancy outcome. **Materials and Methods:** From September 2008 to December 2014, 57 patients undergoing assisted reproduction cycles were retrospectively analyzed for the pregnancy outcome in relation to endometrial thickness. The study was done in the Reproductive Medicine department, Chettinad Hospital and Research Institute, Kelambakkam. All fresh Intra Cytoplasmic Sperm Injection treatment cycles using short flare protocol were included and categorised into two groups based on the pregnancy results: 1. Group A (pregnant), 2. Group B (non-pregnant) **Results:** The mean endometrial thickness in the groups A and B were  $10.02 \pm 1.46$  (7.1 to 13.4mm) and  $10.40 \pm 2.19$  (7.8 to 19 mm) [P < 0.447, Not significant]. The clinical pregnancy rate was 42.10% and the implantation rate was 22.81%. Pregnancy rate was good probably because of the selection of grade 1 embryos and limiting the age of patients to <35yrs. **Conclusion:** From our study, the endometrial thickness is not the deciding factor for the successful implantation of human embryo. We also infer that thin endometrium of < 7 mm is an unlikely occurrence in ART cycles unless there is pathology in the uterus.

**Key Words:** Endometrial thickness, Embryo, Implantation, Pregnancy outcome.

### Background

Despite numerous papers analyzing the influence of endometrial thickness in influencing pregnancy outcome, the issue remains unclear. Compared to the escalating cost, the outcome of pregnancy is low in ART/ICSI cycles which mandates the reevaluation of the predictive factors for success in ART.

### Introduction

Implantation of embryos is the final and most critical step in assisted reproduction. Both embryo quality and endometrial receptivity play a vital role in implantation of embryo<sup>1</sup>. The assessment of endometrial receptivity is by simple 2D ultrasonographic (USG) examination during stimulation. Since USG is a simple, non-invasive, patient friendly and reliable technique for the evaluation of endometrium, it is commonly employed.

For the implantation to take place, priming of endometrium occurs in each and every menstrual cycle. The communication between the blastocyst and the endometrium is expected to be closer if the implantation is to be successful. If these cyclic changes are prevented by abnormalities of endometrium, there are less implantation and more miscarriages<sup>2</sup>.

The relationship between thickness or pattern of endometrium and the receptiveness of the uterus has been analyzed by many authors<sup>3-11</sup>. Some studies reported with increased endometrial thickness pregnancy rates are less<sup>7,12,13</sup>. Some other studies reported that with increase in endometrial thickness, the pregnancy rates also increases<sup>5,14</sup>. Both the endometrial thickness and pattern are analysed in few other studies to prognosticate the pregnancy outcome of ART<sup>12</sup>. Recent studies analyzed the endometrial blood flow by doppler studies to predict the pregnancy outcome in ART<sup>15</sup>. But some others concluded that there is absence of influence over pregnancy outcome by the endometrial thickness and pattern<sup>16-20</sup>.

In the first systematic meta-analysis, the predictiveness of the role of endometrial thickness over ART outcome was investigated. The chances of clinical pregnancy was significantly less in patients when the endometrium was < 7mm compared to > 7mm (23.3% vs 48.1%) and OR was 0.42 (95% CI 0.27 - 0.67)<sup>21</sup>.

### Endometrium:

Distance between endometrial-myometrial junction of one side to the other is measured as the endometrial thickness. The measurement is taken in the longitudinal axis on the day of hCG trigger by using two dimensional transvaginal ultrasound.

The thickness of the endometrium at early follicular phase in the antero- posterior(AP) view is approximately 5-7mm. It becomes triple line around ovulation and is about 8-12mm. Echo pattern becomes homogeneously hyper-echoic in luteal phase. Remarkable changes take place in the endometrium after ovulation. By 13 days post ovulation, the endometrium clearly differentiates into 3 zones:

1. Stratum basalis
2. Stratum spongiosum
3. Stratum compactum

The cardinal morphologic change around implantation is the formation of edema of the endometrial stroma which is on days 21 - 22 of the menstrual cycle. More production of prostaglandin by the endometrium occurs due to sex steroids. Ultimately the permeability of the capillaries are increased with rise in prostaglandins. There are receptors available for the sex steroids in the vasculature of the endometrium.

## Implantation

Implantation is defined as the adhesiveness of the blastocyst with the epithelial lining of uterus and subsequently invading the epithelium, occurring approximately 18-19th day of menstrual cycle<sup>22, 23, 24</sup>.

The objective of our analysis was to observe only the endometrial thickness on the day of hCG trigger during ART cycles and to study the influence of endometrial thickness over ART outcomes.

## Materials and Methods

**Study population:** From September 2008 to December 2014, 57 patients who underwent ART cycles were retrospectively analyzed for the pregnancy outcome in relation to endometrial thickness after excluding the factors discussed later. The study was done in the department of Reproductive Medicine, Chettinad hospital and research institute, Kelambakkam.

## Methodology

All fresh ICSI cycles using short flare protocol who underwent oocyte retrieval and also transfer of embryos were included.

### Inclusion criteria:

1. Age < 35yrs
2. First cycle ART
3. Only short agonist protocol
4. Normozoospermia
5. Transfer of three, grade 1 embryos

### Exclusion criteria:

1. Cycles using donor oocytes /embryos
2. Cycles using cryopreserved embryos
3. Presence of known uterine anomalies
4. Presence of hydrosalpinx
5. Ovarian stimulation method other than the short agonist protocol.
6. Male factor infertility

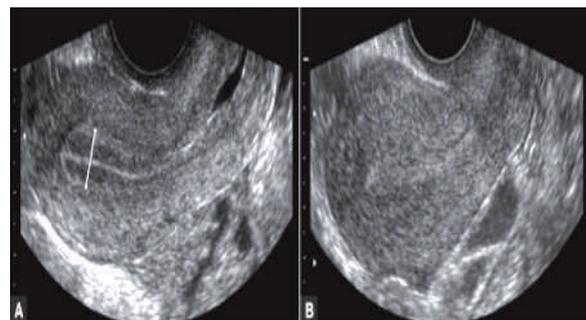
## Procedure:

The pituitary was down regulated with short GnRH agonist (flare) protocol from D2 of menstrual cycle to HCG trigger and stimulation of ovaries was achieved with urinary gonadotrophins. When at least three follicles reached  $\geq 18$  mm by 2D USG, oocyte retrieval was planned. The clinician measured the thickness of the endometrium and recorded in the patient's case sheet. Inj.HCG trigger was given and the oocytes were retrieved 35-36 hours later. ICSI was carried out to achieve fertilization. Embryo transfer was planned post oocyte retrieval (D2/D3/D5). Luteal phase was supplemented with progesterone vaginal pessaries from the day of OPU and continued till day 14 post embryo transfer. Two weeks after positive  $\beta$ HCG, USG was planned. When fetal cardiac activity was present, clinical pregnancy was confirmed.

## Ultrasound examination

The maximum thickness of the endometrium in the longitudinal plane was measured on the day of HCG trigger. Based on pregnancy results, all cycles were categorised into :

1. Group A (pregnant)
2. Group B (non- pregnant)



**Fig 1 -** Ultrasonography picture of endometrium. (A) Multi layered endometrium or triple line pattern and (B) Non-multi layered pattern

## Statistical Analysis

Continuous data are measured as Mean + SD and analysed. To test the equality of mean values of two groups, independent samples t-tests are used and  $P < 0.05$  was considered as statistical significance. To compare the differences between two groups when the characteristic of interest is qualitative in nature, Mann Whitney tests are applied. IBM SPSS (Version 21.0) software was used for statistical analysis.

## Results

All the 57 women who met the inclusion criteria were analyzed in our study. The patients were between 25 and 34 years of age with the mean of 30.86 yrs. The baseline characteristics of the two groups, with pregnancy (group A) and without pregnancy (group B) are shown in table 1. Comparison of baseline characteristics revealed no statistical difference in parameters such as age, BMI and period of infertility in the pregnant and non-pregnant groups. There was also no significant difference seen in the basal FSH and total AFC (Antral Follicle Count).

Baseline Characteristics	Pregnancy outcome						Independent Samples t-test	
	Group A (n = 28)			Group B (n = 29)				
	Mean	SD	SE	Mean	SD	SE	t-Value	P value
Age (yrs.)	31.39	2.59	0.49	30.34	2.44	0.45	1.574	0.121
Period of infertility(yrs.)	6.27	4.26	0.81	6.38	3.42	0.63	-0.112	0.911
BMI (weight in kg/height m <sup>2</sup> )	25.83	3.62	0.68	25.55	3.11	0.58	0.314	0.755
AFC Total	11.52	5.69	1.09	11.86	4.82	0.90	-0.244	0.808
D <sub>2</sub> FSH (m IU/ml)	7.42	2.47	0.47	7.54	2.04	0.38	-0.188	0.852

**Table 1 - Baseline Characteristics**

Both groups have comparable baseline features.

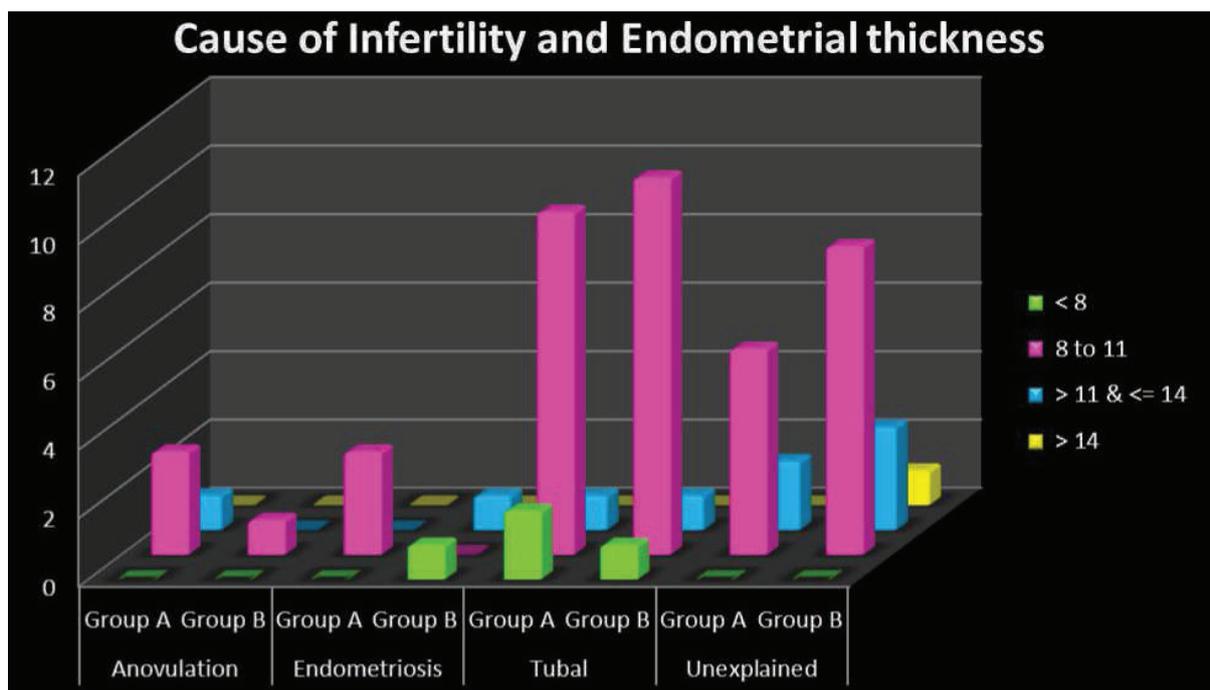
Group A patients had mostly secondary infertility (46.43%) and group B had predominantly primary infertility(72.41%).The predominance of primary infertility in group B and secondary infertility in group

A is not significant (NS) statistically (P<0.144) and the patients were selected based on random allocation. In table 2 and fig 2, the cause of infertility in the two groups was given. The major cause of infertility in both the groups were tubal factor (46.43 and 44.83%).

S.No	Endometrial Thickness (mm)	Anovulation		Endometriosis		Tubal		Unexplained	
		Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
1	< 8	0	0	0	1 (3.45%)	2 (7.14%)	1 (3.45%)	0	0
2	8 to 11	3 (10.71%)	1 (3.45%)	3 (10.71%)	0	10 (35.71%)	11 (37.93%)	6 (21.43%)	9 (31.03%)
3	> 11 & ≤ 14	1 (3.57%)	0	0	1 (3.45%)	1 (3.57%)	1 (3.45%)	2 (7.14%)	3 (10.34%)
4	> 14	0	0	0	0	0	0	0	1 (3.45%)

**Table 2 - Cause of infertility and Endometrial thickness**

Cause of infertility did not influence the endometrial thickness.(P<0.672,NS)



**Fig 2 - Major cause of infertility in both the groups was tubal factor.**

Table 3 shows the clinical findings of the two groups. No significant difference was observed in the duration of stimulation, amount of gonadotrophins utilized for stimulation and the number of dominant follicles. Though the number of oocytes retrieved and mature oocytes (MII) were more in group B, it is not significant statistically.

The endometrial thickness on the day of HCG trigger was between 7.1mm and 19 mm with the mean of 10.21mm .The mean endometrial thickness in the groups A and B were 10.02 + 1.46 ( 7.1 to 13.4 mm) and

10.40 + 2.19 (7.8 to 19 mm) and it was not significant statistically(P < 0.447). In our study, no patient had endometrial thickness < 7 mm. Both the groups had almost similar duration of ovarian stimulation (11.18 + 2.23 vs 10.72 + 2.07). The total dose of gonadotrophins used was comparable between both the groups (3334.82 + 1074.22 vs 3300 + 1091.46). The total number of embryos transferred was 3, grade 1 embryos which is similar in both the groups. It is evident that the cause of infertility has no influence on endometrial thickness.

Clinical Characteristics	Pregnancy outcome						Independent Samples t-test	
	Group A ( n = 28)			Group B ( n = 29)			t-Value	P value
	Mean	SD	SE	Mean	SD	SE		
Endometrial thickness (mm)	10.02	1.46	0.28	10.40	2.19	0.41	-0.766	0.447
Duration of Stimulation (days)	11.18	2.23	0.42	10.72	2.07	0.38	0.798	0.428
Total dose of gonadotrophins (IU)	3334.82	1074.22	203.01	3300.00	1091.46	202.68	0.121	0.904
No. of dominant follicles (DF)	8.32	4.88	0.92	9.66	3.76	0.70	-1.158	0.252
No. of Oocytes retrieved	8.43	3.70	0.70	9.86	4.10	0.76	-1.384	0.172
Total MII oocytes	6.68	3.03	0.57	8.31	2.61	0.48	-2.182	0.033
Fertilised	5.29	2.14	.40	5.83	2.14	0.40	-0.956	0.343
Cleaved	5.11	2.10	.40	5.55	2.21	0.41	-0.778	0.440

Table 3 - Clinical Characteristics

Pregnant and non-pregnant groups show no significant difference in the clinical characteristics.

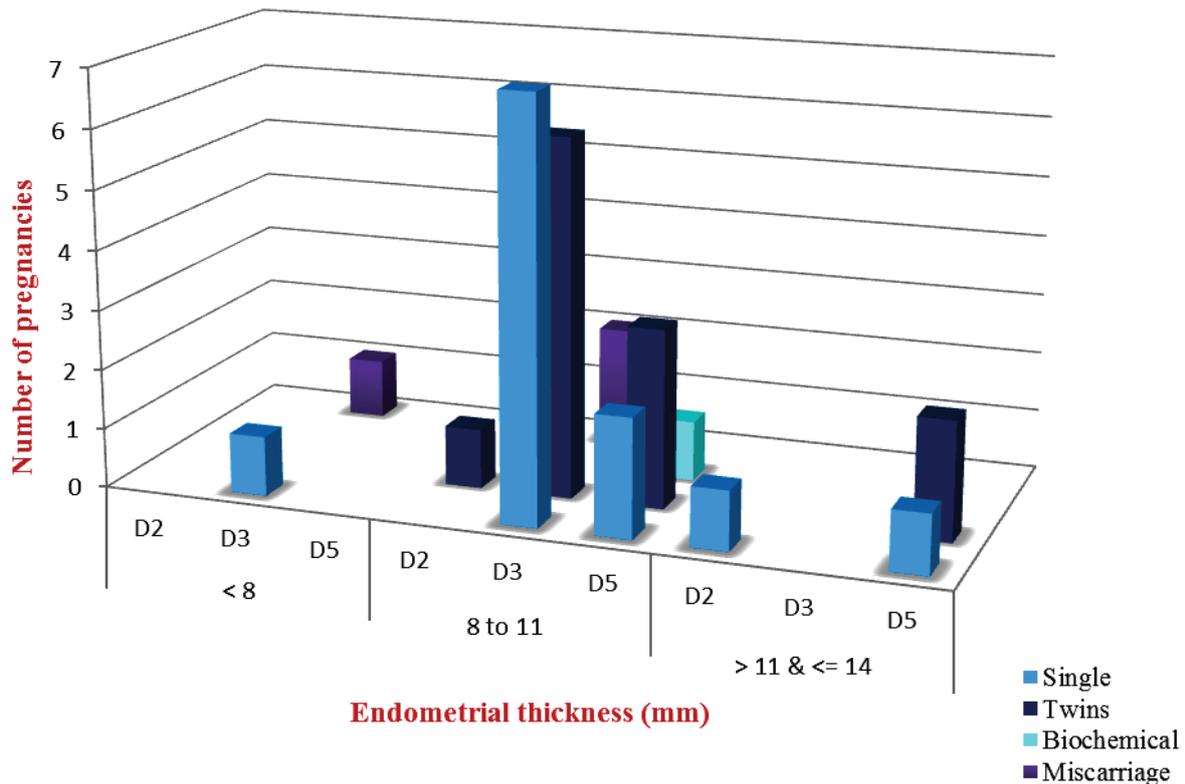
S.No	Endometrial Thickness (mm)	Day of Transfer	Pregnancy Outcome			
			Single	Twins	Biochemical	Miscarriage
1	< 8	D2				
		D3	1			1
		D5				
2	8 to 11	D2		1		
		D3	7	6		2
		D5	2	3	1	
3	> 11 & <= 14	D2	1			
		D3				
		D5	1	2		

Table 4 - Day of embryo transfer with positive outcome and Endometrial thickness

Endometrial thickness has no influence over pregnancy outcome

Table 4 and fig 3 shows the day of transfer with positive outcome and endometrial thickness. The mean day of embryo transfer for group A was 3.57 and group B was 3.66 which were similar between both the groups and not significant statistically. The pregnancy rate and clinical pregnancy rate of the study group were 49.12% and 42.10% respectively. The implantation rate was 22.81%. Pregnancy rate is good probably because of the selection of grade 1 embryos and limiting age of patients to < 35yrs.

Single and twin pregnancies were 12 (42.86 %) and 12 (42.86 %). The number of miscarriages was 3 (10.71 %) and we had one (3.57%) biochemical pregnancy with D5 transfer. The single/twin pregnancies were in the range of 8 to 11 mm endometrium mostly. Also we had miscarriages and biochemical pregnancy in that range of endometrium. Hence we could not arrive at a conclusion regarding influence of endometrial thickness and the outcome of pregnancy.



**Fig 3** - The above diagram shows the different pregnancy outcomes with different range of endometrium and the day of transfer.

## Discussion

Since the introduction of ART by Prof. Edwards and Mr. Steptoe in 1978, the success rate hovers around 40 to 45 %. Hence, to improve the success rate, various factors are analyzed from time to time. The pioneering work on human implantation was done by Hertig and colleagues 50 years ago<sup>25</sup>. Since then different opinions have emerged regarding implantation and now recently the focus is shifted to endometrial receptivity to identify the receptors. The present day receptor mediated model which estimates the window of implantation of the endometrium was described by Yoshinga and Wilcox<sup>26,27</sup>. Different ART cycle parameters and the outcome have been analysed and endometrial thickness is one such parameter which has been evaluated by several authors<sup>13,14,18,22,23,24,28,29,30</sup>. Adequate preparation of the endometrium is essential for a successful implantation to take place. Endometrial thickness reflects the enlargement of endometrium in the absence of uterine pathology.

In a study by Noyes et al (1995), analysis of 516 IVF cycles showed more pregnancies with the endometrial thickness of > 9mm<sup>23</sup>. Weissman et al (1999), found in a study that with thickness of > 14 mm the implantation rate was less. Also they found that the miscarriage rate was more when it was > 14mm on the day of trigger injection<sup>31</sup>. Likewise, in a study by Dickey et al., more biochemical pregnancies were found with endometrial thickness of >14 mm<sup>32</sup>. No pregnancy with endometrial thickness > 12 mm was reported by Rashidi et al<sup>12</sup>. However, there are case series which reported successful pregnancies when endometrial thickness was ≥ 20 mm. Quintero reported a single case of successful

pregnancy when endometrial thickness was ≥ 20 mm. However, later studies found absent influence of endometrial thickness on outcome of pregnancy<sup>13,18,34</sup>. Also in the latest study by Fang et al (2016), no unfavourable pregnancy outcome when endometrial thickness > 14mm was observed<sup>35</sup>.

In our study, one patient with endometrial thickness > 14 mm was negative for pregnancy. Hence it is difficult to comment on influence of increased thickness over pregnancy outcome. When there is an endometrial pathology as in Asherman's syndrome, the usual endometrial changes do not occur. Hence there is less implantation and more miscarriages. Though there are many studies showing successful pregnancies in cycles where the endometrial thickness of < 4mm was observed<sup>20</sup>, we have not seen a patient with < 7mm endometrial thickness in 830 ART/ICSI cycles since 2008 in our centre. Hence endometrial thickness < 7mm is an unusual occurrence in ART patients unless there is presence of uterine anomalies/pathology.

In our study majority of women had endometrial thickness > 8 mm with the mean of 10.21 mm. Our study does not conclude any adverse effect of endometrial thickness >14mm over pregnancy. No conclusive evidence from our study with regard to pregnancy mishaps like miscarriages. Nor does an ideal endometrium (8 to 11mm) guarantee a pregnancy. Though implantation of the embryo happens in the endometrium, we are not able to conclude that the thickness of the endometrium really has an influence on the favorable outcome of ART.

On the contrary, we feel the quality of embryos has a vital role in deciding the implantation of the embryos. Hence it seems obvious that the process of implantation is much more complex than what can be determined by a single and simple USG measurement of the endometrium<sup>36</sup>.

## Conclusion

We have limited the confounding factors which may have effect over implantation and then assessed the influence of endometrium on implantation of embryo. From our study, the endometrial thickness is not the deciding factor for the successful implantation of human embryo. We feel that a good quality embryo has more potential to implant in any reasonable environment and grow further. We also infer that thin endometrium of < 7 mm is an unlikely occurrence in ART cycles unless there is pathology in the uterus. Limitations of our study are it is a retrospective study and small number of patients analyzed.

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# Original Article

## Profile of Low Responders in Assisted Reproductive Technology - A Retrospective Study

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### Abstract

**Aim:** To analyse the various features (categorical and variables) associated with low responders in Assisted Reproductive Technology (ART). **Materials & Methods: Design:** Retrospective Study. **Setting:** Department of Reproductive medicine, Chettinad Hospital and Research Institute, Kelambakkam, Tamil Nadu, India. **Patients:** Out of 200 patients undergoing ART cycles (From January 2008 to March 2010) at Chettinad Hospital, 25 patients who had low ovarian response were analysed. **Intervention:** All of the 25 patients had been down regulated with GnRH analogue (Leuprolide acetate) 1mg in short protocol and stimulated with U. HMG/FSH with a minimum dose of 225 IU and for a period of 10 days. **Main Outcome Measures:** This review will describe the profile of women who showed low response to ovarian stimulation. **Result:** Incidence of low response was 12.5%. The profile of patients with low responders in our study showed a mean age of 34.1 years, mean period of infertility of about 8.1 years, low antral follicular count, interestingly low response was also observed in women with proven fertility that is after tubectomy. **Conclusion:** Women with low response had low antral follicular count, higher basal FSH, Required higher dose and longer period of stimulation. Low ovarian response was observed in younger women also. Prior pelvic surgical history was observed in significant number of women.

**Key Words:** Low Responders in ART, Low ovarian response, GnRH analogue

### Introduction

Despite the vast understanding of controlled ovarian stimulation protocols, there are still a group of women who do not respond well to ovarian stimulation and yield few oocytes at retrieval, resulting in few numbers of embryos and poor pregnancy rates<sup>1</sup>.

This low ovarian response is one of the most controversial and frustrating issues in Assisted reproduction. Though a variety of regimens have been tested to improve ovarian response, the results are not comparable and an ideal stimulation protocol does not exist, as homogenous population was not tested in any clinical trials<sup>2-6</sup>. It is difficult to estimate the exact prevalence of low ovarian responders, because of its varied definition though reported to be 5-24% of patients undergoing In vitro fertilization (IVF)<sup>7</sup>. This review will describe the profile of women who showed low response to ovarian stimulation in our study.

### Definition

The pathogenesis, prediction and possible treatment options for low ovarian response have been published

in numerous journals. Despite the wide spread use of the term low ovarian response to gonadotropins, no standard definition exists<sup>8-11</sup>.

First realistic attempt to standardize a simple and reproducible definition was presented at ESHRE scientific community held in Bologna in 2010<sup>12</sup>. It is defined as low ovarian response when at least two of the following criteria were present:

- (i) Advanced maternal age ( $\geq 40$  years) or any other risk factor for low ovarian response
- (ii) Previous low ovarian response resulting in less than 4 eggs to stimulation &
- (iii) Abnormal ovarian reserve test (AMH 0.5-1.1 ng/ml or AFC 5-7).

In this definition the importance is given to the response to stimulation. Two episodes of low ovarian response after maximal stimulation are sufficient in the absence of advanced maternal age or abnormal ovarian reserve test to define low ovarian response.

Since it is the response to stimulation, it is essential to

have at least one stimulated cycle. However women with abnormal ovarian reserve test and advanced age can be considered as expected low responders<sup>13</sup>.

ESHRE consensus on the definition of low ovarian response was criticized as<sup>14</sup> -

1. The study population was diverse
2. Detailed risk factors were not explained
3. Clear cut cut-off for the ovarian reserve test were not suggested especially, in case of Anti Mullerian Hormone
4. Bologna criteria was based on previous studies rather than scientific experiments
5. The number of oocytes were quantitative rather than qualitative and was not outcome (prognosis) based predicting the results of in vitro fertilization.

### Aetiology of Low Ovarian Response

Beyond the well-established relation between advanced maternal age and low ovarian response to gonadotropins, there are number of other factors, which may be important<sup>15,16</sup>. Previous ovarian surgery, ovarian endometriosis, Pelvic inflammatory disease, systemic illness, radiotherapy, chemotherapy, chronic smoking, environmental factors, and specific conditions affecting the ovaries may all influence the ovarian response to gonadotropin stimulation<sup>17-22</sup>.

Short menstrual cycle, endometriotic cystectomy and chronic smoking have been associated to affect both the quantity as well as quality of retrieved eggs, hence the pregnancy rate<sup>23,24</sup>. Our study analyses the various features associated with Low responders in ART. Numerous categorical and numerical variables were analyzed in the study.

### Materials and Methods

This is a retrospective study of 200 ART cycles between January 2008 and March 2010 at Department of Reproductive medicine, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu, India. All of them had down regulation with GnRH analogue (leuprolide acetate 1mg) in a short protocol and stimulation with u-HMG/FSH with a minimum dose of 225 IU and for a minimum period of 10 days.

Several numericals such as age, body mass index (BMI), number of present children, number of previous IVF cycles, serum follicle stimulating hormone (FSH), total gonadotropin dose administered, number of total and mature oocytes, and number of embryos transferred] and categorical variables (infertility diagnosis, period of infertility, previous ovarian surgery, tubectomy, abnormal menstrual pattern) were recorded.

The eligible cohort were women with follicular response of three or less dominant follicles on the day of HCG trigger. This group of women was taken as low responders and their association with other categorical and numerical variables was analyzed.

### Results

The incidence of low responders was 12.5% [25/200] in our study group(Fig 1). The age distribution was 22

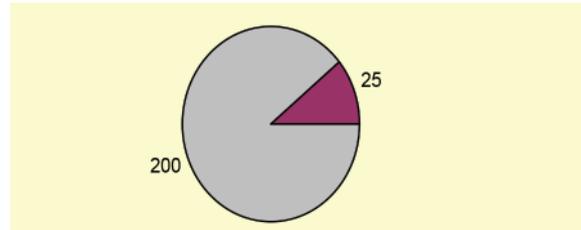


Fig 1 - Incidence of low responders

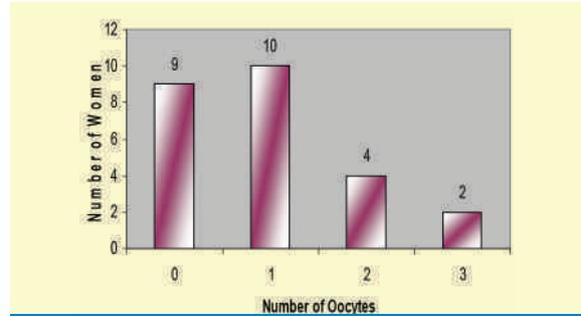


Fig 2 - Oocyte yield in women analysed

women < 40 years, 3 women > 40 years. Primary infertility was the predominant type in 80% women. Prolonged period of infertility was observed in 85% of women [> 5 years]. We had interestingly 9 women out of 25 [36%] with history of pelvic surgeries/ adhesions. Low response was seen in 3 women who had undergone tubectomy (Table 1). 2 out of 25 women [8%] had history of surgery done for endometriosis. Menstrual history was normal in 92% of women. BMI above 30 was observed in 16% of these women.

Stimulation dose of 300 IU of u- FSH/HMG per day for 10-15 days was used in the majority -76%. The total antral follicular count was less than 5 in 68% of women.

Basal FSH value was >10 in 56% and <10 in 44%. Adequate endometrial thickness was seen in 88% of women. No oocyte was obtained in 9/25 women [36%] Fig 2 . Only 9 women reached stage of embryo transfer [36%]. Some prior good responders showed a subsequent low response in repeat cycle [4 women] (Table 2).

PARAMETERS	FREQUENCY (%)
TOTAL NUMBER OF WOMEN WITH LOW OVARIAN RESPONSE	25/200 [12.5%]
CYCLE CANCELLED	5 [20%]
OPU DONE - NO OOCYTE	9 [36%]
OOCYTE OBTAINED	16 [64%]
EMBRYO TRANSFER DONE	9 [36%]

Table 1 - Parameters of the women analysed in the study

### Discussion

Ovarian age is an independent variable critically affecting IVF outcome, while chronological age assumes a less important prognostic role, once the diagnosis of diminished ovarian function has been made<sup>26-28</sup>. This

theory is supported by previous reports that stressed that the age at which the ovarian reserve declines is highly variable and therefore age alone could have a limited predictive value with respect to reproductive potential. In fact, AFC and AMH Levels, as a measure of ovarian reserve, has been shown to be a better predictor of a woman's chance to conceive than her chronological age<sup>24</sup>.

Low Responders	Feature	Percentage
Serum FSH	>10 miu/ml	56%
AFC	<5 AFC	68%
DOSE OF GONADOTROPINS	Required 300 iu and above	76%

**Table 2 - Features of low responders**

In assisted reproduction programs, the performance of "good responders" or "low responders" to exogenous FSH is individualized and the ovarian response to intense gonadotropin stimulation is difficult to predict. The response to stimulation can be low even in some patients, who showed no abnormal ovarian reserve tests.

Even though various predictive markers like antral follicle count, FSH, AMH, age, ovarian volume and ovarian Doppler flow pattern have been studied, serum AMH & antral follicle count takes a better predictive value. Combined application of both has been considered more reliable, whereas Serum AMH has not been assayed in our study<sup>29-31</sup>. Although antral follicle count is measured in all patients, objective reporting by the same observer was not available for all patients<sup>32,33</sup>. The Practice Committee of the American Society for Reproductive Medicine supports the use of AMH as a screening test for low ovarian response than the use of AFC<sup>34</sup>.

It is critical that women considering IVF have proper ovarian reserve testing to be sure that they are not wasting their time, money, or emotions by pursuing IVF, when it has little or no hope of success. Poor success rate in IVF cycle in patients with low responders puts the couple in to a real state of confusion and concern to proceed to fertility treatment of ART.

The ultimate goal of every ART cycle is a live birth. The challenge is more in the low responder group. Although various protocols and drugs have been suggested to improve the outcome, the ideal drug and regime remain elusive.

## Conclusion

The profile of the Low responders in our study showed a mean age of 34.1 years, with mean period of infertility of 8.1 years. Low ovarian response was observed in younger women also [52% in women <35 years]<sup>23,24</sup>.

Low antral follicular count was observed in majority. Low response was not always consistent with higher basal FSH levels<sup>25</sup>. Prior pelvic surgical history was observed in significant number of women. Low response was also observed in women with proven fertility, that is after tubectomy. Higher dose and

longer period of stimulation were required in these women. Higher dose of stimulation did not alter the outcome. None of the poor responders had a positive pregnancy outcome in our study.

The authors declare no conflict of interest.

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# Original Article

## Pre Macular Subhyaloid Haemorrhage- A Prospective Clinical Study

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### Abstract

**Aim:** Subhyaloid hemorrhage is usually a benign condition which does not cause much vision loss and usually will resolve spontaneously. Long standing premacular subhyaloid hemorrhage cause permanent loss of visual acuity as it involves the fovea. The aim of this study is to investigate the effects of drainage of premacular subhyaloid hemorrhage into the vitreous with Argon Green laser treatment. **Materials and Methods:** This study was conducted between February 2014 and March 2015. Six patients with premacular hemorrhage in one eye subjected to Argon Green laser to drain the blood into the vitreous cavity. The causes for hemorrhage was Anaemic retinopathy (1case), proliferative diabetic retinopathy (1 case), Terson syndrome (1 case), pancytopenia (1case ) and blunt ocular trauma (2 cases). **Results:** The mean size of pretreatment hemorrhage was 4.5 disc diameters (range 3.5-8.0). Visual acuity in all cases before laser treatment was hand movement to 6/60 . There was rapid improvement of vision after laser treatment. Drainage was complete within one week and visual acuity improved dramatically. The mean follow-up was 12 months .No retinal damage or rebleeding except ILM folds (not significant) occurred due to the laser. **Conclusion:** Argon green laser posterior hyaloidotomy may be useful for draining a premacular hemorrhage into the vitreous cavity in selected cases as it is a non-surgical procedure. To establish this as a routine procedure, a randomized prospective study is needed to compare observation, primary vitrectomy, and Argon green laser treatment.

**Key Words:** Sub Hyaloids Hemorrhage , Argon Green Laser

### Introduction

Subhyaloid hemorrhage is defined as a localized detachment of vitreous from the retina caused by the accumulation of blood, which can lead to sudden and severe loss of vision, when it takes place in the macular area<sup>1</sup>. The various causes for Subhyaloid hemorrhage include retinal vascular disorders such as proliferative diabetic retinopathy, branch retinal vein occlusion, macro aneurysm, and age related macular degeneration; it may occur in hematological disorders also such as leukemia and chemotherapy induced pancytopenia or after retinal vascular rupture associated with physical exertion (Valsalva retinopathy)<sup>2</sup>. Valsalva retinopathy often occurs in healthy young adults due to lifting heavy things, straining in toilet, vomiting, coughing. Usually there will be spontaneous resorption of the blood entrapped in subhyaloid space. But sometimes it may take months and can cause permanent visual impairment due to pigmentary macular changes or formation of epiretinal membranes and toxic damage to the retina due to prolonged contact with hemoglobin and Iron. There are various methods available to treat premacular hemorrhage<sup>3</sup>. These include conservative treatment, Argon Green laser hyaloidectomy, pars plana deep vitrectomy and pneumatic displacement of hemorrhage by intravitreal injection of gas and tissue plasminogen activator. Puncturing the posterior hyaloid face with argon green or Nd YAG laser is a safe

and easy alternative for releasing the entrapped subhyaloid blood into the vitreous<sup>4</sup>. Consequently, the obscured macular area is cleared and resorption of blood cells is facilitated. In this study we evaluated 6 patients with subhyaloid hemorrhage treated with argon green laser hyaloidotomy.

### Materials and methods

This is an interventional case-series in which 7 eyes of 6 patients with premacular subhyaloid hemorrhage were included between the period of one year (2014 to 2015) in Chettinad Hospital and Research Institute. Patients who gave their consent were included in the study and patients with other retinal hemorrhages were excluded. The patients were subjected to complete evaluation with detailed history taking. Pretreatment and post treatment examination included best corrected visual acuity, slit lamp microscope examination, intraocular pressure, and funduscopy. Fundus photographs were taken to measure the size of the subhyaloid hemorrhage by comparing with optic disc dimensions. After a written consent Tropicamide eye drop was applied to dilate the pupil and paracaine was used for topical anesthesia. ARGON GREEN laser was applied through a slit lamp and a Goldman three-mirror (Volk) lens with an average total energy of 500 mj (range: 200 to 600 mj). Laser was applied to the lower-most dependent part of the blood-containing

subhyaloid pocket in order to enhance the blood release process and better protection of the underlying retina. Patients were periodically followed up on 2nd day, 1st week, 2nd week, and at the end of the study. The main outcome measured in this study were postoperative improvement in visual acuity and postoperative complications. The success rate in performing hyaloidotomy, releasing the entrapped blood into the vitreous cavity and its resorption also were recorded and analyzed.

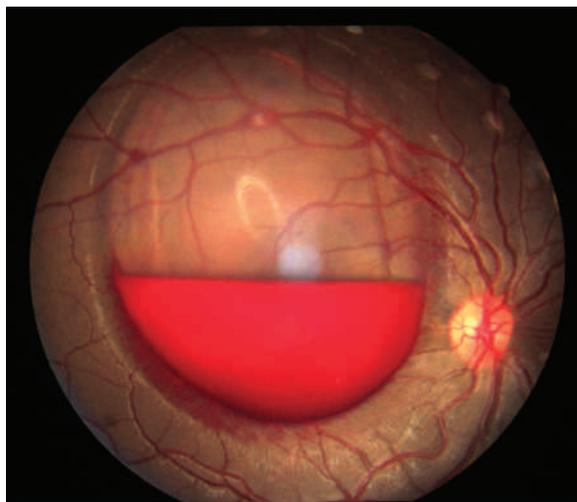
## Results

Totally seven eyes of 6 patients were included out of which 4 were males (60%) and 2 females (40%), with an average age of  $33 \pm 10.33$  years (range: 31 to 67 years). One (66.7%) had diabetic retinopathy, two had blunt trauma, one (8.3%) had a pancytopenia due to chemotherapy, one had Terson syndrome and 1 (25%)

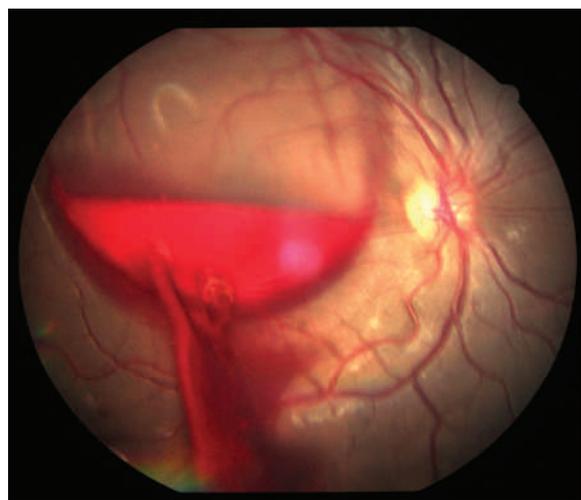
was diagnosed with Anemic retinopathy as the main cause of their premacular hemorrhage. The mean pretreatment hemorrhage measured  $4.5 \pm 1.7$  disc diameters. Argon green laser hyaloidotomy was successful in all cases and the trapped blood was released into the vitreous cavity and resorbed after a mean period of 10 (6 to 16) days. Preoperative visual acuity in the affected eyes of these patients ranged from hand movement to 6/60, which was improved from 20/40 to 20/20 postoperatively. Patients with the diagnosis of blunt trauma retinopathy achieved normal vision after treatment and the improvement was better when compared with others. Table 1 summarizes patients' characteristics and postoperative results. In our study there were no special complications like rise in intraocular pressure, retinal and choroidal hemorrhage, macular hole, or retinal break noted in follow up period of 12 months.

PATIENT	AGE	OD/OS	DIAGNOSIS	DURATION OF HAEMMORRHAGE	VA BEFORE TREATMENT	VA AFTER TREATMENT
1	19/M	OS	BLUNT TRAUMA	1 DAY	3/60	6/6
2	47/F	OS	BLUNT TRAUMA	10 HRS	HM	6/6
3	22/F	OD	ANAEMIC RETINOPATHY	1 DAY	1/60	6/6
4	23/M	OD	TERSON SYNDROME	2 DAY	HM	6/6
5	55/M	OS	NPDR	1 DAY	2/60	6/9
6	24/M	OU	PANCYTOPENIA	16 HRS	2/60 , 1/60	6/12

**Table 1:** Summary of patients' characteristics and postoperative results



**Fig 1:** Showing Right Eye Subhyaloid Hemorrhage Due to Blunt Trauma Before Treatment



**Fig 2:** Showing Laser Mark and Draining of Hemorrhage after 1 Hour of Treatment

## Discussion

A subhyaloid hemorrhage is an intraocular collection of blood that remains contained in a self-created, previously nonexistent space, usually between the posterior limiting layer of the vitreous and the retina<sup>5</sup>.

Posterior hyaloidotomy was done using Argon Green laser in 6 patients who had premacular subhyaloid

hemorrhage. The trapped blood was released into the vitreous and resorbed within 6 to 16 (average: 9) days in all of them. There was at least 4 lines (Snellen chart) improvement in their visual acuity within 16 days of the laser in all of the cases<sup>6</sup>. In our study the visual improvement seen in trauma cases was better than other cases.

The best corrected visual acuity (BCVA) improved to

20/20 following laser in 4 out of 6 cases (66%). This can be explained by lack of retinal vascular lesions<sup>7</sup> or any retinal pathology in the cases except for diabetic retinopathy.

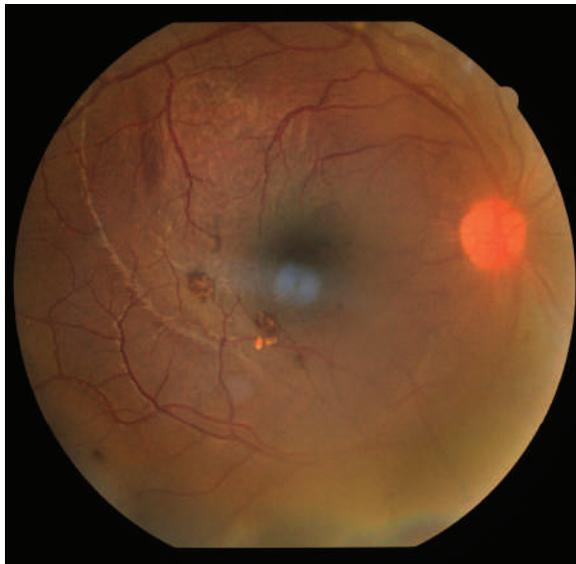
In study by Ulbig et al, which included 21 patients with premacular subhyaloid hemorrhage laser hyaloidotomy was successful in 16 (76.2%) and visual improvement in all of them. This was similar to our study. Final visual acuity was better in patients with Valsalva retinopathy compared with other etiologies<sup>8</sup>.

Similarly Rennie et al., also studied 10 patients with premacular subhyaloid and did Nd-YAG laser hyaloidotomy in 6 patients while he conservatively managed the other 4 patients<sup>9</sup>. There was rapid improvement of hemorrhage in all the patients and there was no complication similar to ours.

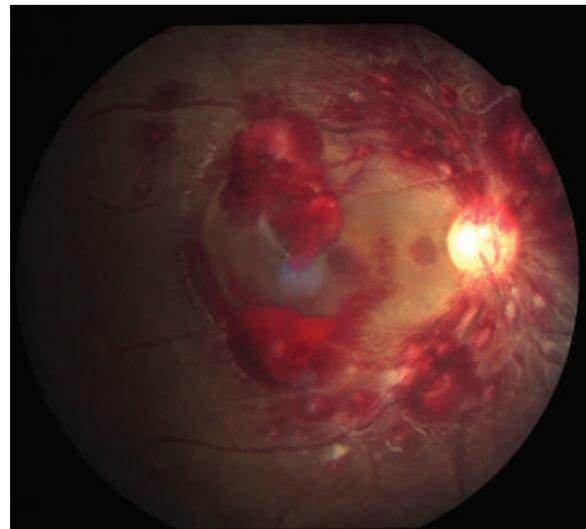
In the study by Gabel et al, 3 patients were managed successfully with Nd-YAG laser hyaloidotomy and one patient with Valsalva retinopathy after military operation gained full vision postoperatively<sup>10</sup>.



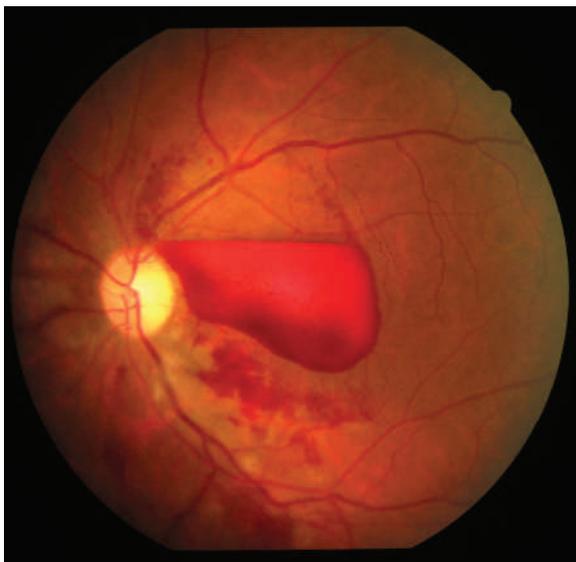
**Fig 5:** Showing Laser Marks and Drainage of Hemorrhage after Laser Treatment



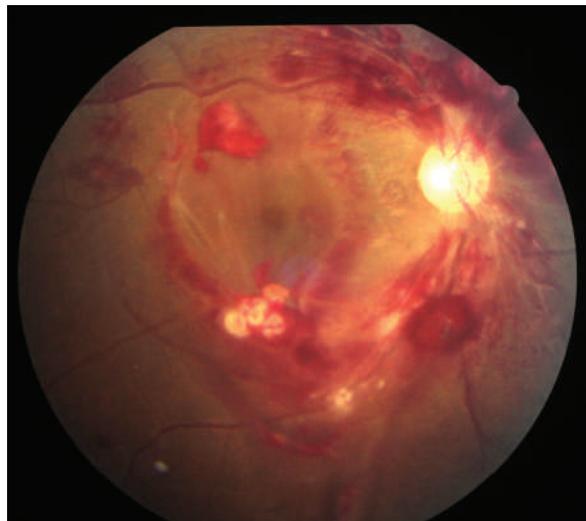
**Fig 3:** Showing Normal Fundus with Laser Mark after 1 Month of Treatment



**Fig 6:** Showing Pancyclopic Retinopathy in Right Eye



**Fig 4:** Showing Subhyaloid Hemorrhage Due to Terson Syndrome Before Treatment



**Fig 7:** Showing Laser Marks and Drainage of Hemorrhage after Laser Treatment

## Conclusion

As observed by our study and several previous studies we can conclude that Argon green laser hyaloidotomy is a simple, inexpensive outpatient procedure which is relatively safe compared with other more complex operations such as deep vitrectomy and its potentially serious complications.

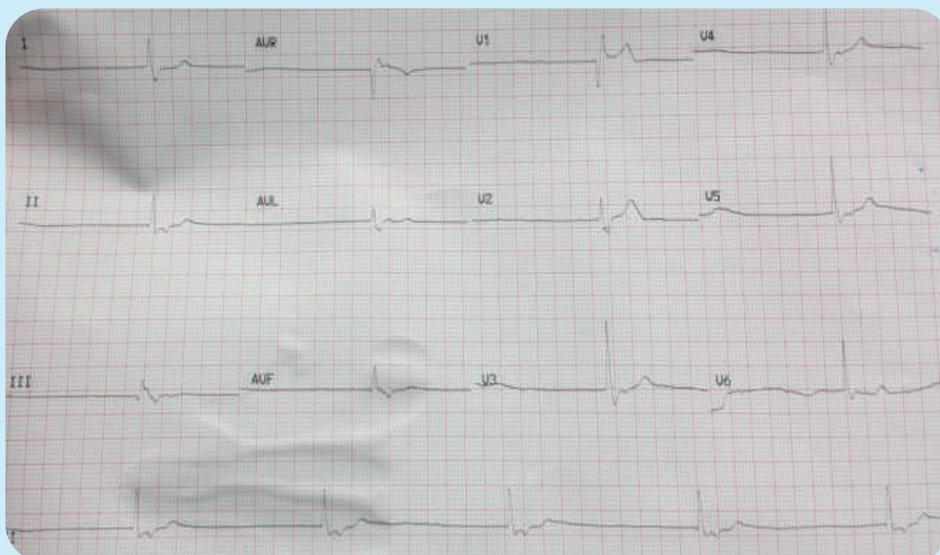
There is a rapid visual recovery in majority of the patients and it can prevent long-term entrapment of blood and its adverse effects on macula including potential permanent loss of vision. However, the drawback of this study is lack of comparison between other methods. So further large centre clinical trials is necessary to compare the visual and functional outcomes between observation, laser and vitrectomy in subhyaloid hemorrhage.

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### Diagnose the condition

A middle aged male presented to our ER with complaints of giddiness for the past 1 hour after taking a dose of T.atenolol 50mg. His ECG is given below



Dr. M.Chokkalingam, Consultant Cardiology, CSSH.

Answer in page : 47

# Review Article

## Otitis Media and Middle Ear Effusion - An Overview

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### Abstract

Otitis media and middle ear effusion are major health care burden across the globe. The prevalence in developing countries mostly exceeds the WHO stipulated emergency level of 4 %. Failure of Eustachian tube function is key pathogenic element of effusion in middle ear cavity involving complex pathophysiology. Acute otitis media accompanies upper respiratory infection or allergy. Its acute symptoms almost always attract treatment yet, on resolution of acute stage effusion over brief period, occurs in middle ear cavity. Recurrences are driven by risk factors. Chronic effusion is not symptomatic but impairs hearing function that adversely affects intellectual and behavioural development of children. Untreated infection coupled to risk factors would cause suppurative otitis media and perforation of ear drum. The later accompanies purulent ear discharge, and threatening complications for middle ear integrity and intracranial abscess and thrombosis. The narrative attempts to overview approaches to timely diagnosis and medical and surgical management in current practice for spectrum of the disease.

**Key Words:** Otitis media, Middle ear effusion, Chronic suppurative otitis media, Ear infection

### Introduction

Otitis media (OM) simply means inflammation of middle ear. Hearing loss due to OM is worldwide public health issue. Acute otitis media complications occur in children and old while those due to chronic disease occur in young adults, particularly as cholesteatoma. Patients with intracranial complications remain hospitalized for long periods of time with significant disability and mortality. High incidence of OM in face of inaccurate diagnosis and possible serious sequel make it important health challenge. The disease spectrum may vary from self-limiting to prolonged and complicated disease.

Acute otitis media (AOM) is mostly due to infection and is among commonest maladies in paediatric outdoors. Spontaneous healing takes place in many during adolescence years, however intervening years cast significant impact on academic performance. Virtually all children by age of 6 may get at least one episode of otitis media. Most regions of developing countries have prevalence of otitis media above 4% constituting emergency as per WHO stratification<sup>1</sup>.

### Otitis media and Middle ear effusion

AOM involves rapid onset of symptoms and signs of up to three weeks duration. After an episode of AOM there is high incidence of persisting middle ear effusion of mean duration of 40 days<sup>2</sup>. It is classified as recurrent acute otitis media (RAOM) if three episodes occur in six months or four in twelve months and there is otoscopic normalization during the inter-crisis period<sup>3</sup>. Chronic otitis media with effusion (CSOM) indicates middle ear inflammation with liquid collection in

middle ear space (ME). Chronic disease is variously stated as serous/secretory OM or glue ear. It implies presence of fluid in middle ear for three months or longer. Tympanic membrane is intact and there may not be signs and symptoms of infection. Middle ear effusion may be serous thin watery liquid, mucoid-thick, viscid, mucus-like liquid or purulent pus like liquid. Discharge from ear is termed otorrhea.

Ventilation is essential for regulation of pressure within ME for optimal hearing function. Normal Eustachian tube (ET) structure and function protects ME from abnormal nasopharyngeal sound pressures and secretions. Pumping action of ET to drain ME fluid involves beginning of passive closure at ME end which progresses toward nasopharyngeal end. Eustachian tube (ET) has ability to open up during swallowing which equilibrates pressure of ME and nasopharynx. Posture also affects ET function. Elevation from horizontal position causes venous engorgement of the ET reducing air passage. Functionally and structurally immature ET as well as the immune system is determinants of susceptibility of babies to otitis media. Role of genetic predispositions have been suggested as well<sup>4</sup>. Children with their short, floppy ETs can reflux nasopharyngeal secretion in to middle ear during an acute respiratory viral infection. Nasopharyngeal secretion cannot enter ME with normal ET function, as gas cushion entrapped in intact ME and mastoid air cell system opposes that.

### Pathogenesis

Pathogens must enter middle ear cavity (ME), through ET from bacteria and virus reservoir in rhinopharynx.

The normal tubo-tympanum is immunologically protected not only by the adaptive immune system, but also by the mucociliary system and the selected molecules of innate immunity<sup>5</sup>. Viruses in nasopharynx damage mucociliary function and facilitate nasopharyngeal bacterial adherence and colonization and subsequent entry in to ET<sup>6,7</sup>. An obstructed ET leads to negative pressure in ME following reduced ventilation. Such state when prolonged causes overgrowth of mucus producing cells and fluid transudation in ME.

Bacterial and viral infection as well as sterile effusion stimulates release of proinflammatory cytokines from mucosal immune cells. Adhesion receptors in submucosa are up-regulated mediating lymphocyte invasion and accumulation, which secrete cytokines and other inflammatory mediators. The later affect leakage of fluid from mucosa<sup>8</sup>. Nitric oxide and free radicals are implicated in persistent ME effusion<sup>9,10</sup> at stage when there is vascular engorgement and angiogenesis increasing mucosal blood flow. Increase of nitrogen in microcirculation adds creation of negative ME pressure<sup>11</sup>.

When clearing function and immune system fails to eliminate them otitis media results. Mucus accumulation allows proliferation of infecting *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*. Bacterial endotoxin may impair mucociliary activity, induce effusion, enhance mucus production and cause mucosal metaplasia. Such changes help transformation of planktonic pathogens in to biofilm. Biofilm bacteria are difficult to culture and resistant to antibiotics, hence long persists. Emerging evidence indicates that, following upper respiratory tract infection, biofilm activity in the adenoid produces a cascade of immune mediators, causing inflammation and up-regulation of mucin genes in the middle ear mucosa, with associated reduction of ciliary function and clearance. It is likely that middle ear ventilation helps disrupt the biofilm infection by increasing and maintaining high middle ear oxygen tension.

Otitis media with effusion, OME is said to result from "hydrops-ex-vacus" mechanism. It is postulated that failure of ET opening causes gas exchange from ME to microcirculation of mucus membrane. As per Doyles postulate, possible increase in circulating inflammatory mediators from local allergic reaction in nose or stomach mucosa inflict alteration of ME-mucosal permeability and thus altered gas exchange<sup>11</sup>. This results in under-pressure within ME that enforces transudation and effusion. Upper respiratory infection may cause ET block inducing effusion as above. Allergic reaction also may adversely affect structure of ET mucus blanket<sup>12</sup>.

Chronic suppurative otitis media is the chronic stage following AOM, when there is TM perforation and continuous discharge. CSOM pathogenesis involves loss of ME gas cushion due to TM perforation. In such state, allergic or inflammatory states of nasopharynx promote reflux of infected fluid through ET to ME. When tympanic membrane is perforated or following radical mastoidectomy, the gas pocket is lost. Nasopharyngeal fluid can now reflux through ET in to ME<sup>13</sup>. Similar mechanism is basis of otorrhea after

tympanostomy tube insertion or mastoidectomy. Initially it is organisms as *H. influenzae* and *Streptococcus pneumoniae*. With setting of otorrhea, organisms from external auditory canal such as staphylococci and *Pseudomonas* invade ME causing chronic infection.

## Risk Factors

Adenoids serve as bacterial reservoirs<sup>14</sup>. Frequent upper respiratory infections predisposes to RAOM and COME by way of inflammation and harm to mucociliary movement of ET epithelium. This may lead to atelectasis of tympanic membrane-middle ear (the high negative middle ear pressure), sterile OME or acute bacterial otitis media. Passage of nasopharyngeal fluid through ET to effusion containing ME may create mixed state seen as recurrent acute bacterial otitis media. Bacterial biofilm formation on ME mucosa fosters chronic effusion state<sup>15</sup>. Significant mucus content in ME effusion indicates antecedent acute infective otitis media.

Allergy is one of etiological factors of otitis media, as evident from strong association. The OME children have 4 fold higher incidence of atopic symptoms<sup>16</sup>. In a study increased IgE in middle ear effusion was found in 14 of 32 children with allergic rhinitis in contrast to only 2 of 45 non allergic cases<sup>17</sup>, IgE does affect ME effusion.

Involvement of gastro-esophageal reflux is also believed to contribute to pathogenesis<sup>18</sup>. Exposure to pH under 4 of the ET results in ciliostasis, inflammation, edema and epithelial damage.

## Epidemiology

Otitis media with effusion (OME) is most prevalent in children of 2 to 5 year age. The natural course shows constant improvement in half the sufferers over next three months. Recurrence is high in almost half the cases over a year period. The factors that cause persistence and recurrence in the victims need characterization for primary and secondary prevention.

Otitis media is universally present in infants with untreated cleft palate. Primary cause is failure of opening mechanism of ET. The risk factors influence one or more causal mechanisms viz. race, sex, age which influence structure and function of ET. Age affects immune competence also.

Age is important and several predisposing anatomical, physiological and immunological determinants make children vulnerable. Early first episode itself increases risk for recurrence and chronic otitis media. Male sex appears to have marginally higher susceptibility. Socio-economic strata are important determinants as well. ET obstruction may be acute or chronic. Periodic ET opening helps prevent accumulation of ME effusion. ET dysfunction is seen prominently during pregnancy and during puberty in female suggesting hormonal influence also<sup>19</sup>. Significant hereditary determinants are understood from high familial aggregation of the disease<sup>20</sup>.

Children with anatomical defects (cleft palate, submucous cleft), altered physiological defenses (ET dysfunction, barotraumas), congenital or acquired

immunologic deficiencies (immunoglobulin deficits, chronic granulomatous disease, AIDS, immunosuppressive drugs) are at vulnerable to severe and recurrent or persistent disease<sup>21</sup>. Infants exclusively breast fed in first 3 to 6 months are somewhat less vulnerable<sup>22</sup>. Crowded living conditions, poor sanitation and inadequate medical care have been associated with otitis media<sup>23</sup>. Increased incidence associated with exposure to passive smoke is reported<sup>22</sup>. Sulphur dioxide pollution of environment increases both pneumococcal diseases and otitis media. Seasonal preponderance with upper respiratory infections in winter is also seen.

## Diagnosis

Redness of eardrum is relied as diagnostic sign of AOM. Most important distinction between OME and acute otitis media (acute suppurative otitis media) is that the signs and symptoms of acute infection (eg. otalgia, fever) are lacking. Diagnosis cannot be based on symptoms alone because they are too vague. OME diagnosis, estimate of accompanying hearing loss and risk of complications critically determine development of quality screening, treatment and intervention programme. Specific subjective and objective measures help this<sup>24</sup>.

Four characteristics of tympanic membrane, position, mobility, colour and degree of translucency are evaluated. Microscopic otoscopy is of utmost importance for examination of the ear. It also offers the possibility of documentation of the pathology. Pneumatic otoscopy is also a sensitive and specific method for the detection of otitis media. Opacification of the tympanic membrane can be frequently detected. Pneumatic otoscopy reveals either a retracted or convex tympanic membrane with decreased mobility. Tympanometry is useful for assessing tympanic membrane mobility and middle ear function. Pure-tone audiometry or visual reinforcement audiometry (VRA) can be used to diagnose mild hearing loss associated with OME in infants. Adjunct procedures in evaluating recurrent disease include X-ray of nasopharynx and nasopharyngeal fibroscopy to assess adenoid size, nasal examination (septum deviation, enlarged turbinates), immunologic evaluation, allergy testing, etc. Tympanocentesis is the gold standard to detect fluid in ME and sampling the same for culture or PCR typing is when there are craniofacial malformations, or the degree of hearing loss is disproportionate to clinical findings or when sensorineural hearing loss is detected, high resolution CT and MRI scans are helpful to identify the middle ear abnormalities.

OME patients do not present primarily for hearing loss, instead poor speech and language development, inattentiveness in class, behavioural problems and reduced or poor social interaction with other children are the reported concerns. In most cases hearing loss is major sign or symptom. Some children also suffer balance problems and become clumsy<sup>25</sup>. History of recurrent episodes of OM or developmental concerns and audiometric hearing loss detection facilitate diagnosis. Three month monitoring of hearing status helps decision for surgical intervention. Hearing in better ear at 25-30 dB or worse constitutes indication for surgery.

It is important to identify children at risk for possible developmental sequel of OME, including speech language delay, and behavioural problems. Children who develop OME and have additional disabilities including sensorineural hearing loss, autism, syndromes (eg. Down syndrome), learning disabilities as well as other conditions, are at greater risk of persistent OME and conductive hearing loss.

## Management perspectives

Organisms causing AOM are *Streptococcus pneumoniae* or *Haemophilus influenzae* in over third of cases each. A quarter of cases are due to *Moraxella catarrhalis*. Rhinovirus infection contributes to prolong ME effusion<sup>26</sup>. In half the instances *S pneumoniae* is penicillin resistant.

50% of cases of OME, effusion is not sterile and PCR is positive in up to 75% for microbial DNA. Initial benefits of antibiotic therapy are only transient and hence not recommended as routine. There is limited evidence for short term improvement of OME with intranasal steroids<sup>27</sup>. Currently only limited evidence exists on benefit of pneumococcal vaccine in OME prevention. It may be advised in cases with underlying predisposing factors<sup>28</sup>.

Newly diagnosed OME in children is found to resolve in half the cases within 1 month, in three fourth cases by 6 month to around in 90 percent in one year. The recurrence rate is high and over some years 30 to 40 percent children suffer repeated episode. Most children with persistent OME require insertion of grommet tube. In older children nasal auto-inflammation is helpful before surgical help. Following grommet surgery, otorrhea can occur either following an upper respiratory infection or water contamination through the grommet. The tube may get blocked or extruded. Otorrhea responds to short course of antibiotic ear drops.

Chronic suppurative otitis media (CSOM), is chronic inflammation of middle ear and mastoid cavity with perforation of tympanic membrane and purulent discharge through same. The disease has usual beginning in childhood. CSOM is heavy disease burden in developing countries with reported 72 cases per 1000 population prevalence<sup>29</sup>. Untreated CSOM has broad range of complications related to spread of infection in adjacent structures and damage of middle ear itself. The complication range from persistent otorrhea, mastoiditis, labyrinthitis, facial nerve palsy and intracranial abscess and thromboses<sup>30</sup>. The aim of management is to achieve safe dry ear, eradication of disease and hearing improvement.

Early effective treatment helps avoid complications. Treatment can be medical therapy directed at eradicating pathogenic aerobic and anaerobic organisms<sup>31</sup>. Cases resistant to medical therapy need surgical intervention. Uncomplicated CSOM treatment involves meticulous aural toilet (with suction /mopping up of ear debris and discharges followed by instillation of topical and systemic antimicrobial agent. In CSOM *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Corynebacterium*, *Klebsiella* species cause infection. Anaerobes survive in cholesteatoma.

Amoxicillin-Clavulanic acid is generally safe and effective antibiotic. Second generation cephalosporins eg, cefprozil, cefpodoxime, are effective on resistant *S pneumoniae* and group A Strepto cocci. Cefuroxime is also satisfactory for controlling H influenza. The antibiotics need be administered for 10 to 15 days. In half the cases effusion would persist.

Amoxicillin/ampicillin was more frequently used earlier but micro organisms display changing pattern of sensitivity to quinolones, cephalosporins and gentamycin. Ciprofloxacin drops are non ototoxic. Gentamycin drops though believed to possess ototoxicity are still useful as effective agent, since CSOM itself also causes sensorineural hearing loss<sup>32</sup>. Keeping in view the high prevalence of *S.aureus* and *P.aeruginosa* and their susceptibility to quinolones (ciprofloxacin) and cephalosporin (ceftazidime), ciprofloxacin ear drops or systemic therapy of ciprofloxacin, piperacillin or ceftazidime can be used safely in all age groups.

The study of microbial patterns and their antibiotic sensitivity determines the organisms prevalent in locations and can guide empirical treatment of the disease and its complications and also prevention of emergence of resistant strains. Control of environmental risk factors (breast feeding, passive smoke etc) makes sense in OME prevention. A causal relationship between allergy and OME has been suggested but not quantified. Management of inhalant and food allergy appears prudent. Inflammatory or infectious processes in nose, nasopharynx or paranasal sinuses also need control to avoid compromise of ET function by secondary mucosal edema. Opening of ET by autoinflation of nose has not proved beneficial<sup>33</sup>.

### Surgical treatment

Management decisions in children with OME depend on duration of effusion, laterality, and presence and severity of associated symptoms. Signs and symptoms that support clinical assessments may include: Mild intermittent ear pain and sense of fullness; Pain related rubbing of ear, irritability and sleep disturbance; inadequate response to sound in direction and extent; inattentiveness; need for loud tone communication suggest hearing loss.

There may be balance problems, delayed motor milestones, and speech language development, problems in school. The episodes of acute otitis media may recur with persisting OME in between. Tympanic membrane alteration eg posterior retraction pocket. The laterality (unilateral versus bilateral), duration of effusion and presence and severity of associated symptoms need documentation in medical record at each instance of OME.

OME and recurrent OM may be treated with myringotomy and insertion of tympanostomy tubes. The principle is to ventilate ME when ET function has failed. In most cases, adenoiditis causes ascending infection up the ET, its malfunction and obstruction<sup>34</sup>. By ventilating the middle ear with grommet tube, effusion is cleared, helping mucosal inflammation to subside and better elimination of established pathogen biofilm. Adenoidectomy reduces burden of nasopharyngeal infection.

Persistent and recurrent otitis media is often addressed by adenoidectomy as initial surgical procedure. Such cases have bacterial colonization of postnasal space early in childhood<sup>35</sup>. There is evidence that myringotomy and adenoidectomy can be effective treatment for OME.

Tympanostomy tube may cause early or late postoperative otorrhea. Adenoidectomy is thus preferred despite some risk of early post-op bleed and rare complications of velopharyngeal insufficiency or even nasopharyngeal stenosis. The procedure does more benefit than harm<sup>36</sup>. Adenoidectomy is recommended for OME (unless child has an overt or submucous cleft palate), and reduces need for future operations by 50 percent<sup>37</sup>. Benefit of adenoidectomy is apparent at age of 2 years and best in 3 year and older, irrespective of adenoid size. There is no role for tonsillectomy<sup>38</sup>.

### Tympanic membrane perforation

Major consequence of tympanic membrane perforation is conductive hearing loss. Normal hearing is defined as an air-bone hearing gap of less than 25 dB. Hearing aids may be an alternative to cope with hearing disability but definitive therapy is surgery. Surgical closure is recommended in children with established chronic otitis media with perforation. Successful myringoplasty closes perforation and improves hearing. Ossicular damage requires specific correction with tympanoplasty.

Myringoplasty and tympanoplasty are valid for application at any age. Prior adenoidectomy predicts greater success of the functional outcomes<sup>39</sup>. Myringoplasty is closure of the perforation of pars tensa of tympanic membrane, undertaken to restore hearing capability, mixed infections and persistent ear discharge. The graft material commonly used is temporalis fascia. Cartilage or perichondrium from tragus may also be used. Graft takes up and hearing improvement depends on size and site of perforation and surgical technique and skill. Age and gender of patient, past perforation history, duration of dry ear prior to surgery and presence or absence of infection during surgery are important determinants of success. Underlay technique of myringoplasty is simpler and widely used. Overlay technique suits repair of anterior quadrant perforations of tympanic membrane<sup>39</sup>. Patients with small perforation display most hearing gain soon after healing. Patients with large perforation exhibit progressive gain in hearing function as closure of air-bone gap over more than year after surgery.

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### Nicotine redemption

Nicotine has a bad reputation as it is the chief ingredient of tobacco products. It is addictive and is responsible for the physical dependence associated with cigarette smoking. But it is a powerful nAChR agonist. This action may be beneficial in neurodegenerative disorders. In a new study done in mice, the effects of low, medium and high doses of nicotine on appetite, body weight, anxiety and nAChR levels were investigated. It was found that nicotine in high doses induced reduction in food intake and weight gain but caused elevated levels of nAChR without inducing anxiety. These results suggest a possible role for nicotine in the treatment of neurodegenerative disease and in prevention of aging of brain. However, nicotine use is forbidden in children and adolescents. The authors are careful to point out that this is definitely not an advertisement for tobacco smoking.

(Texas A&M University news release, accessed 23 September 2016.  
<http://www.newswise.com/articles/can-nicotine-protect-the-aging-brain>)

- Dr. K. Ramesh Rao

# Review Article

## Calcium Hydroxide in Dentistry

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### Abstract

Calcium hydroxide has been used in dentistry for almost a century. Its mechanism of actions are achieved through the ionic dissociation of  $\text{Ca}^{2+}$  and  $\text{OH}^{-}$  ions and their effect on vital tissues, the induction of hard-tissue deposition and the antibacterial properties. Some of its indications include inter-appointment intracanal medicaments, endodontic sealers, pulp capping agents, apexification, pulpotomy and weeping canals. The purpose of this article is to review the properties, mechanism of action, applications, advantages, disadvantages and various indications for the use of calcium hydroxide in endodontics.

**Key Words:** Biomineral, Calcium hydroxide, Intracanal medicament, Weeping canal

### Introduction

Bones and teeth are biocomposites that require controlled mineral deposition during their self-assembly to form tissues with unique mechanical properties<sup>1</sup>. Biominerals such as calcium and phosphate synthetically produced or obtained from natural sources thus has an important function in the preventing demineralization and encouraging remineralization of hard tissues of the tooth along with the preservation and maintenance of the health of the pulp<sup>2</sup>.

Calcium hydroxide was introduced to the dental profession in 1921, Hermann demonstrated the formation of dentinal bridge in an exposed pulpal surface and it is now considered the "gold standard" for direct pulp capping agents<sup>3</sup>. The use of the medication for root canal system disinfection has been supported to improve the treatment outcome<sup>4,5</sup> as the complexity of the root anatomy makes more difficult their cleaning and shaping<sup>6</sup>. Intracanal medications such as calcium hydroxide are used to reduce or eliminate bacteria located in the root canal system and prevent their proliferation between sessions<sup>4,5,6</sup>. Since the introduction to dentistry of calcium hydroxide by Hermann (1920, 1930), this medicament has been indicated to promote healing in many clinical situations. However, the initial reference to its use has been attributed to Nygren (1838) for the treatment of the 'fistula dentalis', whilst Codman (1851) was the first to attempt to preserve the involved dental pulp<sup>7</sup>. According to Cvek (1989) calcium hydroxide became more widely known in the 1930s through the pioneering work of Hermann (1936) and the introduction of this material in the United States (Teuscher & Zander 1938, Zander 1939). The first reports dealing with successful pulpal healing using calcium hydroxide appeared in the literature between 1934 and 1941. Since then, and mainly after the Second World War, the clinical indications for its use were expanded and now this chemical is considered

the best medicament to induce hard tissue deposition and promote healing of vital pulpal and periapical tissues (Garcia 1983)<sup>7</sup>.  $\text{Ca}(\text{OH})_2$  is a white odorless powder with a molecular weight of 74.08. The material is chemically classified as a strong base with a high pH (12.5) and is only slightly soluble in water with a solubility of 1.2 g/l, at a temperature of 25°C<sup>7</sup>. The dissociation of  $\text{Ca}(\text{OH})_2$  into calcium and hydroxyl ions results in increased pH locally. High pH of  $\text{Ca}(\text{OH})_2$  causes irritation of the pulp tissue, which stimulates repair of dentin by the release of bioactive molecules such as Bone Morphogenic Protein and Transforming Growth Factor-Beta One<sup>3,8</sup>.

### Properties

#### Structure:

1. Arrangement= amorphous matrix, crystalline fillers.
2. Bonding= covalent; ionic.
3. Defects=pores, cracks.
4. Setting reaction= acid base reaction.

#### Physical Properties:

1. L.C.T.E= low.
2. Thermal conductivity= insulator.
3. Electrical conductivity= insulator.
4. pH=12.5-12.8.

#### Chemical Properties:

1. Solubility- 0.3-0.5

#### Mechanical Properties:

1. Elastic mod=588
2. Compressive strength >24 hr=138

#### Biologic Properties:

1. Biocompatible.

**Bactericidal Properties:**

Ca(OH)<sub>2</sub> is bacteriocidal on contact. It must be in direct contact with the bacteria to be lethal. Ca(OH)<sub>2</sub> has been shown to be active and not active against *E. faecalis* and *Pseudomonas aeruginosa*<sup>9,10</sup>. Asgary and Kamrani tested Ca(OH)<sub>2</sub> against *Pseudomonas aeruginosa*, *E. faecalis*, *Staphylococcus aureus*, and *Escherichia coli* and found it to inhibit growth of these bacteria<sup>11</sup>.

**Mechanism of action****Antimicrobial activity:**

The antimicrobial activity of Ca(OH)<sub>2</sub> is related to the release of hydroxyl ions in an aqueous environment (Siqueira 2001). Hydroxyl ions are highly oxidant free radicals that show extreme reactivity with several biomolecules. This reactivity is high and indiscriminate, so this free radical rarely diffuses away from sites of generation (Siqueira & Lopes 1999). The lethal effects of hydroxyl ions on bacterial cells are probably due to the following mechanisms (Siqueira & Lopes 1999):

- damage to the bacterial cytoplasmic membrane;
- protein denaturation; and
- damage to the DNA<sup>5</sup>

**Mineralization activity:**

When used as a pulp-capping agent and in apexification cases, a calcified barrier may be induced by calcium hydroxide (Eda 1961). Because of the high pH of pure calcium hydroxide, a superficial layer of necrosis occurs in the pulp to a depth of up to 2 mm (Estrela & Holland 2009). Beyond this layer, only a mild inflammatory response is seen and, provided the operating field is kept free from bacteria when the material was placed, hard tissue may be formed (Estrela et al. 1995)<sup>5</sup>.

**Applications<sup>12</sup>**

1. **Intracanal Medicament:** It is the most commonly used dressing for treatment of the vital pulp. It also plays a major role as an inter-visit dressing in the disinfection of the root canal system. Calcium hydroxide cannot be categorized as a conventional antiseptic, but it kills bacteria in root canal space. Calcium hydroxide is a slowly working antiseptic. Direct contact experiments in vitro require a 24 hour contact period for complete kill of enterococci. Calcium hydroxide not only kills bacteria, but it also reduces the effect of the remaining cell wall material lipo-polysaccharide. It has a wide range of antimicrobial activity against common endodontic pathogens, but is less effective against *Enterococcus faecalis* and *Candida albicans*. Calcium hydroxide is also an effective anti-endotoxin agent. However, its effect on microbial biofilms is controversial.
2. **Endodontic Sealer:** To be therapeutically effective calcium hydroxide must be dissociated into Ca<sup>++</sup> and OH<sup>-</sup>. Therefore to be effective, an endodontic sealer based on calcium hydroxide must dissolve and the solid consequently lose content.

3. **Pulp Capping Agent:** Calcium hydroxide is generally accepted as the material of choice for pulp capping. Histologically there is a complete dentinal bridging with healthy radicular pulp under calcium hydroxide dressings. When calcium hydroxide is applied directly to pulp tissue there is necrosis of adjacent pulp tissue and an inflammation of contiguous tissue. Dentinal bridge formation occurs at the junction of necrotic tissue and vital inflamed tissue. Beneath the region of necrosis, cells of underlying pulp tissue differentiate into odontoblasts and elaborate dentin matrix.

4. **Apexification:** In apexification technique canal is cleaned and disinfected, when tooth is free of signs and symptoms of infection, the canal is dried and filled with stiff mix of calcium hydroxide and CMCP. Histologically there is formation of osteodentin after placement of calcium hydroxide paste. There appears to be a differentiation of adjacent connective tissue cells; there is also deposition of calcified tissue adjacent to the filling material.

5. **Pulpotomy:** It is the most recommended pulpotomy medicament for pulpally involved vital young permanent tooth with incomplete apices. It is acceptable because it promoted reparative dentin bridge formation and thus pulp vitality is maintained.

6. **Weeping Canals:** For such teeth dry the canals with sterile absorbent paper points and place calcium hydroxide in canal. Calcium hydroxide converts the acidic pH of periapical tissue in the weeping canal to basic pH.

**Method of preparation**

The easiest method to prepare a calcium hydroxide paste is to mix calcium hydroxide powder with water until the desired consistency is achieved<sup>7</sup>.

Leonardo et al. (1982) stated that a paste prepared with water or other hydrosoluble non-viscous vehicle does not have good physicochemical properties, because it is not radio-opaque, is permeable to tissue fluids and is rendered soluble and resorbed from the periapical area and from within the root canal. For these and the following reasons, Leonardo et al. (1982) recommended the addition of other substances to the paste:

1. To maintain the paste consistency of the material which does not harden or set;
2. To improve flow;
3. To maintain the high pH of calcium hydroxide;
4. To improve radiopacity;
5. To make clinical use easier;
6. Not to alter the excellent biological properties of calcium hydroxide itself.

**Composition of calcium hydroxide paste**

Calcium hydroxide paste for use in endodontics is composed of the powder, a vehicle and a radiopacifier. Other substances may be added to improve physicochemical properties or the antibacterial action<sup>7</sup>.

## Vehicles

According to Fava (1991), the ideal vehicle should:

1. Allow a gradual and slow Ca<sup>2+</sup> and OH<sup>-</sup> ionic release;
2. Allow slow diffusion in the tissues with low solubility in tissue fluids;
3. Have no adverse effect on the induction of hard tissue deposition<sup>7</sup>.

The vehicles mixed with Ca(OH)<sub>2</sub> powder play an important role in the overall dissociation process because they determine the velocity of ionic dissociation causing the paste to be solubilized and resorbed at various rates by the periapical tissues and from within the root canal. The lower the viscosity, the higher will be the ionic dissociation. The high molecular weight of common vehicles minimizes the dispersion of Ca(OH)<sub>2</sub> into the tissues and maintains the paste in the desired area for longer periods of time (Athanasiadis et al. 2007)<sup>5</sup>.

There are three main types of vehicles:

1. Water-soluble substances such as water, saline, anaesthetic solutions, carboxymethylcellulose, methylcellulose and Ringers solution.

2. Viscous vehicles such as glycerine, polyethyleneglycol (PEG) and propylene glycol.
3. Oil-based vehicles such as olive oil, silicone oil, camphor (the oil of camphorated parachlorophenol), some fatty acids (including oleic, linoleic, and isostearic acids), eugenol and metacresylacetate (Fava & Saunders 1999)<sup>5</sup>.

Staeble et al. (1995) reported that an aqueous suspension allows a more efficient release of hydroxyl ions. According to Simon et al. (1995), distilled water or camphorated paramonochlorophenol result in better diffusion than phosphate buffered saline or propylene glycol<sup>13</sup>.

**Radiopacifier :** Calcium hydroxide mixed with any of the quoted vehicles lacks radiopacity and is not easily seen radiographically. This is the main reason radiopaque materials are added to the paste, thereby allowing identification of lateral and accessory canals, resorptive defects, fractures and other structures (Smith & Woods 1983, AlacÈ am et al. 1990). A radiopacifier should have an atomic weight higher than calcium for radiopacity purposes (Tavano et al. 1978). Some examples of such substances are barium sulphate and bismuth, and other compounds containing iodine and bromine (AlacÈ am et al. 1990)<sup>7</sup>.

Clinical application of biomaterials	Enamel remineralization	Dentino-genesis	Cemento-genesis	Apexification	Perforation repair	Repair of resorption defects	Repair of bony defects
Calcium phosphate Cement	+	-	+	-	+	-	+
B-tricalcium phosphate	+	-	+	-	+	-	+
Bioactive glass	+	-	+	-	-	-	-
Synthetic hydroxyapatite	+	-	-	-	-	-	+
Calcium hydroxide	-	+	+	+	+	+	-
Portland Cement	-	+	-	+	+	+	-
Mineral trioxide aggregate	-	+	+	+	+	+	+
Biodentine	+	+	+	+	+	+	-

**Table1 :** Clinical restorative application of biomineral based biomaterials

## Characteristic of calcium hydroxide paste

When calcium hydroxide powder is mixed with a suitable vehicle, a paste is formed and, because the main component is calcium hydroxide, Maisto (1975) classified these formulations as alkaline pastes because of their high pH. According to some authors (Maisto 1975, Goldberg 1982, Leonardo et al. 1982), these pastes should have the following characteristics:

1. Composed mainly of calcium hydroxide which may be used in association with other substances to improve some of the physicochemical properties such as radiopacity, flow and consistency;
2. Non-setting;

3. Can be rendered soluble or resorbed within vital tissues either slowly or rapidly depending on the vehicle and other components;
4. May be prepared for use at the chairside or available as a proprietary paste;
5. Within the root canal system they are used only as a temporary dressing and not as a definitive filling material<sup>7</sup>

## Advantages of Calcium hydroxide<sup>14</sup>

- Initially bactericidal then bacteriostatic.
- Promotes healing and repair.
- High pH stimulates fibroblasts.

- Neutralizes low pH of acids.
- Stops internal resorption.
- Inexpensive and easy to use.

### Disadvantages of Calcium hydroxide<sup>15</sup>

- Does not exclusively stimulate dentinogenesis.
- Does exclusively stimulate reparative dentin.
- Associated with primary tooth resorption.
- May dissolve after one year with cavosur face dissolution.
- May degrade during acid etching.
- Degrades upon tooth flexure.
- Marginal failure with amalgam condensation.
- Does not adhere to dentin or resin restoration.

### Conclusion

Calcium hydroxide is widely used material in endodontic treatment due to its high alkalinity and bactericidal properties. It is a material which is readily available, simple to prepare and restorable. Calcium hydroxide is still a material of choice which is widely being used for various reasons in Endodontics.

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# Case Report

## A Rare Case of Herpes Simplex Virus Type 2 Induced Acute Retinal Necrosis

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### Abstract

29 year old healthy female came with complaints of defective vision in left eye for one week duration along with pain, redness and floaters. On examination, patient was found to have pan uveitis, retinal vasculitis, vitritis and necrosis of the peripheral retina in the left eye. A diagnosis of acute retinal necrosis was made. PCR analysis of aqueous and vitreous revealed Herpes Simplex Virus type 2 which is a rare cause for acute retinal necrosis.

**Key Words:** Acute Retinal Necrosis, Immunocompetent, Herpes Simplex Type 2

### Introduction

Acute retinal necrosis (ARN) is a rare but potentially devastating syndrome characterized by progressive peripheral necrotizing retinitis. It was first described in 1971<sup>1</sup>. It is usually caused by Varicella zoster and occurs in immunocompetent individual<sup>2</sup>.

Progressive outer retinal necrosis (PORN) is also type of necrotizing retinitis and characterized by multifocal lesions without granular borders in deep retinal layers<sup>3</sup>. The main difference between both ARN and PORN is ARN occurs in immunocompetent and PORN in immunocompromised and absence of inflammation in PORN<sup>4</sup>.

Herpes simplex virus is a DNA virus belonging to herpes family is two types – type 1 and type 2. Herpes Simplex Virus 1 is transmitted by oral contact and direct contact. In eye it causes herpes keratitis which is the leading cause of corneal blindness in U.S.A<sup>5</sup>. Herpes Simplex Virus 2 causes genital herpes and sexually transmitted. 3.7 billion people have Herpes Simplex Virus 1 and 417 million people have Herpes Simplex Virus 2 infection<sup>6</sup>.

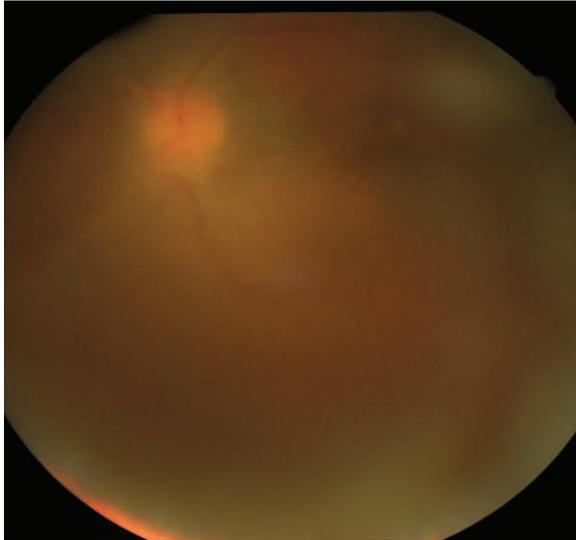
### Case History

A 29 year old female came with complaints of defective vision in left eye for one week duration. There is a history of fever, vomiting and headache for 2 weeks for which she was admitted and treated. There is also history of joint pain. On examination, right eye appears to be normal with normal unaided visual acuity. Left eye anterior segment showed circumciliary congestion of conjunctiva with fine keratic precipitates in cornea and anterior chamber showing cells 3+. Patient's best corrected visual acuity in left eye was 6/12. The patient was given topical steroids and was reviewed after 1 week. Patient vision worsened to 3/60 in spite of

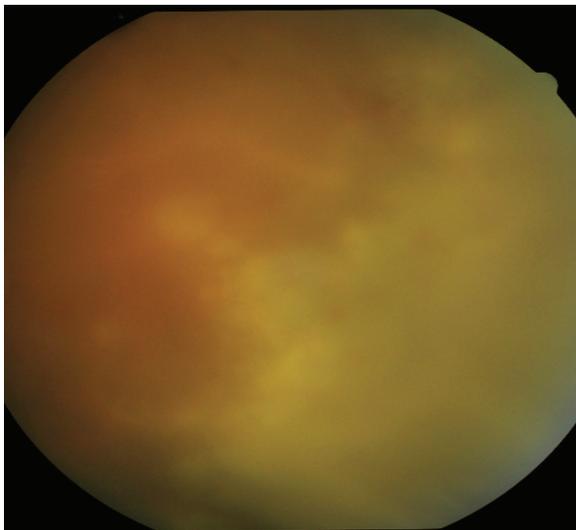
treatment with pupil sluggishly reacting to light. Fundus examination of right eye was within normal limits. Fundus examination of left eye showed hazy media due to vitreous inflammation. Vitreous cells were 2+. Optic disc showed edema with blurring of disc margins(Fig1). The superior retinal quadrant showed pale and thin retina with granular borders which are well demarcated(Fig 2). There was evidence of retinal vasculitis with sheathing of arteries and occluded peripheral retinal vessels in superior quadrant of retina(Fig 3). With the above clinical findings, a presumptive clinical diagnosis of acute retinal necrosis in the left eye was made. Routine blood investigations, ANA, RA factor VDRL, HIV serology, Mantoux, Chest X-ray were within normal limits.



**Fig 1:** Optic disc edema with vitritis



**Fig 2:** Thinning and sheathing of retinal arterioles



**Fig 3:** Necrosed peripheral retina with granular borders

## Discussion

Acute Retinal Necrosis is caused by viral infection mostly by Varicella zoster virus or Type 1 Herpes Simplex. Type 2 Herpes Simplex Virus causing Acute Retinal Necrosis is very rare<sup>7</sup>. American Uveitis Society defined ARN based on following clinical criteria<sup>8</sup>:

- 1) One or more foci of retinal necrosis with discrete borders located in the peripheral retina
- 2) Rapid progression in the absence of antiviral therapy
- 3) Circumferential spread
- 4) Evidence of occlusive vasculopathy with arterial involvement
- 5) A prominent inflammatory reaction in the vitreous and anterior chambers

Our patient had all the above clinical findings and hence was diagnosed clinically as Acute Retinal Necrosis. The confirmation of organism is usually by Polymerase Chain Reaction with aqueous or vitreous samples. We went on to do a PCR analysis of aqueous and vitreous and it showed type 2 herpes simplex virus which is very

rare. Rarely in non-responding cases is diagnostic vitrectomy or retinal biopsy needed<sup>9</sup>.

Antiviral therapy can be given systemically as well as intravitreally. Commonly used systemic antiviral used are acyclovir, famciclovir, valacyclovir<sup>10</sup> antiviral agents given intravitreally are ganciclovir (200 microgram/0.1 ml) foscarnet (1.2 mg/0.1ml). They are given in retinitis threatening macula or optic disc<sup>11</sup>.

The patient completed the course of oral Valacyclovir 1gm TID for 6 weeks and her renal function was stable throughout the treatment. Intravenous anti-viral medications were not given as the patient is immunocompetent and had responded to oral valacyclovir. The patient is currently on regular follow up for recurrence of disease in both eyes.

## Conclusion

Acute retinal necrosis is a severe ocular inflammatory syndrome in immunocompetent associated with poor visual outcome. It is commonly caused by Varicella zoster virus, Herpes Simplex virus type 1 and less commonly by Herpes simplex virus type 2 as in our case which was confirmed by PCR analysis of vitreous and aqueous samples. The patient responded well to oral Valacyclovir which was given for 6 weeks along with steroids. Retinal inflammation subsided, but retinal thinning still persisted as the retina was necrosed.

Patient is currently on follow up for recurrent involvement in same eye and for involvement of other eye. Photocoagulation of retina is planned in left eye for prevention of Retinal Detachment.

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### Spirituality Boost in a Nasal Spray

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(Social Cognitive and Affective Neuroscience, doi: 10.1093/scan/nsw078, published online 17 June 2016)

- Dr. K. Ramesh Rao

# Case Report

## Bisphosphonate Induced Recurrent Anterior Uveitis

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### Abstract

A 68 year old female patient presented to ophthalmology OPD with recurrent episodes of anterior uveitis in both eyes since 2 years. Routine uveitis work-up was found to be within normal limits except elevated ESR and CRP levels. The patient had been taking oral alendronate 150 mg every two weeks for the past two years, which correlated with the duration and onset of uveitis. Uveitis improved drastically on stoppage of the drug with no further evidence of uveitis for past 6 months in both eyes. Patient is currently on follow up.

**Key Words:** Anterior Uveitis, Hyphema, Bisphosphonates

### Introduction

Bisphosphonates are used to inhibit bone reabsorption in post-menopausal women and to manage hypercalcaemia associated with osteolytic bone lesions<sup>1</sup>. It can cause both systemic and ocular inflammatory response. Ocular side effects range from conjunctivitis, episcleritis, scleritis, uveitis and rarely retrobulbar optic neuritis<sup>2</sup>. No case of unilateral or bilateral scleritis resolved until bisphosphonates therapy was discontinued. The mechanism is unclear. Proinflammatory cytokines such as TNF-alpha and IL-6 may play a role in pathogenesis of ocular inflammation<sup>3</sup>. Here we present a rare case of bisphosphonate induced recurrent anterior uveitis.

### Case History

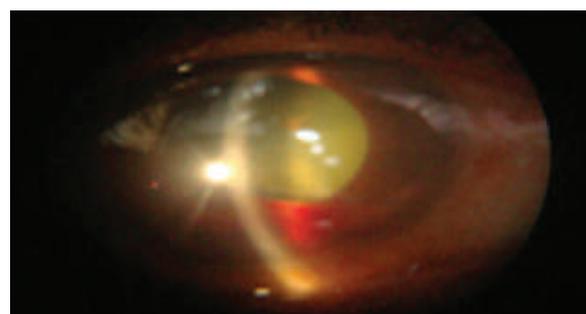
A 68 year old female presented to Ophthalmology OPD, Chettinad Hospital and Research Institute with chief complaints of defective vision, pain and redness in right eye since one day. History of similar complaints in the past were noted in both the eyes for past two years intermittently. The patient was a known diabetic since 2 years on regular follow up and treatment. The patient was on oral alendronate (150 mg every two weeks) since 2 years for postmenopausal osteoporosis.

On examination, anterior segment of right eye showed lid oedema, conjunctival congestion with circumcorneal congestion, flare and cells (3+), hyphema in the anterior chamber (Fig 1 & Fig 2). Visual acuity of right eye decreased to 6/12 with glasses. B scan of right eye was done which was in normal limits. Anterior segment of both eyes showed signs of previous attacks of anterior uveitis with pigment dispersion at the back of cornea and atrophic iris. Blood investigations were in normal limits except elevation of C reactive protein and ESR levels. Blood sugars were under control (HbA1c-5.2). A presumptive diagnosis of

Bisphosphonates induced uveitis was made. The patient was advised to stop the drug immediately. The patient was started on topical cycloplegics and topical steroids. The patient vision improved to 6/9 within one week and hyphema resolved completely. Steroids were gradually tapered and no further attacks of uveitis were noted in a 6 month follow up.



**Fig 1:** Showing Circumcorneal Congestion and Hyphema in the Right Eye



**Fig 2:** Showing Turbid Aqueous and Hyphema in Anterior Chamber of Right Eye

## Discussion

Bisphosphonates are used in osteoporosis to prevent bone resorption. Hypercalcaemia resulting from metastatic disease of bone, Paget's disease<sup>4</sup>, osteolytic cancers are treated with bisphosphonates. Bisphosphonates (nitrogen and non-nitrogen-containing) are known to cause ocular inflammation when given orally or intravenously, though intravenous use tend to cause earlier ocular inflammation. Ocular inflammation caused by pamidronate disodium<sup>5</sup> has been reported more frequently than other bisphosphonates<sup>6,7</sup>. Bisphosphonates activates specific T-cell groups which reduce bone resorption<sup>8</sup>. Cytokine activation induces immunological reaction resulting in ocular inflammation<sup>5</sup>. Discontinuation of Bisphosphonates and administration of steroid resulted in resolution of inflammation in many patients<sup>8</sup>. Our patient was on oral alendronate (150 mg every 2 weeks) for the past two years during which she had recurrent episodes of non-granulomatous uveitis in both eyes. Her latest episode of uveitis resulted in hyphema and caused her defective vision. After the stoppage of alendronate, patient had no recurrence of uveitis in both eyes in 6 months follow up.

## Conclusion

Ocular side effects of bisphosphonates though rare must be made to known to physicians and ophthalmologists and early diagnosis must be initiated for stoppage of the drug (Table 1). Less than 2% of patients develop systemic side effects which includes ocular inflammation, electrolyte imbalance, renal failure, nephrotic syndrome, maxillary and mandibular bone necrosis<sup>4</sup>. For patients who develop ocular symptoms, prompt ophthalmologic evaluation is crucial to determine the safety of a subsequent bisphosphonate therapy<sup>4</sup>. Increased C - reactive protein, ESR levels and leucopenia may be a non-specific indicator of Bisphosphonates induced uveitis as in our case. Patients who receive long-term bisphosphonate therapy should be evaluated at regular intervals for early signs of ocular inflammation, electrolyte imbalances and for hypocalcaemia<sup>2</sup>.

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BISPHOSPHONATES	ADVERSE EFFECTS <sup>9</sup>
PAMIDRONATE DISODIUM	Nonspecific conjunctivitis Uveitis Abnormal or blurred vision Scleritis Ocular pain Photophobia Episcleritis
ALENDRONATE SODIUM	Abnormal or blurred vision Ocular pain Non-specific conjunctivitis Uveitis Scleritis
ETIDRONATE DISODIUM	Abnormal or blurred vision Non-specific conjunctivitis
RISENDRONATE SODIUM	Non-specific conjunctivitis Abnormal or Blurred vision Scleritis
SODIUM CLODRONATE	Abnormal or blurred vision Photophobia

**Table 1:** Ocular adverse effects of commonly used Bisphosphonates

# Case Report

## Unilateral Ocular Myasthenia Gravis

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Chettinad Health City Medical Journal 2016; 5(1): 43 - 44

### Abstract

Myasthenia gravis, an acquired auto immune disease of the neuromuscular junction, has ophthalmic manifestations as integral part. Herewith we report a rare uniocular involvement of the eye in a 38yrs old male. He presented with the drooping of right upper eye lid since two years, worsening by evening and after exertion. Though the blood investigations and Ach antibody titres were normal, he responded well to 1.5mg neostigmine intramuscularly.

**Key Words:** Ocular myasthenia gravis, Neostigmine

### Introduction

Myasthenia gravis (MG) is an acquired auto-immune disease of the neuromuscular junction which causes rapid muscle fatigue and weakness<sup>1</sup>. Ocular manifestations are an integral part of Myasthenia gravis. Ptosis and diplopia are the initial complaint in around 75% to 90% cases. Ocular MG, in which weakness remains confined to the ocular muscles only, is encountered in up to 17% to 58% of all myasthenics<sup>4</sup>. Some less common or rare ocular signs like paradoxical reversal of ptosis, enhanced ptosis, total external ophthalmoplegia, internuclear ophthalmoplegia, chronic progressive external ophthalmoplegia and lid retraction contralateral to the ptotic eye<sup>5</sup>. Although bilateral ophthalmological involvement of disease is quite common, it is rare to find a case of unilateral Ocular Myasthenia Gravis.

### Case Report

A 38 year old male presented to Ophthalmology OPD, Chettinad Health and Research Institute with a chief complaint of drooping of right upper eyelid since two years which was worsened by evening and on excessive work. He has no other systemic illness and no ocular complaints of diplopia.

On examination, visual acuity was 6/6 and extra ocular movements were full. Right eye revealed ptosis of 4mm, Bell's phenomenon was normal, Levator palpebral action 7 mm by Berke's method with rest of the anterior segment and posterior segment being normal. Anterior and posterior segments were found to be in normal limits in left eye except mild lid retraction. Ice pack test was positive. The routine blood investigations were found to be in normal limits except the mild elevation of ESR levels. USG abdomen and HRCT chest were found to be in normal limits. The acetyl choline receptor antibody titres were found to be in normal titres. The patient was subjected to

neostigmine test after obtaining anaesthetic fitness and with cardiac monitoring. After injection neostigmine 1.5 mg intramuscularly, the ptosis showed significant improvement after 30 minutes, confirming the diagnosis of Unilateral Ocular Myasthenia gravis. Neurologist opinion was obtained and advised tablet Pyridostigmine 60 mg thrice daily 8.

### Discussion

Myasthenia gravis is a disease characterized by fatigue and weakness of the striated muscle within the body. Although the exact cause is unknown it is thought to be an acquired autoimmune disorder the defect lies at the postsynaptic membrane. 70 percent of patients with myasthenia gravis have visual symptoms in the initial presentation. Generally the female:male ratio in generalized myasthenia is 3:2 or higher. But on the contrary ocular myasthenia is more in especially after the age of 40 years. In addition, the average age of onset for generalized myasthenia is 33 years, while that of ocular myasthenia is 38 years. 2 Common clinical features seen in patients with ocular MG are ptosis (droopy eyelids), diplopia (double vision) and incomplete eye closure. Environmental, emotional, and physical factors also found to influence the symptoms for the patients. The major factors found to affect them are bright sunlight, extreme temperature, emotional stress, illness, surgery, menstruation, and pregnancy. Symptoms were found to be worse at the end of the day during the evenings or after exertion of the muscle.

Diagnostic Criteria For Ocular Myasthenia <sup>3</sup>	
1	Ptosis present in one or both upper lids not due to local eyelid disease, preferably that is fatigue and recovers with rest.
2	Extraocular muscle weakness in one or both eyes but does not follow strict third nerve muscle innervation pattern.

3	Weakness in one or both orbicularis oculi but no weakness of other head and neck muscles
4	No pupillary abnormality
<b>A Plus B or C or D or E</b>	
A	Fatigue of the affected muscle with clear cut worsening of the ptosis after upward gaze for 30 to 60 seconds or worsening of the monocular duction after 120 seconds of gaze in the direction of action.
B	Recovery of the upper lid ptosis to almost normal after 30 seconds to 10 minutes of eyelid closure. Recovery of the monocular duction after 120 – 180 seconds of gaze in the direction of the antagonist muscle.
C	A positive edrophonium/ neostigmine test (fig 1 to fig 3).
D	Abnormal repetitive stimulation electromyography with a minimum decrement of 10%
E	Abnormal serum acetylcholine receptor binding level.



**Fig 1:** Patient before the test



**Fig 2:** Patient showing improvement in ptosis -30 min after the test

Elevated Ach receptor antibody confirms the diagnosis of Myasthenia gravis in 80 % to 90% cases of Myasthenia gravis and 30-77% cases of Ocular myasthenia gravis. Of these patients, 30% will have autoantibodies against muscle specific kinase (anti MuSKAb) expressed on skeletal muscle. Patients who are

negative for both Ach and MuSK antibodies are classified as "seronegative" Myasthenia gravis. CT scan should be done to rule out thymic hyperplasia. Thyroid function tests should be done to rule out autoimmune thyroid disease<sup>4</sup>.

Treatment is chiefly medical and aims at improving muscle weakness (thereby alleviating symptoms of diplopia and ptosis), achieving disease remission, minimizing drug induced side effects, and slowing or preventing progression to generalized Myasthenia<sup>2</sup>. Medications include cholinesterase inhibitors such as Mestinon, pyridostigmine, steroids such as Prednisone, or other immunosuppressants used alone or in combination<sup>7</sup>. Other options include plasmapheresis, or IV IG therapy. These treatments offer only a temporary improvement and repeated treatments are necessary to sustain the effect. Supportive measures include the use of prisms or occlusion therapy for those with persistent diplopia and crutch glasses for severe ptosis<sup>2</sup>.

## Conclusion

Eventhough Myasthenia gravis is a common neuromuscular junction disorder. Ocular myasthenia in the early stages is often misdiagnosed. So clinicians should examine each case with a high degree of suspicion. The diagnosis can be made with simple clinical and pharmacological tests.

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# Case Report

## Aortic Dissection in a Young Male Body builder Requiring Complex Repair

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Emily Stevens is a junior doctor working at Western Health, Melbourne, Australia. She graduated from Deakin University, Geelong, in 2015. Emily aims to provide the best care for her patients locally and contribute to the greater scientific community in the form of research and redesign, globally. Emily developed a keen interest in vascular surgery as a medical student and accordingly, is pursuing a surgical career. She is concurrently involved in multiple research projects across the fields of neurology and radiology.

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### Abstract

We present here a case of thoracic aortic dissection requiring complex open and endovascular repairs in a 41 year old male bodybuilder in the context of recreational use of a sports supplement, Res 100, which is marketed as an anabolic steroid agent. He did not suffer from hypertension, aortic coarctation or atherosclerosis. He did not have any pre-existing aortic aneurysm or congenital aortic valve defects and had neither evidence of Marfan's nor Turner's syndrome. Genetic testing for chromosomal abnormalities was negative. Laboratory testing did not support inflammatory or infectious conditions. Additionally, the mean age of patients with acute aortic dissection is 62 years old as per the International Registry of Acute Aortic Dissection, which is in contrast with our patient's 41 years of age. However, anecdotal reports of dissection in bodybuilders feature ages ranging from 19 to 53 years old. These reports also found strenuous activity to precede dissection, our case demonstrates symptom onset during minimal exertion and a potential link to performance enhancing drugs. This case highlights the variability in the risk factor profile for aortic dissection pathology.

**Key Words:** Aortic Dissection, Body Builders, Res 100

### Case Report

A 41-year-old male weightlifter presented to the emergency department after experiencing chest pain radiating to his jaw whilst vacuuming, on the background of recreational use of 'Res 100', a compound used by bodybuilders to increase autologous testosterone and inhibit oestrogen. He was otherwise well with no history or family history of aortic disease. His blood pressure was initially 169/92 mmHg with the rest of his vital signs being within normal limits.

Echocardiogram revealed an aortic dissection rupturing into the pericardium with tamponade. CT angiography demonstrated extensive aortic dissection involving the ascending aorta, arch and the descending aorta; and ending at the renal arteries (Fig1). There were no radiological or clinical signs of compromised perfusion distally.

He underwent emergency surgery for an ascending aortic repair an hour later. Cannulation for cardiopulmonary bypass was via the right femoral artery and vein. His pericardial effusion was evacuated. A primary tear was identified within the proximal ascending aorta and no intimal tear was seen within the arch. The ascending aorta was replaced with a 30mm Dacron graft, with resuspension of the aortic valve. On table DSA then revealed adequate perfusion of cerebral and visceral segments via the true lumen.

On his first post-operative day, increasing lactate and creatinine levels were noted and a CTA was performed which showed near total obliteration of the true lumen in the proximal descending aorta due to a pressurised false lumen.

He was returned to the operating theatre and had a redo median sternotomy with debranching of the innominate and left common carotid arteries from the ascending aortic graft to provide a sufficient landing zone for a stent graft. A thoracic endovascular stent graft was deployed from within the ascending aortic graft to the mid-descending thoracic aorta. An uncovered self-expanding stent was deployed down to the origin of the coeliac axis to scaffold the true lumen. He was then transferred to the intensive care unit in a haemodynamically stable state. Subsequently, his visceral perfusion stabilised. The patient was discharged home three weeks postoperatively.

### Discussion

Aortic dissection is a rare and potentially lethal condition. A tear in the aortic intimal layer creates an intramural lumen into which high velocity blood flow can track, creating a false lumen, capable of causing severe morbidity and mortality<sup>1,2</sup>. Known risk factors for this condition include connective tissue abnormalities and/or systemic hypertension<sup>1,3</sup>. More recent associations include strenuous activities and substance abuse<sup>4-6</sup>.

There is a large evidence base correlating strenuous activities with aortic dissection. Extreme haemodynamic loading is observed in activities such as weightlifting where blood pressure has been reported to reach 480/350 mm Hg<sup>5</sup>. Elefteriades et al, demonstrated acute aortic dissection in the setting of strength training in men aged 19-53<sup>3</sup>. Additionally, multiple case reports describe aortic dissection in otherwise healthy adult male body-builders<sup>7-14</sup> and one case report has



**Fig 1:** CT angiography demonstrated extensive aortic dissection involving the ascending aorta, arch and the descending aorta, and ending at the renal arteries

highlighted concurrent performance enhancing substance use<sup>15</sup>. Iskander et al, found that whilst aortic disease is rare and an infrequent cause of mortality in elite athletes, extreme haemodynamic loading can cause aortic dilatation with severe sequelae, suggesting patients with genetic susceptibility be advised to avoid vigorous activities<sup>16</sup>. Similarly, Aparci et al, described a relationship between strenuous occupations (ie military, weight-lifting, security) and aortic dilatation, which predisposing to aortic dissection, suggesting pre-employment screening and monitoring to improve safety as these occupations may be implicated in the development of aortic disease<sup>17</sup>.

This case describes a patient with an unusual history and presentation. He is young, with no history of aortic disease or hypertension. He was 41 years of age at onset in contrast with IRAD's average age of 62 years. His onset of symptoms occurred with minimal exertion and he was concurrently taking a testosterone supplement. This case also highlights the appropriate combination of cardiac surgical and endovascular skills to culminate in a good outcome in a time period where branched stent grafts are not available for the arch.

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### Just Like adults

Prevailing understanding is that the adults and the children are different when it comes to making moral judgements. The adults appear to give greater emphasis to intention rather than the outcome of an action. For example, hurting someone intentionally is considered morally worse than accidentally doing the same. But the children are believed to base their moral judgements on the outcome of an action rather than on intention. But this has been challenged in a recent study involving 138 children aged between 4 and 8 and 31 adults in which the study subjects were told, and questioned about, four stories about accidental (good intention/bad outcome) and attempted (Bad intention/good outcome) harms; but unlike in earlier studies, the authors rephrased the acceptability questions. The results were dramatically different from the earlier conclusions. Children above the age of 4 made moral judgements much like adults i.e. they too based their judgments on intention than on outcome.

*Cognition*, doi: 10.1016/j.cognition.2016.08.019, published 17 September 2016.

- **Dr. K. Ramesh Rao**

### Answer to : Diagnose the condition

ECG shows bradycardia with obvious QRS complexes at the rate of 30/min. Possibility could be a Junctional rhythm but with low rate.No obvious sinus P waves are seen. But retrogradely conducted P wave can be seen after each QRS complex. These features are suggestive of complete Sinus Arrest (SICK SINUS SYNDROME) with escape rhythm.This patient did not respond to Atropine. Probably the site of impulse generation is His bundle.

**Dr. M.Chokkalingam**, Consultant Cardiologist, CSSH.

# Case Report

## Spontaneous Recanalization of an Occluded Internal Carotid Artery

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My name is Alex Matthews and I am currently working as a Junior Doctor for Barwon Health in Geelong, Victoria. Throughout the course of my studies I have maintained an interest in surgery, critical care and pre-hospital medicine. Whilst rotating through different areas of the hospital environment I have enjoyed the variety of patient presentations and unusual cases across each speciality. In order to continue my learning and contribute in my field I aim to publish further studies of interest which will influence practice and improve patient outcomes.

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Chettinad Health City Medical Journal 2016; 5(1): 48 - 51

### Abstract

We describe here a case of spontaneous recanalization of a left occluded Internal Carotid Artery (ICA) on the background of a previous Carotid Endarterectomy (CEA) on the contralateral symptomatic side. This rare event with only anecdotal evidence describing its incidence and natural history was picked up with ultrasound scanning. Initially, only trickle flow was demonstrated and after 12 months, the stenosis in the left internal carotid artery was graded as less than 50% on ultrasound. Our report highlights the importance of following up carotid system lesions and contributes to the discussion of how such events should be managed.

**Key Words:** Internal Carotid Artery (ICA), Carotid Endarterectomy (CEA)

### Case Report

Mr EL is a 70 year old man who presented to the Vascular Surgery Outpatient Clinic for routine surveillance of his carotid artery disease; having previously undergone a right CEA in June 2011. This was in the setting of a 70-79% symptomatic stenosis of the right ICA and an occluded left ICA. He suffered from a left middle cerebral artery territory stroke in January 2011. Mr EL maintains a complex past medical history including radical prostatectomy and abdominoperineal resection for bowel cancer. He also has regular surveillance for a 44mm infra-renal abdominal aortic aneurysm and is treated pharmaceutically for hypertension, hyperlipidaemia, and type 2 diabetes mellitus.

Mr EL is an ex-smoker with a 40 pack year history. He drinks moderate amounts of alcohol and lives independently with his wife. Mr EL was followed up 4 weeks post-operatively in July 2011. He underwent carotid ultrasound studies which demonstrated no stenosis in the right ICA and occlusion of the left ICA. He has since been followed up annually as an outpatient and has experienced no symptom of cerebral ischaemia. Routine ultrasound surveillance of the carotid arteries in July 2012 and August 2013 reported no change. However in August 2014 carotid ultrasound of the left ICA demonstrated a trickle of flow, while the right ICA remained unchanged. This new finding was discussed during clinic with the vascular consultant and repeat surveillance was arranged in 12 months' time.

Mr EL's latest carotid ultrasound study from August 2015, (50 months after contralateral surgical intervention) demonstrates that the left internal carotid artery is now open with <50% stenosis, while the right ICA remains unchanged. Each carotid ultrasound report was undertaken at the same location but was reported by a different radiologist and undertaken by different ultrasound technologists. There is currently no

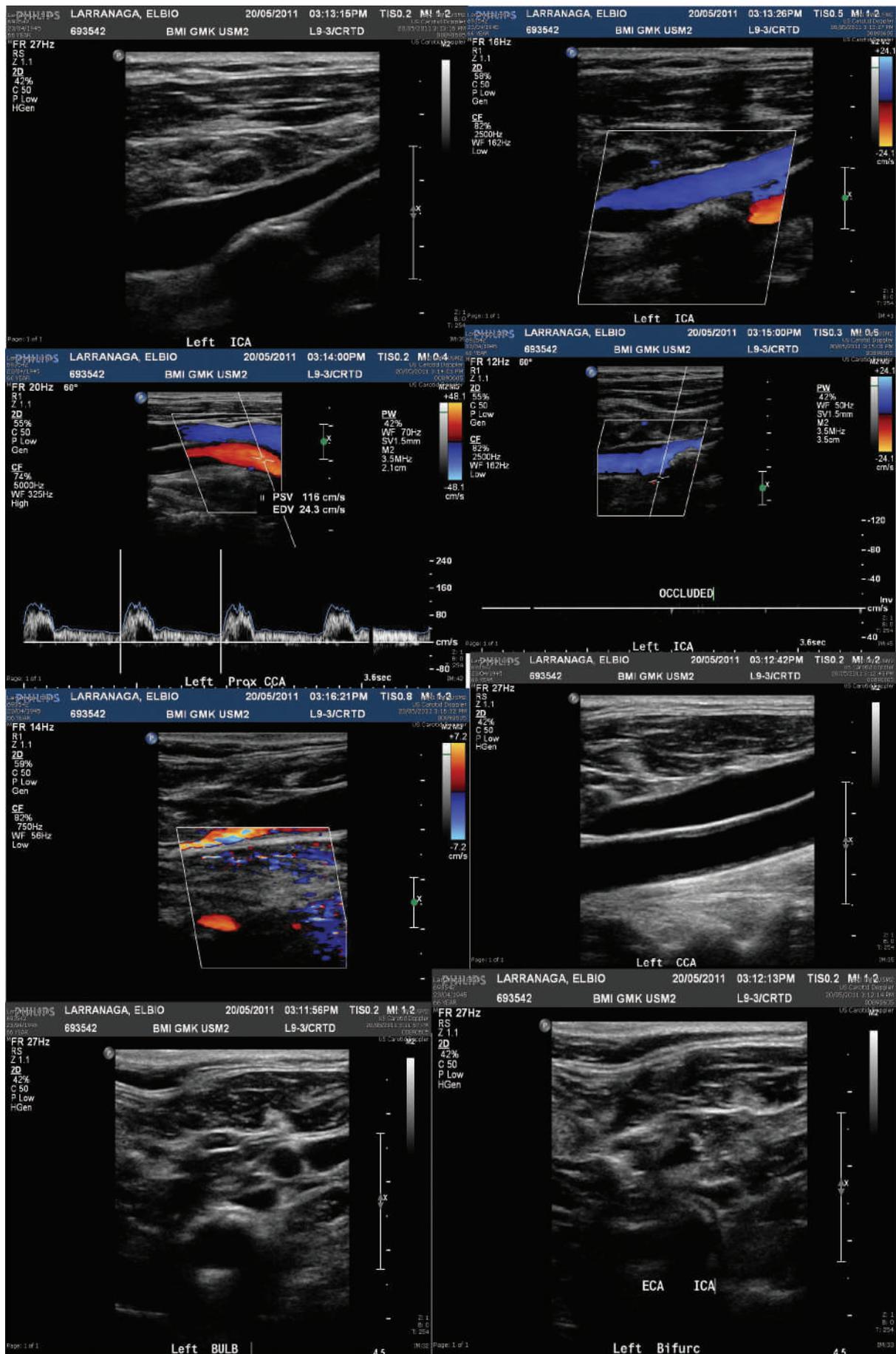
explanation or clear aetiology which can account for the late spontaneous recanalization of Mr EL's left ICA<sup>1</sup>.

Mr EL decided not to have any further follow-up or surveillance in regards to his vascular disease and does not want open arterial or endovascular repair should a problem arise in the future. He was subsequently discharged from clinic with no further plans for medical imaging.

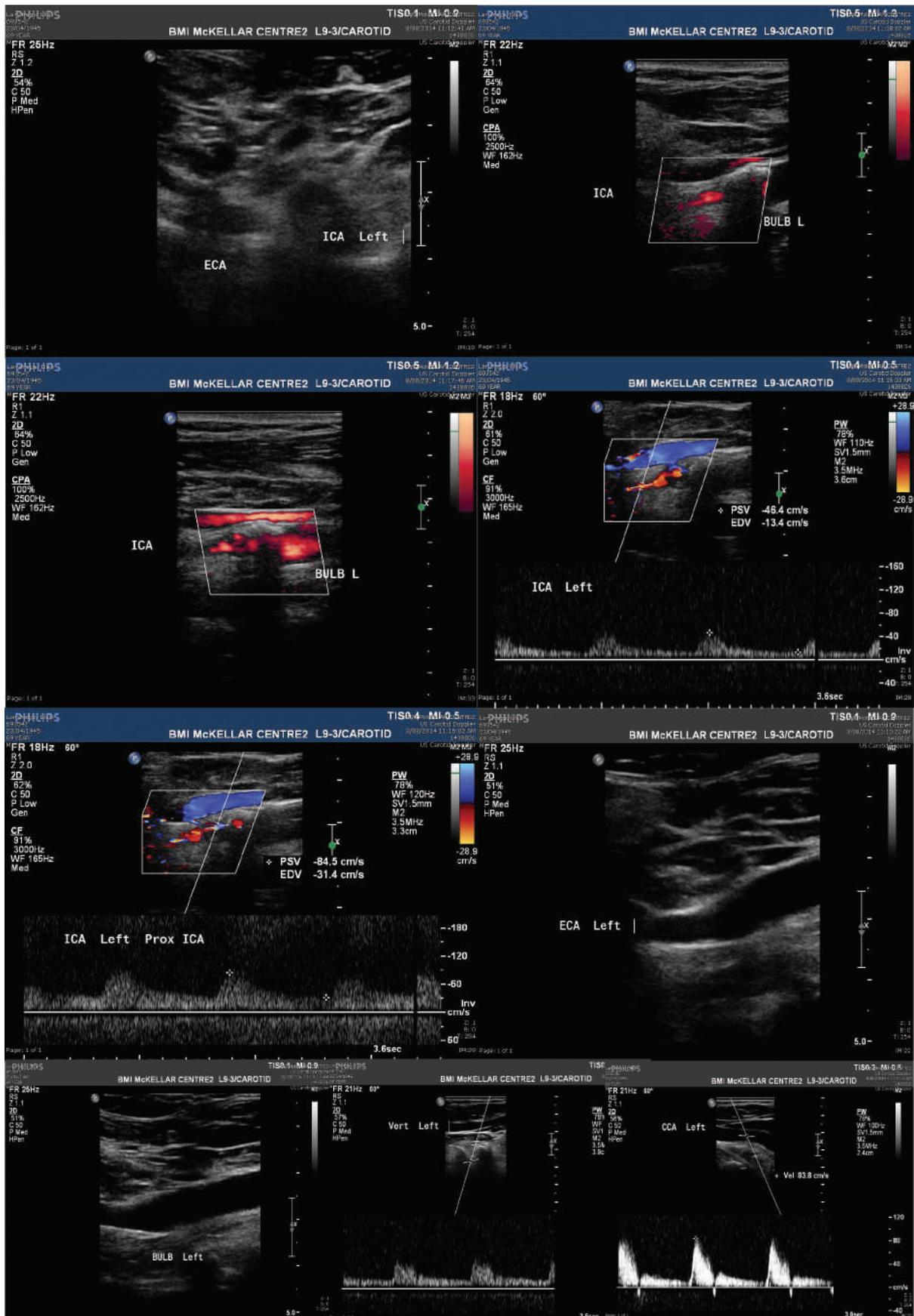
### Discussion

Spontaneous recanalization of the internal carotid artery is not uncommon in the acute phase<sup>2</sup>. However late spontaneous recanalization remains rare with only anecdotal evidence including five similar case studies and one prospective cohort study published within the last 10 years<sup>1,3-5</sup>. The imaging modality during follow-up surveillance is varied with ultrasound (US), magnetic resonance angiogram (MRA) and computerized tomographic angiography (CTA) all routinely used. Despite the increased cost and risk associated with MRA and CTA these are both commonly selected instead of US imaging<sup>3</sup>. However, a recent study demonstrated that US equals the accuracy of CTA for carotid artery disease surveillance and given its clear advantages should be the imaging modality of choice<sup>3</sup>.

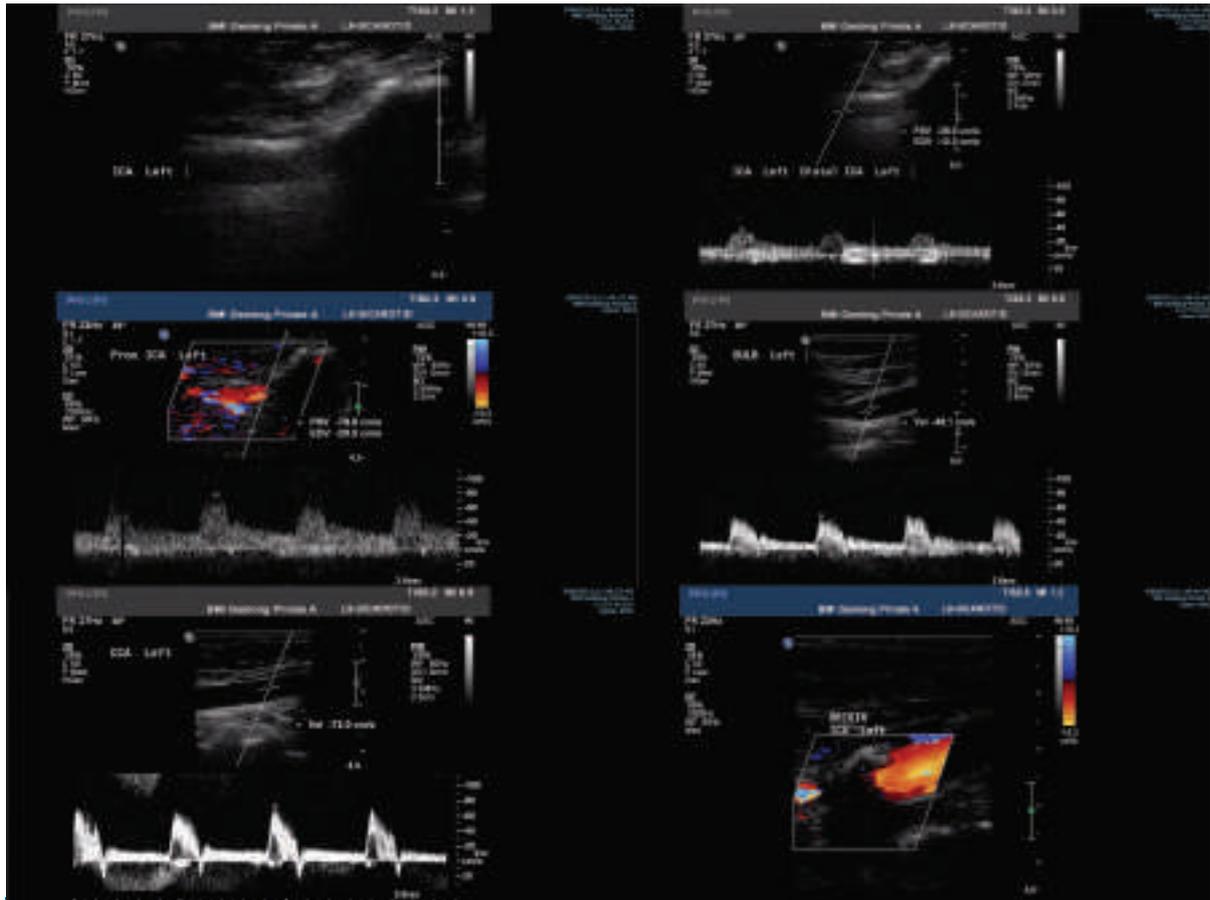
A review of the literature also demonstrates a wide range of clinical followup times for patients with contralateral carotid artery occlusion, which makes assessing the time course of recanalization difficult<sup>6</sup>. However, the likelihood of this occurring does decrease with time, highlighting that older atheroembolic clot is more resistant to recanalization<sup>6</sup>. There are numerous hypotheses to explain spontaneous recanalization in the acute setting; however the aetiology behind chronically occluded carotid arteries remains known<sup>1</sup>.



2011 Carotid Ultrasound : The left ICA is completely occluded. No stenosis of the left CCA or origin of the ECA.



**2014 Carotid Ultrasound** : A normal appearance of the left CCA. Whereas previously the left ICA was thought to be occluded, there appears to be trickle flow through it on today's examination. Normal directional flow of the left vertebral artery.



**2015 Carotid Ultrasound** : Normal appearance to the left common carotid artery. No visible intimal thickening or plaque. Minor calcified plaque is present at the origin of the internal carotid artery and at the bulb. There are no elevated velocities within the bulb or internal carotid artery.

A prospective study demonstrated acute phase recanalization occurring in up to 33% of patients within 7 days of internal carotid artery occlusion<sup>5</sup>. Further prospective analysis of a larger patient cohort with carotid artery dissection demonstrated that spontaneous recanalization was most likely to occur in the first 6 months<sup>7</sup>. Camporese et al. demonstrated within a sample size of 696 patients with chronic ICA occlusion that only 2.3% (16 patients) would go on to have spontaneous recanalization over 38 months, therefore highlighting the lower rates of recanalization in the late setting<sup>3</sup>. Within the individual cases studies identified, all five patients underwent successful endarterectomy following late spontaneous recanalization<sup>1,4,5</sup>. However, the 16 patients identified by Camporese et al. did not undergo further surgical intervention and demonstrated benign clinical outcomes after mean follow-up times of 66.2 months<sup>3</sup>. This outcome is also reflected in our case study as Mr EL experienced no further neurological symptoms in the 12 months following initial identification of spontaneous recanalization. These findings therefore question the clinical benefit and cost of surgical intervention following late spontaneous recanalization and therefore the benefit of regular surveillance imaging in chronic asymptomatic carotid artery occlusions<sup>1</sup>. More research is required to determine the best timeline for follow-up imaging in order to maximise the cost-benefit ratio and avoid potentially unnecessary surgical intervention in patients with internal carotid artery occlusion.

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# Class Room Article

## What is Anti - VEGF

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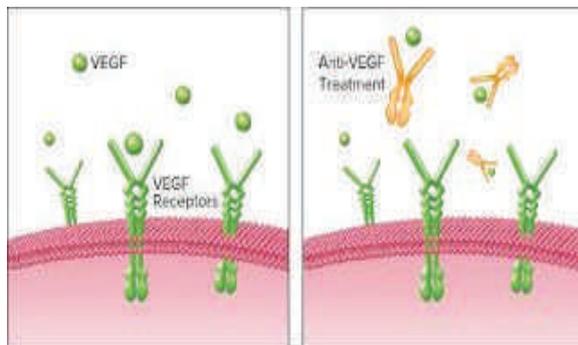
Dr. Shankar has completed his MS from Madras Medical college. His fields of interests include anterior segment microsurgery, medical retina and teaching.

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Vascular endothelial growth factor<sup>1</sup> antagonists play an important part in treatment of retinal disorders. To know more about this, a brief explanation of what is vascular endothelial growth factor is necessary. VEGF is a protein which causes vasculogenesis and angiogenesis. Vasculogenesis is important in development of vessels in embryo whereas angiogenesis plays a part in formation of collateral circulation in ischaemia.

VEGF is a type of growth factor. Increased presence in body can lead to diseases. This happens in carcinoma, which leads to increased growth and metastasis. Similarly presence of VEGF causes vascular diseases in retina due to diabetes<sup>2</sup> and Age related macular degeneration. There are five isoforms of VEGF, A, B, C, D and fifth is a placental growth factor. VEGF A is important in angiogenesis after hypoxia. VEGF- B plays an important part in myocardial vasculature, other factors are involved in lymphangiogenesis.



These factors bind to tyrosine kinase receptors on cell surface and become activated by transphosphorylation<sup>3</sup>, which causes vasculogenesis, angiogenesis and lymphangiogenesis. Hypoxia stimulates release of VEGF- A which in turn stimulates angiogenesis. In diabetic retinopathy, hypoxia due to retinal ischaemia releases VEGF which leads to neovascularisation of retina leading to vitreous hemorrhage and later tractional retinal detachment. It also plays a part in wet form of Age related macular degeneration.

VEGF antagonists has become a common method of treatment of neovascularisation of retina due to diabetes or other disorders, in vascular occlusion leading to macular edema, Age related degeneration and Neovascular glaucoma<sup>4</sup>. They are also used in macular edema, neovascularisation due to branch retinal vein occlusion, central retinal vein occlusion<sup>5</sup>. Recently they are used in

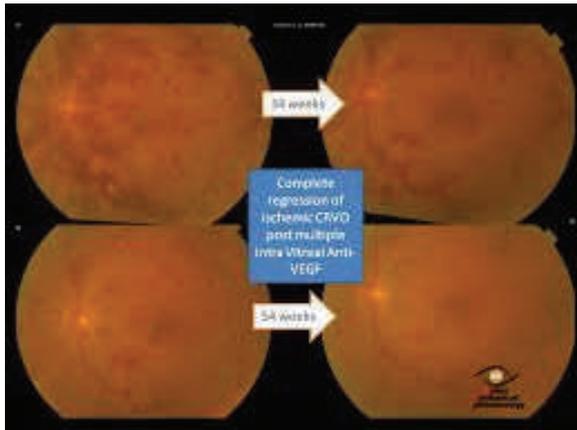
retinopathy of prematurity to prevent progression of retinopathy. They block VEGF and reduce formation of harmful new vessels and there by decrease leakage and retinal edema, It is given as intravitreal injections. There are many anti- VEGF like bevacizumab, Ranibizumab, Pegaptanib, aflibercept, Anecortave acetate. Commonly used drugs are Ranibizumab, Bevacizumab and Aflibercept.



Pegaptanib is a single strand nucleic acid that binds to VEGF 165, which is important in angiogenesis. It is used as 0.3 mg injection once every 6 weeks.

Bevacizumab (Avastin) is a humanized monoclonal antibody to all isoforms of VEGF. It was initially used for colorectal cancer metastasis. It binds directly to VEGF and forms a protein complex which inhibits further action of VEGF. It is used as off label drug in dose of 1.25 mg in 0.05 ml as intravitreal injection every 4-6 weeks. It is not approved by FDA. Intra-vitreous low dose of 0.375mg in 0.03 ml is used in retinopathy of prematurity with good outcome<sup>6</sup>.

Aflibercept ( Trap Eye) is similar to Bevacizumab and Ranibizumab. It is a fusionprotein with portion of receptors of VEGF (R-1, R-2). It has FDA approval for use in wet ARMD and is also used in macular edema due to diabetes and vascular occlusions. It is given as 2mg in 0.05 ml every 4 weeks for 3 months and once every 2 months later. All these drugs given by intra-vitreous injections can lead to floaters, increased intra-ocular pressure and rarely lead to endophthalmitis and retinal detachment. Since Bevacizumab half life is more(20 days) compared to Ranibizumab the chance of systemic side effects like stroke was found to higher.



Ranibizumab (Lucentis) is a f-ab fragment of Bevacizumab. It is a monoclonal antibody fragment with strong binding to VEGF-A. it is given as 0.5 mg in 0.05 ml every 4-6 weeks as intra-vitreal injection.

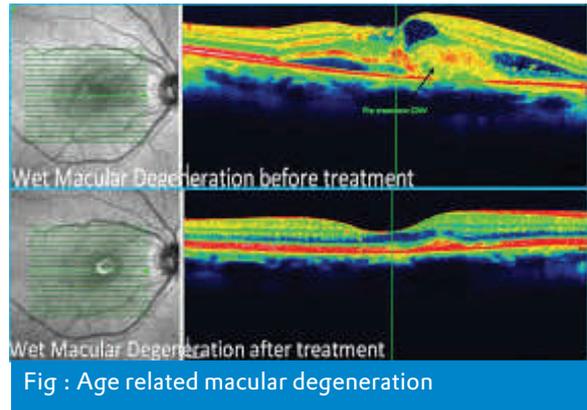


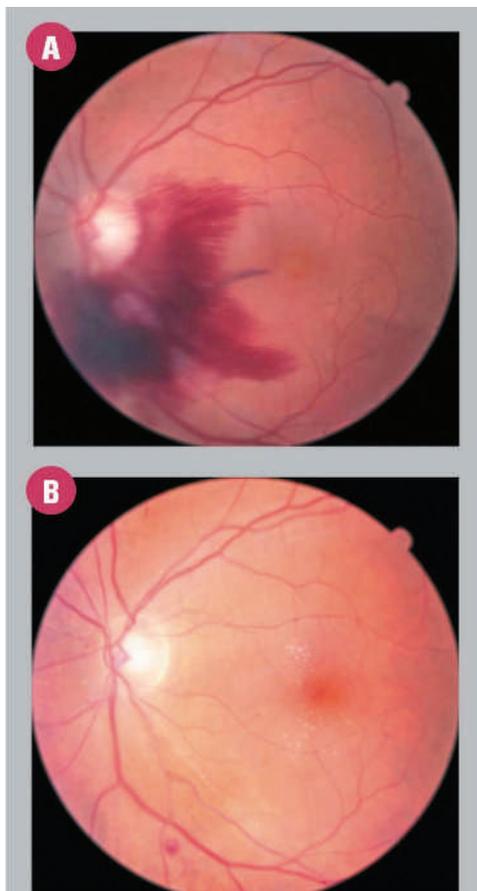
Fig : Age related macular degeneration

### Conclusion

In spite of limitations and cost, the advent of anti-VEGF has become a boon for patients to reduce severe visual loss. Newer anti- VEGF are being tested to get better results compared to Ranibizumab and Bevacizumab.

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**A** Fundus photo of the left eye focused at the plane of the RNFL showing striations of blood within that layer of the retina. There is macular swelling, which accounts for the reduced visual acuity.

**B** Fundus photo of the left eye demonstrating almost complete resolution of the pre-retinal hemorrhage. The visibility of the macula has improved consistent with her improvement in visual acuity. Note the presence of asteroid bodies, as well.

# From the Pages of History

## History of Intra Ocular Lens

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### History

Human crystalline lens is a transparent structure in eye, which along with cornea helps in focusing of light on retina. As ageing occurs this transparency is lost leading to formation of cataract. Even though cataract surgery was practiced 2000 years ago, modern cataract surgery started only 50 years back. In the past opaque cataractous lens was removed leaving the patient with compromised vision after surgery. Italian scientist Tadni in 18th century first considered intra ocular lens implantation. In 1795 Casamata implanted an glass intraocular lens with poor outcome.

In 1949, Sir Harold Ridley<sup>1</sup> first implanted the successful intra ocular lens in London. This was due to the curiosity of his student who commented to Ridley that he did not replace anything after removing the cataract. At the same time Ridley was treating many World War II fighter pilots who had shattered windshield of cockpit in eyes, which did not cause reaction as a foreign body. This made him use this material called polyethyl methacrylate (PMMA) for intra ocular lens which was found to be accepted well by the eye. This started the journey of IOL.



Fig1: Sir Harold Ridley

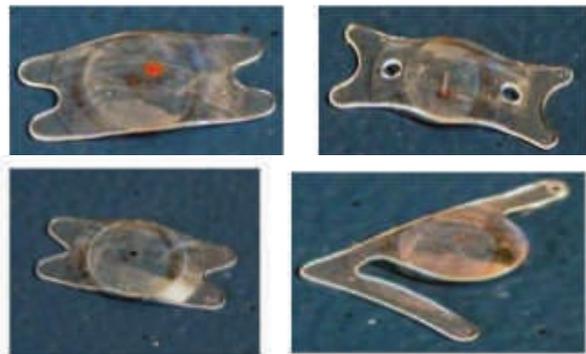


Ridley Posterior Chamber Lens 1949

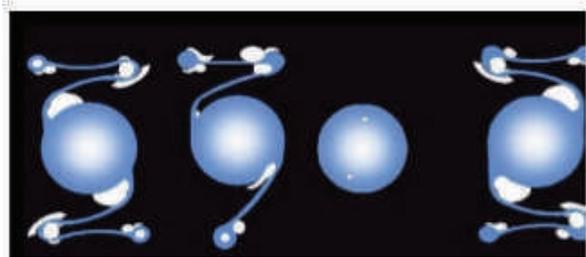
### Development

Development of IOL was with great success and disasters. Major development took place during seventies by Dr. Binkhorst, Dr. Worst in Europe and Dr. Shearings in America. They removed cataract leaving behind the lens capsule and implanting the IOL in the bag which improved the outcome dramatically. At the same time Dr. Charles Kelman was developing phacoemulsification, a new method of removing cataract through a small incision which paved way for development of foldable lens which when implanted unfolds within the eye giving better visual outcome.

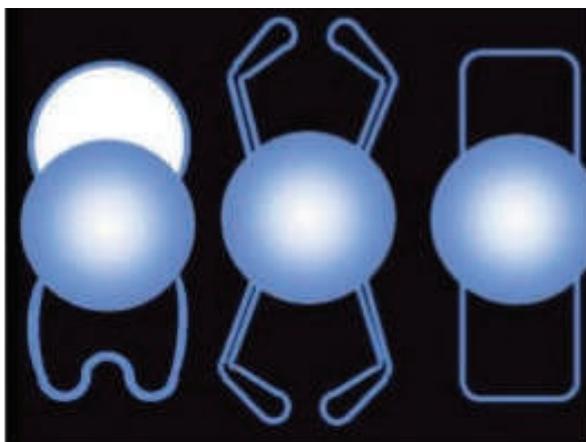
Improved surgical techniques led to the development of IOL. The generation in which it occurred is described as  
 1st generation – Posterior chamber IOL  
 2nd generation – Anterior chamber IOL  
 3rd generation – Iris supported IOL  
 4th generation – Anterior chamber Kelman IOL  
 5th generation – again Posterior chamber IOL  
 6th generation – from 1990 till date the newer IOL



Mark VIII, Mark IX, flexible ACIOL, Kelman, Kelman flexible tripod, Kelman quadraflex, Kelman multiplex 4 point fixation

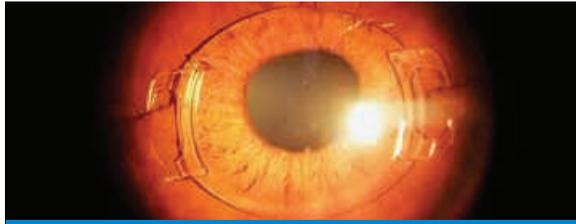


Kelman multiflex AC-IOL (1982)  
 Kelman flexible Tripod AC-IOL (1981),  
 Intermedics Inc Dubroff AC-IOL (1981),  
 Modern, one-piece, flexible PMMA AC-IOL (Kelman design) with Choyce foot plates (various manufacturers).



Azar 91Z AC-IOL (1982)  
 ORC Inc Stableflex AC-IOL (1983)  
 Surgidev Inc Style 10 Leiske ACIOL (1978)

Fig 2: 2<sup>nd</sup> Generation IOLs



**Fig 3:** Kelman IOL

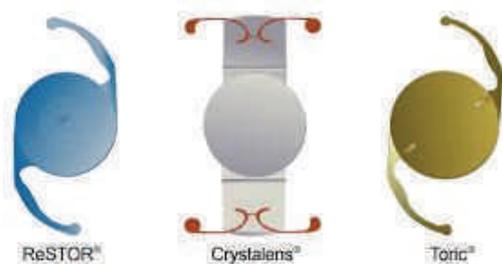


**Fig 4:** AC IOL

The search for ideal IOL is still on. IOL has evolved from replacement for cataractous lens to cosmetic refractive surgery. The outcome of surgery is determined by the pre and post operative astigmatism, and loss of accommodation due to the procedure. The patient after surgery has only proper distant vision with compromised near vision due to loss of accommodation.

### Premium IOL

Newer premium IOL have redefined the way patient sees after surgery. The change from simple rigid PMMA lens which has to be implanted through a large incision to foldable lens being implanted through small incisions. These lenses are made of hydrophilic, hydrophobic acrylic material and silicone which can be folded or rolled.



**Fig 5:** Premium IOLs

Aspheric lenses where the edges of lens are flattened to reduce the aberration induced by regular lenses, to lenses with yellow chromophores which prevents damage to eye by ultra-violet light. Toric<sup>3</sup> lenses are available which can overcome astigmatism and give clear vision with good contrast sensitivity. Multifocal lenses (Restor, Crystalens<sup>4</sup>) have redefined surgery leading to better distance, intermediate and near vision (fig5). Myopic patients with high refractive error can be corrected with Phakic<sup>5</sup> IOL which can be implanted over the normal clear lens leading to better vision (fig6). This has made IOL has refractive surgery counterpart.



**Fig 6:** Phakic IOL

Patients with low vision due to retinal problems can have telescopic IOL<sup>6</sup> implanted which improve distant vision and used as low visual aids. This lens was first discovered by Dr. Lipshitz. He later modified this with mirrors to improve peripheral field and called it as Telescopic macular implant (fig7).



**Fig 7:** Telescopic IOL

### Future

Light adjustable IOL have also rapid strides in improvement. After IOL has been implanted the curvature of the IOL can be altered by application of laser. The search for better IOL with youthful vision is still leading the charge.

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# Instruction to Authors

Chettinad Health City Medical Journal 2016; 5(1): 56 - 58

The following are the uniform requirements for manuscripts submitted to the Chettinad Health City Medical Journal, which are in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journal" developed by International Committee of Medical Journal Editors (October 2001).

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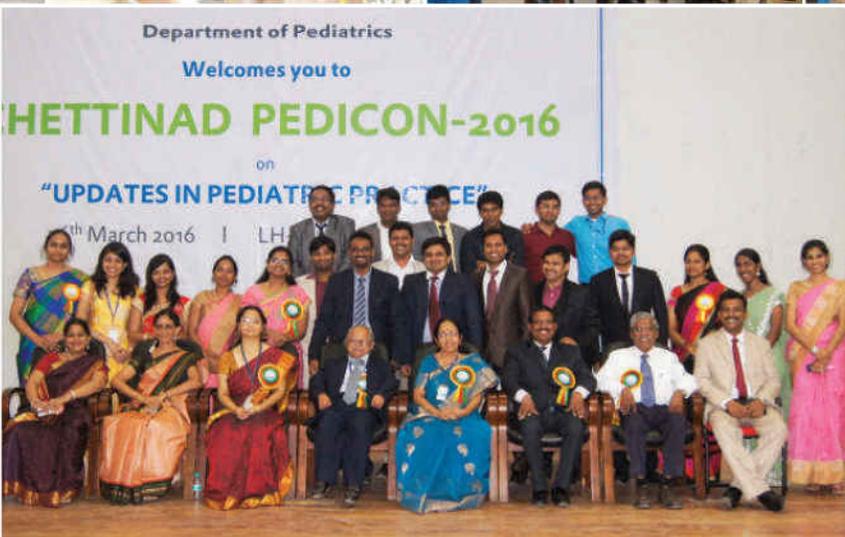
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