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- Statin up and forget it - Does it work for Indians
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Editorial

Vanakkam.

This issue of the journal carries an original article, several interesting review articles and a case report, besides the usual columns.

An original article reports on the prevalence of medical disorders in a dental population; some patients presented with the medical disorder and in others, the disorder was picked up at a routine dental examination thereby indicating that even the unspoken mouth often tells about the underlying medical condition.

Traumatic brain injury is increasing worldwide more so in India, road traffic accidents being the major cause. Unruly traffic, poorly maintained roads, unregulated drivers, drunken driving, negligent riding and an absolute disregard for the law, all contribute in no small measure to this avoidable epidemic. A review article outlines the intensive care management of traumatic brain injury.

Food is the primary source of nourishment to all human beings. Food both in excess and in the deficient state can cause disease; Thiruvalluvar has very well stressed the importance of food in the famous couplet –

No need of medicine to heal your body’s pain,
If, what you ate before digested well, you eat again

Explanation
No medicine is necessary for him who eats after assuring (himself) that what he has (already) eaten has been digested.

Neutraceuticals is a 68 billion dollar industry. However, the role of such nutritional supplements – nutraceuticals and antioxidants in health and disease is not so clear.

An invited article on ‘Antioxidants in health and disease’ reviews the different trials in different disease conditions and gives a candid view of the role of antioxidants. Neutraceuticals claim to enhance male fertility. Nutraceuticals are primarily antioxidants given to men with infertility based on the assumption that reactive oxygen species found in the semen sample of these men are detrimental. A review article discusses the role of Neutraceuticals in male infertility.

A Medical update emphasizes the beneficial role of walking in the prevention of fractures and another one highlights the situation where informed consent may not be required. A case report where a three-dimensional augmentation of a deficient alveolar ridge is proposed as a treatment is an interesting read.

Pages of history outline the life and time of Harvey Cushing. Interesting informative medical updates complete the issue and volume. Hope you enjoy going through this issue. Please do give us your valuable feedback.

Dr. N. Pandiyan
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Commentary
Definition of Oligozoospermia - A Commentary
Prathima. T*, Dr. Pandiyan. N**

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Ms. Prathima graduated from Bangalore University, Bangalore. She finished her Masters in Molecular Biology coming second in the university. She worked in the field of embryology for 3 years in Bangalore. She is currently working as the Assistant Embryologist in the Dept. of Reproductive Medicine, Chettinad Health City.

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Semen analysis is an important tool in male infertility investigation. Through its cellular and chemical components, human semen can provide information on the functional properties of the organs producing this fluid, i.e., the testes, epididymis and accessory glands. The history of semen analysis dates back to 1677 when Anton von Leeuwenhoek made a remarkable discovery of the spermatozoa, which he called animalcules or spermatozoon. In his letter to The Royal Society of London, he described the structure of spermatozoa so accurately that in retrospect, his illustrations with the help of such a primitive microscope seem incredible. Leeuwenhoek was also the first to discover the presence of spermatozoa in the fallopian tubes and uterus of an animal apart from demonstrating that the sperm are produced in the testicles.

Upon discovery of the sperm, analysis of semen entered a more scientific realm. Semen analysis was developed by pioneers in the field like Lode, MacLeod Heim and Hotchkiss, not to forget Eliasson and Gold. It was Edward Martin, in the year 1902, who first put forth the inclusion of semen analysis in male infertility investigation. Even with all the efforts put in by such brilliant scientists to standardize semen analysis, it still is, as Christopher De Jonge rightly said, the subject of both commendation and condemnation. Semen analysis remains a numbers game.

In 1980, the WHO published its first manual on semen analysis thereby establishing standards internationally. It has been updated periodically; five manuals have been published over the last three decades. It has undergone numerous changes over the years, the initial ones being more consensus-based while the last one seems evidence-based, despite its discrepancies. The current edition value of 15 million/ml for sperm concentration also seems arbitrary though evidence-based. It’s anybody’s guess as to how this can result in 39 million/ejaculate with a volume of 1.5 ml. The expression of sperm concentration per ml and not per ejaculate seems incorrect as it is the output of sperm in the semen that is of interest. A 2 ml sample of 30 million per ejaculate will have 15 million per ml but a 5 ml sample of 30 million per ejaculate will have only 6 million per ml. So to report the former as ‘normal’ and the latter as ‘subnormal’ or ‘abnormal’ seems unjustified.

It is imperative to remember that reference ranges given by the WHO manual are not absolute and definitely not diagnostic cut-off values but only results obtained out of an observation of a fertile population, which reflects an ‘approximate’ probability that the fertility potential could be high. Also, the reference values for the latest edition of the WHO manual were based on a single sample from each participant. The WHO contradicts itself with such an evidence when it has clearly mentioned in the very same manual that, “a man’s semen quality cannot be characterized from a single semen sample”. A semen sample shows high intra-individual variation and therefore categorizing a sample as oligozoospermic based on a single analysis is incorrect.

<table>
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<tbody>
<tr>
<td>Volume (ml)</td>
<td>--</td>
<td>2.0 - 2.0</td>
<td>2.0 - 2.0</td>
<td>2.0 - 2.0</td>
<td>2.0 - 2.0</td>
</tr>
<tr>
<td>Sperm concentration (10^6/ml)</td>
<td>20 - 200</td>
<td>20 - 200</td>
<td>20 - 200</td>
<td>20 - 200</td>
<td>20 - 215</td>
</tr>
<tr>
<td>Total sperm concentration (% of)</td>
<td>2.0</td>
<td>2.40</td>
<td>2.40</td>
<td>2.40</td>
<td>2.40</td>
</tr>
<tr>
<td>Total motility (% motile)</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>Progressive motility</td>
<td>2.25</td>
<td>2.25</td>
<td>2.25 (grade A)</td>
<td>2.25 (grade A)</td>
<td>2.02 (A+B)</td>
</tr>
<tr>
<td>Vitality (% alive)</td>
<td>2.50</td>
<td>2.75</td>
<td>2.75</td>
<td>2.75</td>
<td>2.75 (grade A+B)</td>
</tr>
<tr>
<td>Morphology (% normal)</td>
<td>80.5</td>
<td>80.5</td>
<td>80.5</td>
<td>80.5</td>
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</tr>
</tbody>
</table>

Table 1 - Variations in values of semen across the years
There are multiple factors which can result in a low sperm count. Loss of portion of sample during collection, days of abstinence, infection, partial obstruction of genital tract, drugs, environmental pollutants and other toxic factors due to unhealthy lifestyle. There are numerous papers stating that the use of cell phones, long periods of watching television and stress could result in decline of sperm count and motility. It has also been reported that oligozoospermia and azoospermia are caused by micro-deletions in the AZF region in the long arm of the Y chromosome, which is related to spermatogenesis.

A man’s sperm count is determined by the number of Sertoli cells in his testes, whose number is ascertained early in development i.e. six months before and after birth. As the germ cells develop they depend on Sertoli cells for support, physically and metabolically. However, each Sertoli cell is restricted to support only a certain number of germ cells. So the number of Sertoli cells, which by itself cannot increase after puberty, in each testis determines the overall sperm output. If the testis is exposed to any adverse factors later in life, like toxins, pollutants, disease or drugs, it might result in a drop in the sperm count but nothing can increase it.

Oligozoospermia is not an isolated condition; it is frequently associated with compromised sperm quality, including reduced motility and abnormal morphology, as in oligoasthenoteratozoospermia (OATS). The cause of this is still unknown thereby making the efficacy of any treatment for the same very doubtful.

Male infertility cannot be determined solely on the result of a semen analysis as there is no evidence stating what number and quality of sperm are required for a man to be considered fertile. Oligozoospermia also has to be seen in the context of female fertility as infertility involves the couple and not just the male or female. There is no definite number below which pregnancy is impossible nor is there a number above which pregnancy is certainly possible.

Oligozoospermia (except in extreme cases of occasional sperm in the ejaculate), even in 2014, remains undefined.

Acknowledgements
We thank the faculty of the Dept. of Reproductive Medicine for their support through important discussions and valuable comments on this topic.

References
Original Article

The Frequency of Medically Compromised Patients Visiting Chettinad Dental College and Research Institute: A Retrospective Study

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Ms. Amritha & Ms. G. Priyadarshini******

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Abstract

“Mouth Is The Mirror Of The Body”. The incidence of systemic diseases has increased presently due to changes in the life style of an individual. There is a rapid advancement in the treatment modality of systemic disease which has resulted in the enhanced life span of an individual. A two way relationship exists between oral diseases and systemic diseases which is the prime focus today. Hence this study analyzes the frequency of systemic problems among patients visiting the Chettinad Dental College and Research Institute. Materials and Methods: In this retrospective study medical records of patients visiting CDCRI was analyzed for the year 2011, 2012, and 2013 in the presence of systemic disease. The list of extracted data from each patient’s documents contained the history of cardiovascular diseases, respiratory, renal diseases, endocrine diseases like diabetes mellitus and thyroid, hematological disorders, gastrointestinal diseases. This data was tabulated and frequency distribution of each disease was analyzed using SPSS software. Results: Around 92,177 patients’ medical records were analyzed retrospectively for 3 years (2011, 2012, and 2013). 3,820 patients had medically compromised conditions which accounted for 4.14%. The percentage of systemic disease accounted are the following: cardiovascular disease (39.29%), Diabetes mellitus (35.45%), Respiratory disorders (8.69%), thyroid (6.23%), Hepatitis (2.46%), Skin (2.43%), Epilepsy (2.02%), Renal disorders (2.01%), Blood dyscrasias (1.34%), which is depicted in the tabulation and graph. Conclusion: As there is increased prevalence of systemic disorders, primarily, a modification in the treatment modality can be done only with a perfect medical charting. Secondly, more emphasis should be given to annual dental checkups as a “healthy mouth leads to healthy body”.

Key words: Systemic disorders, Prevalence, Focal infection.

Introduction

“Mouth is the mirror of the body”. The incidence of systemic diseases has increased presently due to changes in the life style of an individual. There is a rapid advancement in the treatment modality of systemic disease which has resulted in the enhanced life span of an individual. A two way relationship exists between oral diseases and systemic diseases which is the prime focus today.

Hence a good oral health is necessary to maintain a healthy systemic condition. The knowledge of the importance of focal infection causing systemic diseases resulted in increased number of medically compromised patients visiting the dental college. Hence this study analyzes the frequency of systemic problems among patients visiting the Chettinad Dental College and Research Institute (CDCRI).

Materials and Methods

In this retrospective study medical records of patients visiting CDCRI was analyzed for the year 2011, 2012, and 2013 for the presence of systemic disease. The list of extracted data from each patient’s documents contained the history of cardiovascular, respiratory, renal, endocrine diseases like diabetes mellitus, thyroid, hematological disorders, and gastrointestinal diseases. This data was tabulated and frequency distribution of each disease was analyzed using a SPSS software.

Results

Around 92,177 patients’ medical records visiting the Chettinad Dental College and Research Institute were analyzed retrospectively for 3 years (2011, 2012, and 2013). 3,820 patients had medically compromised conditions which accounted for 4.14% of the total population with oral disease who had visited the Chettinad Dental College and Research Institute. Between 4.14% of the medically compromised patients visiting Chettinad Dental College and Research Institute the frequency of each systemic problem is mentioned below as a percentage. The percentage of systemic disease accounted are as follows: cardiovascular disease (39.29%), Diabetes mellitus (35.45%), Respiratory disorders (8.69%), thyroid (6.23%), Hepatitis (2.46%), Skin (2.43%), Epilepsy (2.02%), Renal disorders (2.01%), Blood dyscrasias (1.34%), which is depicted in the tabulation and graph (Table 1), (Graph-1).
Discussion

The prevalence of medically compromised patients visiting the Chettinad Dental College and Research Institute was studied from the medical records of the dental patients for 3 years retrospectively - (2011, 2012, 2013). A total of 92,177 patient’s medical records were screened. Among these records 3820 patients were medically compromised, which accounted for 4.14%. The frequency distribution of each systemic disease accounted for the following, cardiovascular disease (39.29%), Diabetes mellitus (35.45%), Respiratory disorders (8.69%), thyroid (6.23%), skin (2.43%), hepatitis (2.46%), renal (2.01%), blood dyscrasias (1.34%), epilepsy (2.02%).

Hence the focus in the present study was to analyze the number of medically compromised patients visiting the dental college. It enables us to lay more emphasis on the modification of treatment modality for these patients. Secondly, the awareness of the relationship between oral and systemic disease among patients can be analyzed. Today, oral diseases are interrelated with systemic diseases. There is a two way relationship between cardiovascular and periodontal disease. Periodontal disease is the 6th complication of diabetes.

Al-bayaty et al, stated that among 303 medical conditions encountered, 289 individuals were medically compromised and showed a prevalence rate of 42%, Hypertension (12.6%), Diabetes mellitus (6.1%), asthma (5.8%), arthritis (4.7%), allergy (8.3%). Fenlon et al, revealed the medical status of 1500 patients attending a primary health care centre. The incidence of each disease accounted for the following: cardiovascular disease (10.4%), endocarditis risk (5.8%), hepatitis (7.8%), leukemia (0.3%), bleeding disorders (3%), and allergy (7%). Cottone et al, surveyed 4,365 patients between 1975 and 1976. 1833 patients were medically compromised. The frequency of the positive response in the various groups were the following: genito-urinary disease (19.8%), allergy (19.2%), respiratory disorders (19.2%), gastrointestinal disorders (17.9%), cardiovascular diseases (15.8%), endocrine disorders (8.3%), and musculoskeletal disorders (15.1%). Increased prevalence of genitourinary disease was seen which is attributed to variations in the locality. Natto et al, assessed periodontal bone loss among medically compromised patients visiting a dental hospital in Saudi Arabia. The most common prevalent disease was diabetes mellitus. Nery et al, revealed that in a total of 581 patients out of 581 periodontal patients studied, the most prevalent medical problem encountered was cardiovascular disease. Dhanuthai et al, surveyed 58,317 patients and discovered that 7,167 patients were medically compromised. The incidence of heart disease was more prevalent which is correlated with our study. Almask, Awtarani et al, studied the medical records of 740 patients between Jan 2002 to June 2002. The age range was 18-64yrs; diabetes mellitus, hypertension, asthma, rheumatic heart disease were commonly seen. This is compatible with our study. Georgiou et al, discovered that the prevalence of cardiovascular disease was highest among 1000 adult patients visiting the dental clinic which is in concurrence with our study. Aggarwala et al, related the increased prevalence of cardiovascular disease among 3,786 medically compromised patients studied. This also correlated with our study. Burgausz et al, however, in contrary to our study, in a study among 1,509 patients the incidence of gastrointestinal


<table>
<thead>
<tr>
<th>YEAR</th>
<th>TOTAL OP</th>
<th>CSV</th>
<th>DIABETES</th>
<th>THYROID</th>
<th>RENAL</th>
<th>SKIN</th>
<th>HEPATITIS</th>
<th>RESPIRATORY</th>
<th>BLOOD DYSCRASIAS</th>
<th>EPILEPSY</th>
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<tbody>
<tr>
<td>2011</td>
<td>27456</td>
<td>592</td>
<td>546</td>
<td>94</td>
<td>24</td>
<td>26</td>
<td>155</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>27161</td>
<td>516</td>
<td>476</td>
<td>78</td>
<td>29</td>
<td>16</td>
<td>25</td>
<td>71</td>
<td>24</td>
<td></td>
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<tr>
<td>2013</td>
<td>37560</td>
<td>393</td>
<td>332</td>
<td>66</td>
<td>27</td>
<td>33</td>
<td>43</td>
<td>106</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>TOTAL</td>
<td>92177</td>
<td>1501</td>
<td>1354</td>
<td>238</td>
<td>80</td>
<td>93</td>
<td>94</td>
<td>332</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

disease was more prevalent\textsuperscript{10}. The results of the present study showed increased incidence of cardiovascular disease followed by diabetes mellitus, and respiratory disease. All the above mentioned disorders are associated with a medical emergency. Hence, further studies are required to assess the etiology, the interlinked pathogenesis and risk factors of the disease. One of the most prevalent dental causes of these systemic diseases is periodontal disease. Periodontal disease can precipitate cardiovascular disease, respiratory disease, and it’s the 6th complication of diabetes. Hence it’s advisable to have regular dental check up annually as “prevention is better than cure”.

\textbf{Conclusion}

Based on the results of the study there seems to be an increased incidence of cardiovascular disease followed by diabetes and respiratory disorder which is attributed to environmental changes, life style and age. As there is increased prevalence of systemic disorders, primarily a modification in the treatment modality can be done only when a perfect medical charting is done. Secondly, more emphasis should be given to annual dental checkups as a "healthy mouth leads to healthy body". Hence further studies are required to analyze the etiology of these disorders.

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\textbf{If it is Alzheimer’s, your judgment is as good as your physician’s!}

Have you noticed significant memory lapses that you felt are worthy of being reported in the recent past? Then you are potentially a candidate for developing Alzheimer’s later in your life. That appears to be the conclusion of a study conducted in Sanders-Brown Center on Aging, University of Kentucky. In that study, the investigators asked 3701 men aged over 60 a simple question: “Have you noticed any change in your memory since you last came in?”. The responses obtained led the investigators to conclude that the subjective memory complaints are early markers of Alzheimer disease. This has also been the observation of several other epidemiologists. The researchers consider that encouraging as it is now possible to intervene early to reduce the effects of cognitive memory impairment. (Science Daily, 21 February 2014. (\texttt{www.sciencedaily.com/releases/2014/02/140221114124.htm})

- Dr. K. Ramesh Rao
Invited Article

Antioxidants in Health and Disease: Review of Clinical Trials

Namrata Sanjeevi

Doctoral candidate, University of Texas, USA

Namrata Sanjeevi graduated from PSG College of Technology with a degree in Biotechnology. Currently, she is a doctoral candidate in Nutritional Sciences at the University of Texas, Austin with a solid foundation in research methods and fundamentals of nutrition. Research interests include the design and implementation of a multifaceted approach to identify factors that influence suboptimal diets in Supplemental Nutrition Assistance Program (SNAP) participants.

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Abstract

Free radicals play an important role in several biological processes such as cell signaling and redox regulation. However, prolonged exposure to free radicals leads to oxidative damage. Subsequently, it has been implicated in the progression of several diseases like cancer, cardiovascular disease, neurological disease, pulmonary disease, rheumatoid arthritis, nephropathy, ocular disease and pre-eclampsia. The antioxidant defense system within the body may confer protection to oxidative damage by scavenging free radicals. Antioxidants also may be obtained from dietary sources/supplements. The efficacy of antioxidant intake on initiation and progression of chronic diseases will be reviewed.

Chettinad Health City Medical Journal 2013; 2(4): 113 - 122

Introduction

Oxygen is an element that is crucial for the sustenance of life on earth. It is paradoxical that this indispensable element can cause harmful effects in humans under certain circumstances. Much of the detrimental consequences of oxygen are attributed to its ability to form free radicals. A free radical is a reactive molecule that contains at least one unpaired electron in its outer orbit, and is capable of independent existence. Accumulation of these molecules in the body results in oxidative stress, a process by which physiologically important molecules such as carbohydrates, proteins and lipids are damaged. However, the body can employ antioxidants to impede the threat of free radical attack. Antioxidants are potent scavengers of free radicals. They function by donating an electron to a free radical or by eliminating initiators of free radicals. Antioxidants may be classified as endogenous or exogenous depending on their mode of acquisition by the body. Endogenous antioxidants are naturally produced by the body. Superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase are enzymatic systems within the body that function as antioxidants. Lipid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid and bilirubin are examples of non-enzymatic antioxidants that are produced during metabolism. On the other hand, exogenous antioxidants cannot be synthesized biologically, and must be supplied through the diet and/or supplements. Vitamin E (alpha-tocopherol), vitamin C (ascorbate), beta-carotene (provitamin A carotenoid), trace elements such as selenium, manganese, zinc, flavonoids, lycopene, omega-3 and omega-6 fatty acids are some antioxidants that can be obtained from the diet. Fruits, vegetables, nuts, herbs, spices and beverages are identified as natural sources of such exogenous antioxidants. A delicate balance between prooxidant and antioxidant substances is achieved by the production and scavenging of free radicals. Under optimal physiological conditions, this equilibrium marginally shifts to favor a prooxidant status and maintains mild oxidative stress within the body. Antioxidants perform a dual role; of scavenging free radicals while still allowing a sufficient amount to persist and carry out vital functions. Some of the important biological functions of free radicals are cell signaling and redox regulation. However, an acute shift towards prooxidant status will lead to oxidative damage. Additionally, lack of regulation of free radicals is implicated in the pathogenesis of several disease states such as cancer, cardiovascular disease, neurological disease, pulmonary disease, rheumatoid arthritis, nephropathy, ocular disease and pre-eclampsia. The purpose of this paper is to review some of the clinical trials that have explored the influence of antioxidant intake from food and supplements on the prevention of initiation and progression of certain chronic diseases. Additionally, the paper will discuss about the use of antioxidants in health maintenance.

Cancer

Mortality and morbidity associated with cancer is a major public health problem. It was estimated that 12.7 million people were affected by cancer worldwide in 2008. Furthermore, about 7.6 million deaths were attributed to cancer. Breast cancer and lung cancer are the leading causes of cancer death among females and males, respectively. The development of cancer is a multistage process that involves initiation, progression
and promotion of the tumor. Free radicals can wreck havoc at all stages of cancer development. The influence of free radical induced deoxyribonucleic acid (DNA) alterations on carcinogenesis may be mediated by epigenetic effects on gene expression, mutations and chromosomal rearrangements. Tobacco smoke, ultraviolet (UV) radiation, consumption of red meat and alcohol, and obesity have been identified as risk factors for various types of cancer owing to their ability to generate oxidative stress. The antioxidant status of cancer patients has been found to be significantly lower than that of normal individuals, as demonstrated by reduced levels of glutathione, glutathione peroxidase, superoxide dismutase, vitamin C and E in cancer patients. Observational studies have reported that the intake of fruits and vegetables confer protection against cancers of the lung, breast, stomach, pharynx, esophagus and pancreas. Given that fruits and vegetables are rich sources of antioxidants, it can be reasoned that antioxidant supplementation reduces the risk of cancer. On the contrary, clinical trials testing the efficacy of antioxidant supplementation for cancer prevention have yielded limited success. The alpha-tocopherol and beta-carotene (ATBC) study sought to determine the effectiveness of alpha-tocopherol and beta-carotene supplementation in reducing the occurrence of lung cancer among male smokers, aged 50-69 years. Results of this trial demonstrated that the incidence of lung cancer was significantly higher among individuals receiving beta-carotene. The Beta-Carotene and Retinol Efficacy Trial (CARET) also found that the relative risk of lung cancer was greater in participants who received beta-carotene and retinol supplementation when compared to placebo.

Participants for this trial included men who were substantially exposed to asbestos due to their occupation. The Linxian study was conducted in Linxian, a rural county belonging to north-central China. The population in this region was reported to be disproportionately affected by high rates of esophageal and gastric cancers, as well as subclinical deficiencies of retinol, carotenoids, tocopherols and other vitamins. The following combination of supplements were used in the Linxian study: Supplement A consisting of retinol palmitate and zinc; Supplement B including riboflavin and niacin, Supplement C comprising of vitamin C and molybdenum, and Supplement D consisting of beta-carotene, selenium and alpha-tocopherol. The eight intervention groups received AB, AC, AD, BC, BD, CD, ABCD, or placebo. The only significant outcome was that the group which received supplement D had a lower risk for stomach cancer mortality when compared to the other groups. The Women’s Antioxidant Cardiovascular Study (WASC) indicated that vitamin C, alpha-d-tocopherol acetate and beta-carotene did not reduce total cancer incidence in women with a history of cardiovascular disease (CVD) or three or more risk factors for CVD. A reduction in non-Hodgkin’s lymphoma risk was observed in women receiving beta-carotene. However, lung cancer incidence was higher among women receiving vitamin C.

Results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) established that selenium, vitamin E or selenium and vitamin E combination did not reduce prostate cancer risk in a group of healthy men. Thus, results from human clinical trials that explore the efficacy of antioxidant supplementation on cancer incidence have been inconclusive.

Cardiovascular disease (CVD)

CVD is the leading cause of death worldwide, and accounted for approximately 17 million deaths in 2008. Diseases of the cardiac muscle tissue and the vascular system, such as atherosclerosis, ischemic heart disease (IHD), stroke, congestive heart failure (CHF), are responsible for CVD. An inappropriate diet, obesity, physical inactivity, alcohol abuse and cigarette smoking are some of the modifiable risk factors of CVD. The effects of risk factors on CVD may be mediated by oxidative stress, which in turn can cause oxidation of low-density lipoprotein (LDL) and disruption of vascular homeostasis. Thus, a diet rich in antioxidants may protect against the risk of CVD. A greater intake of fruits and vegetables has been associated with a lower risk of CVD. The Heart Outcomes Prevention Evaluation (HOPE) was a large scale trial that reported no significant differences in myocardial infarction (MI), stroke and death from cardiovascular causes between vitamin E supplemented and placebo groups. In contrast to the HOPE Trial, other studies that have researched the influence of antioxidant supplementation on CVD risk illustrate the beneficial effects of vitamin E. The Secondary Prevention using Antioxidants of Cardiovascular Disease in Endstage renal disease (SPACE) trial showed a significant decrease in fatal and non-fatal AMI, ischemic stroke, peripheral vascular disease, and unstable angina in CVD patients receiving vitamin E supplement when compared to the placebo group. Similarly, Cambridge Heart Antioxidant Study (CHAOS) study indicated that vitamin E supplementation decreased the incidence of CVD death and non-fatal MI in coronary artery disease (CAD) patients. The Nurses Healthy Study (NHS) determined vitamin A, vitamin C and vitamin E intake obtained from food sources and supplements in a population of middle-aged women. Results from this study reported no association between vitamin A, vitamin C and coronary disease risk. However, intake of vitamin E from food sources was inversely related to risk of death from major coronary events. The use of vitamin E supplements for more than 2 years was associated with a reduction in coronary disease risk. The Physician’s Health Study (PHS) showed that beta-carotene did not reduce cardiovascular mortality in the supplemented group versus the placebo group. Results from the CARET trial indicated an increased risk for cardiovascular death in individuals treated with beta-carotene and retinol than the control group. Additionally, the ATBC study did not establish a beneficial effect of beta-carotene on cardiac-related mortality in male smokers with a history of MI. Thus, vitamin E supplements have shown a greater therapeutic potential for CVD when compared to other antioxidants.

Pre-eclampsia

Pre-eclampsia during pregnancy is marked by high
blood pressure and proteinuria. Clinical manifestations of pre-eclampsia include birth of small-for-gestational-age infant, poor growth of the infant and premature birth, neonatal morbidity and mortality, and conditions that affect liver, kidneys, brain or blood clotting system for the woman. The presence of free radicals may lead to injury of endothelial cells that line the inside surfaces of blood vessels, which in turn results in the clinical symptoms of pre-eclampsia. Predisposition for LDL, resistance to oxidative stress, and antioxidant intake are the major determinants of a woman’s response to oxidative stress. Since a dietary deficiency of antioxidants is associated with this disorder, antioxidant supplementation may be employed as a potential measure to help prevent and treat this condition. Intervenational studies have evaluated the use of vitamin C and E combination, vitamin C and E in combination with alloporin, vitamin C alone, red palm oil, lycopene and selenium in pre-eclampsia. Pregnant women at low, moderate or high risk of developing pre-eclampsia were included for participation in these studies. Women with pre-eclampsia were excluded from participation. The primary outcomes examined were pre-eclampsia, severe pre-eclampsia, preterm birth, small-for-gestational age infants, and infant mortality. No significant differences were reported in the risk of any of the primary outcomes between the antioxidant supplemented and control group for the trials. Women allocated to lycopene had a greater reduction in the relative risk of pre-eclampsia. However, results from this study were based on a small group of women. The existing body of literature does not favor the use of antioxidants during pregnancy to reduce pre-eclamptic risk.

**Diabetes mellitus**

Diabetes mellitus is a chronic, multiorgan disease that can severely damage the eyes, kidneys, nerves, heart and/or blood vessels. Globally, it is estimated that the number of adults affected by diabetes was 285 million in the year 2010, and will increase to 439 million in 2030. India and China are expected to be disproportionately burdened by the increase in diabetes prevalence. This condition is characterized by hyperglycemia that arises out of abnormalities in insulin secretion or insulin action. Hyperglycemia can trigger generation of free radicals, thereby creating a state of oxidative stress that is involved in pathogenesis of diabetes and its related complications. Small scale trials have shown the beneficial effects of antioxidants on diabetes-related complications. Supplementation with vitamin E and vitamin E plus C64 positively influenced endothelial-dependent vasorelaxation in Type I diabetic patients. However, a positive effect was not observed for Type 2 diabetic patients supplemented with vitamin E plus C65. In another study, significant improvement in renal function was observed in Type 2 diabetic patients supplemented with vitamin E plus C66. The Primary Prevention Project (PPP) trial demonstrated no beneficial effect of vitamin E for diabetic subjects. However, the population for the PPP trial was not restricted to diabetic patients. In contrast, the alpha-lipoic acid in Diabetic Neuropathy (ALADDIN)68, ALADIN II49, ALADIN III9, DEKAN (Deutsche kardiopathologie)55 and SYDNEY2 trials were limited to a population of diabetic subjects. ALADIN, ALADIN II and ALADIN III studies demonstrated significant improvements in patient symptoms, nerve function, and neuropathy impairment score, respectively, in diabetic patients who were supplemented with alpha-lipoic acid. In the DEKAN study, cardiac autonomic neuropathy was found to be improved in the alpha-lipoic acid treated group versus placebo group. The SYDNEY trial showed advancements in sensory symptoms of diabetic polyneuropathy upon alpha-lipoic treatment. In summary, large scale clinical trials that involve alpha-lipoic acid treatment have proved to be more effective than trials involving vitamin E treatment. More basic and clinical research is required to test the efficacy of antioxidants, such as alpha-lipoic acid, in improving the prognosis of diabetes.

**Chronic obstructive pulmonary disease (COPD)**

COPD is a common lung disease characterized by airflow limitation attributed to disrupted alveolar attachment, mucus hypersecretion and inflammatory obstruction of the airway. It is a major public health burden worldwide, and is estimated to affect about 14 million people in the United States. Smoking and environmental pollution are two major risk factors for COPD. Oxidative stress from exposure to tobacco and air pollutants may deplete plasma antioxidant capacity, thereby leading to inflammation and mucus secretion. Intake of antioxidants via diet/supplements has been suggested as an ideal way to boost the lung antioxidant system. Moreover, it has been associated with improved lung function, and is suggested as a strategy to enhance COPD outcomes. The Women’s Health Study (WHS) established that vitamin E supplementation lead to a decrease in the risk of chronic lung disease in women. Lykkesfeldt et al, have shown that supplementation of vitamin C, vitamin E and beta-carotene enabled repletion of ascorbic acid in smokers. N-acetyl-L-cysteine (NAC) is a nutritional supplement that has been used to strengthen antioxidant defense system in patients with COPD. NAC has been found to decrease oxidative stress in airways of COPD patients, and alleviate bronchial hypersecretion. Although the use of antioxidants in COPD shows potential, more research is required to formulate recommendations on antioxidant supplementation for COPD management.

**Antioxidants in health maintenance**

A prolonged exposure to free radicals may occur as a consequence of normal physiological processes, such as aging and intense exercise, thereby disrupting the delicate balance that exists within our body. Normal individuals can incorporate antioxidant rich foods into their diet to protect against oxidative stress damage, and thus maintain their health. Anlasik et al, reported a positive association between fruit and vegetable intake and antioxidant status in a group of healthy elderly subjects. On the other hand, intake of antioxidant supplements is recommended only when a reduced antioxidant status is identified. For example, several...
micronutrient deficiencies have been associated with increased morbidity and mortality in children belonging to Africa and Asia\textsuperscript{62}. Some of the deficient micronutrients include vitamin A and zinc\textsuperscript{62}, which also function as antioxidants. In such cases, supplementation may markedly improve clinical manifestations of the deficiency\textsuperscript{63,64}. It is vital to apply caution when using supplements for healthy individuals since intake of high amounts of antioxidant supplements may lead to antioxidative stress\textsuperscript{65}. Hence, precise determination of individual's free radical and antioxidant levels is required before prescribing antioxidant supplements \textsuperscript{7}.

### Conclusions

Several observational studies have demonstrated the beneficial effect of antioxidant rich diets on disease outcomes. However, discrepancy exists between observational studies and clinical trials that test the efficacy of antioxidants in disease prevention. The lack of adequate success in clinical trials can be viewed from different perspectives. Firstly, several physiological factors influence nutrient bioavailability. Some of the factors include age, gender, ethnicity, body weight, genetic composition and stage of the disease. These factors affect the extent to which antioxidants are utilized by the body, as well as the ability of an individual to respond to antioxidant supplementation. Knowledge of physiological variables that influence antioxidant bioavailability is essential to determine critical aspects of clinical trials, such as effective supplement dosage and duration of treatment. Moreover, a host of lifestyle behaviors are responsible for determining the health of individuals. Antioxidant intake in combination with physical activity, alcohol and tobacco moderation may yield profound benefits in disease management. Thus, multifactorial interventions may serve as alternative strategies in disease management. Finally, investigations on the effects of nutrients in isolation may provide valuable information regarding its mode of action, but do not elucidate the phenomenon of total diet. The intrinsic nature of diet is characterized by several interactions between bioactive dietary components, some of which still remain unexplained. Hence, antioxidant supplements must be prescribed with caution and the use of antioxidant rich foods as disease prevention agents may hold promise in future clinical trials.

### Table 1. Summary of selected clinical trials testing efficacy of antioxidants in cancer\textsuperscript{66}

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Trial</th>
<th>Primary outcome</th>
<th>Study population</th>
<th>Relative Risk (Confidence Interval)</th>
<th>Interpretation of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC</td>
<td>(\alpha)-tocopherol (50 mg), or (\beta)-carotene (20 mg), or both versus placebo (\beta)-carotene (20 mg), or placebo</td>
<td>Lung cancer incidence</td>
<td>29,133 male smokers 50–69 years of age, with a history of MI, followed for 5–8 years</td>
<td>Lung: 0.98 (0.81–1.19) (\alpha)-tocopherol vs placebo 1.16 (0.97–1.38) (\beta)-carotene vs placebo 1.15 (0.96–1.38) both vs placebo</td>
<td>A significant increase in incidence of lung cancer for (\beta)-carotene supplemented group. No significant decrease in incidence of lung cancer for any of the other supplemented groups</td>
</tr>
<tr>
<td>CARET</td>
<td>(\beta)-carotene (30 mg) plus retinol (2500 IU) vs placebo</td>
<td>Lung cancer incidence</td>
<td>14,254 smokers+4060 asbestos workers followed for 4 years</td>
<td>Lung: 1.36 (1.07–1.75) (\beta)-carotene plus retinol vs placebo</td>
<td>A significant increase in lung cancer incidence in (\beta)-carotene plus retinol supplemented group</td>
</tr>
<tr>
<td>Linxian Study</td>
<td>Intervention groups: AB, AC, AD, BC, BD, CD, ABCD, or placebo. Supplement A: retinol (3000 IU), zinc (22.5 mg). Supplement B: riboflavin (3.2 mg) Supplement C: vitamin C (120 mg), molybdenum (30 (\mu)g). Supplement D: (\beta)-carotene (15 mg), selenium (50 (\mu)g), (\alpha)-tocopherol (30 mg)</td>
<td>Gastric and esophagel cancer mortality</td>
<td>29,584 male adults ages 40–69 followed for 6 years</td>
<td>Esophagus: 0.97 (0.81–1.17) A vs no A 0.90 (0.75–1.08) B vs no B 1.06 (0.88–1.28) C vs no C 1.00 (0.84–1.21) D vs no D Stomach: 1.05 (0.86–1.27) A vs no A 1.08 (0.89–1.31) B vs no B 1.06 (0.87–1.28) C vs no C 0.81 (0.66–0.98) D vs no D</td>
<td>A significant decrease in stomach cancer mortality for group supplemented with D.</td>
</tr>
<tr>
<td>WASC</td>
<td>Vitamin C (300 mg), vitamin E (600 IU qOD), (\beta)-carotene (50 mg qOD), 3 combinations of 2 agents, And all 3 vs placebo.</td>
<td>CVD incidence</td>
<td>7627 women at least 40 years of age who did not have cancer. Average follow-up 9.4 years</td>
<td>Lung: 1.84 (1.42–2.97) any vitamin C vs placebo 1.25 (0.79–1.97) any vitamin E vs placebo 1.26 (0.80–1.99) any (\beta)-carotene vs placebo</td>
<td>Lung cancer incidence was significantly higher in women receiving vitamin C. No significant decrease in incidence of total cancer/ specific cancer in any other supplemented group.</td>
</tr>
<tr>
<td>SELECT</td>
<td>selenium (200 (\mu)g), vitamin E (400 IU), or both vs placebo</td>
<td>Prostate cancer incidence</td>
<td>35,553 men age 50 years without any suspicion for prostate cancer followed for 7-12 years</td>
<td>Prostate: 1.13 (0.99–1.29) vitamin E vs placebo 1.04 (0.90–1.18) selenium vs placebo 1.03 (0.91–1.20) both vs placebo</td>
<td>No significant decrease in incidence of prostate cancer in any of the supplemented groups</td>
</tr>
<tr>
<td>Name of study</td>
<td>Trial</td>
<td>Primary outcome</td>
<td>Study population</td>
<td>Relative Risk (Confidence Interval)</td>
<td>Interpretation of results</td>
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<tr>
<td>HOPE</td>
<td>Vitamin E (400 IU) vs placebo and ramipril (10 mg/day) vs placebo</td>
<td>Myocardial infarction, stroke and death from cardiovascular causes</td>
<td>Patients aged ≥ 55 with a high risk for CVD. 1838 and 1816 subjects were diabetic in the treatment and control arm, respectively</td>
<td>CVD death: 1.05 (0.90-1.22) vitamin E vs placebo MI: 1.02 (0.90-1.15) vitamin E vs placebo Stroke: 1.17 (0.95-1.42) vitamin E vs placebo</td>
<td>No apparent beneficial effect of vitamin E</td>
</tr>
<tr>
<td>SPACE</td>
<td>Vitamin E (800 IU) versus Placebo</td>
<td>Total CVD endpoints</td>
<td>196 patients with CVD and undergoing chronic hemodialysis</td>
<td>Total CVD endpoints (including sudden death): 0.54 (0.33-0.89) vitamin E vs placebo MI (including sudden death): 0.45 (0.20-0.99) vitamin E vs placebo</td>
<td>Significant reductions in total CVD endpoints and MI in subjects receiving vitamin E</td>
</tr>
<tr>
<td>CHAOS</td>
<td>Vitamin E supplements (400-800 IU) vs placebo</td>
<td>Incidence of cardiovascular death and non-fatal MI</td>
<td>2,002 patients with coronary artery disease (CAD)</td>
<td>Cardiovascular death and non-fatal MI: 0.53 (0.34-0.83) vitamin E vs placebo</td>
<td>A significant reduction in cardiovascular death and non-fatal AMI in subjects receiving vitamin E</td>
</tr>
<tr>
<td>NHS</td>
<td>Classification of participants into quintiles based on vitamin A, vitamin C, vitamin E intake from food and supplements</td>
<td>Incidence of cardiovascular death</td>
<td>34,486 postmenopausal women with no cardiovascular disease followed for 7 years</td>
<td>Coronary Heart Disease (CHD) death: 0.38 (0.18-0.86) vitamin E vs placebo</td>
<td>A significant decrease in vitamin E intake from food and death from CHD</td>
</tr>
<tr>
<td>PHS</td>
<td>aspirin (325 mg on alternate days), β-carotene (50 mg on alternate days), both active agents vs placebo</td>
<td>Incidence of CVD death, MI and stroke</td>
<td>22,071 male physicians, aged 40 to 84 years with no history of CVD events</td>
<td>CVD death: 1.09 (0.93-1.27) β-carotene vs placebo MI: 0.96 (0.84-1.09) β-carotene vs placebo Stroke: 0.96 (0.83-1.11) β-carotene vs placebo</td>
<td>No significant decrease in CVD endpoints in the supplemented group.</td>
</tr>
<tr>
<td>CARET</td>
<td>β-carotene (30 mg) plus retinol (23000 IU) vs placebo</td>
<td>Lung cancer incidence</td>
<td>14,254 smokers + 4060 asbestos workers followed for 4 years</td>
<td>CVD death: 1.26 (0.99-1.61) β-carotene plus retinol vs placebo</td>
<td>Increased risk in incidence of cardiovascular death in supplemented group</td>
</tr>
<tr>
<td>ATBC</td>
<td>α-tocopherol (50 mg), or β-carotene (20 mg), or both versus placebo</td>
<td>Lung cancer incidence</td>
<td>29,133 male smokers, aged 50-69 years with a history of MI, followed for 5-8 years</td>
<td>CHD deaths: 1.75 (1.16-2.64) β-carotene vs placebo 1.33 (0.86-2.05) α-tocopherol vs placebo 1.53 (1.03-2.40) both vs placebo</td>
<td>Significant increase in incidence of fatal deaths from CHD in β-carotene and β-carotene plus α-tocopherol groups.</td>
</tr>
<tr>
<td>Author of study</td>
<td>Trial</td>
<td>Main outcome</td>
<td>Study population</td>
<td>Relative Risk (Confidence Interval)</td>
<td>Interpretation of results</td>
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<tr>
<td>Beazley D et al.</td>
<td>Vitamin C (1000 mg) and vitamin E (400 IU) vs placebo</td>
<td>Rate of pre-eclampsia</td>
<td>100 women pregnant at 14 weeks 0 days to 20 weeks 6 days with a history of pre-eclampsia, chronic hypertension, insulin-requiring diabetes mellitus, or multiple gestation</td>
<td>Rate of pre-eclampsia: 0.92 (0.4-2.13) treatment vs placebo</td>
<td>No significant reduction in the incidence of main outcomes in the supplemented group when compared to the placebo group</td>
</tr>
<tr>
<td>Rumbold AR et al.</td>
<td>Vitamin C (1000 mg) and vitamin E (400 IU) vs placebo</td>
<td>Incidence of pre-eclampsia, death of infant and small-for-gestational age infants</td>
<td>1877 nulliparous women pregnant between 14 and 22 weeks with normal blood pressure at the first measurement in pregnancy, and at trial entry</td>
<td>Pre-eclampsia: 1.20 (0.82-1.75) treatment vs placebo Death of infant: 0.79 (0.61-1.02) treatment vs placebo Small for gestational age infants: 0.87 (0.66-1.16) treatment vs placebo</td>
<td>No significant reduction in the incidence of main outcomes in the supplemented group when compared to the placebo group</td>
</tr>
<tr>
<td>Spinnato JA et al.</td>
<td>Vitamin C (1,000 mg) and vitamin E (400 IU)</td>
<td>Incidence of pre-eclampsia</td>
<td>739 women diagnosed with pre-eclampsia or with a history of pre-eclampsia</td>
<td>Pre-eclampsia: 0.87 (0.61-1.25) treatment vs placebo</td>
<td>No significant reduction in incidence of pre-eclampsia in supplemented group when compared to the placebo.</td>
</tr>
<tr>
<td>Gülmezoglu AM et al.</td>
<td>Vitamin E (800 IU), vitamin C (1000 mg), and allopurinol (200 mg)</td>
<td>Prolongation of pregnancy and assessment of lipid peroxides</td>
<td>56 women with severe pre-eclampsia between 24 and 32 weeks of gestation</td>
<td>Delivery within 14 days: 0.68 (0.45-1.04) treatment vs placebo</td>
<td>No significant differences in prolongation of pregnancy in study group when compared to placebo. Furthermore, there were no differences in lipid peroxide levels</td>
</tr>
<tr>
<td>Steyn PS et al.</td>
<td>Vitamin C (350 mg) two times a day until 34 weeks’ gestation</td>
<td>Incidence of pre-eclampsia, preterm labor</td>
<td>200 women less than 26 weeks’ gestation and with a history of a previous mid-trimester abortion or previous preterm labor</td>
<td>Pre-eclampsia: 1.00 (0.21-4.84) vitamin C vs placebo Preterm birth: 1.43 (1.03-1.99) vitamin C vs placebo</td>
<td>The incidence of preterm birth was higher in women supplemented with vitamin C</td>
</tr>
<tr>
<td>Merchan t AT et al.</td>
<td>Multivitamin containing thiamine (20 mg), riboflavin (20 mg), B-6 (25mg), B-12 (50 microg), C (500 mg), E (30 mg), and folic acid (0.8 mg), β-carotene (30 mg) plus preformed vitamin A (5000 IU) versus placebo</td>
<td>Hypertension during pregnancy</td>
<td>1028 HIV-positive pregnant Tanzanian women between 12 and 27 week gestation</td>
<td>Hypertension during pregnancy: 0.62 (0.40-0.94) multivitamin vs placebo 1.00 (0.66-1.51) vitamin A vs placebo</td>
<td>Women supplemented with multivitamin were less likely to develop hypertension during pregnancy</td>
</tr>
<tr>
<td>Mahdy ZA et al.</td>
<td>Tocotrienol-rich fraction (TRF) of palm oil (100 mg) vs placebo</td>
<td>Hypertension during pregnancy</td>
<td>Healthy women pregnant between 12 and 16 weeks gestation</td>
<td>Pregnancy induced hypertension: 0.36 (0.12-1.09) palm oil vs placebo</td>
<td>No benefits of palm oil in reducing the risk of pregnancy induced hypertension</td>
</tr>
</tbody>
</table>
Table 4. Summary of selected clinical trials testing efficacy of antioxidants in diabetes

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Trial</th>
<th>Primary outcome</th>
<th>Study population</th>
<th>Relative Risk (Confidence Interval)</th>
<th>Interpretation of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPP</td>
<td>Aspirin (100 mg) vs placebo and vitamin E (300 mg) vs placebo</td>
<td>CVD deaths</td>
<td>2062 diabetic patients aged 250 years</td>
<td>Cardiovascular death: 1.23 (0.69-2.19) aspirin vs placebo Cardiovascular death: 1.07 (0.61-1.90) vitamin E vs placebo</td>
<td>Vitamin E supplementation did not significantly reduce incidence of CVD death in diabetic subjects</td>
</tr>
<tr>
<td>ALADIN</td>
<td>α-lipoic acid (1200 mg, 600 mg, or 100 mg) vs placebo for 3 weeks</td>
<td>Symptoms of diabetic peripheral neuropathy</td>
<td>328 non-insulin-dependent diabetic patients with symptomatic peripheral neuropathy</td>
<td>-</td>
<td>Significant improvement in symptoms in α-lipoic acid supplemented group</td>
</tr>
<tr>
<td>ALADIN II</td>
<td>α-lipoic acid (1200 mg or 600 mg) vs placebo for 24 months</td>
<td>Neuropathic symptoms</td>
<td>65 diabetic patients</td>
<td>-</td>
<td>Statistically significant improvements in peripheral nerve function parameters</td>
</tr>
<tr>
<td>ALADIN III</td>
<td>α-lipoic acid (600 mg) vs placebo for 6 months</td>
<td>Neuropathy impairment score</td>
<td>509 Type II diabetic patients aged 18-65 years</td>
<td>-</td>
<td>Improvements in neuropathy impairment score after 19 days of treatment, which was maintained for up to 7 months</td>
</tr>
<tr>
<td>DEKAN</td>
<td>α-lipoic acid (800 mg) vs placebo for 4 months</td>
<td>Cardiac autonomic neuropathy, as indicated by heart rate variability</td>
<td>73 non-insulin-dependent diabetes mellitus patients</td>
<td>-</td>
<td>Improved cardiac autonomic neuropathy in α-lipoic acid treated group</td>
</tr>
<tr>
<td>SYDNEY</td>
<td>α-lipoic acid (600 mg) vs placebo for 14 treatments</td>
<td>Neuropathic sensory symptoms</td>
<td>120 diabetic patients with symptomatic diabetic sensorimotor polyneuropathy</td>
<td>-</td>
<td>Improvement in sensory symptoms such as pain, pricking and numbness in α-lipoic acid treated group</td>
</tr>
</tbody>
</table>

Table 5. Summary of selected clinical trials testing efficacy of antioxidants in COPD

<table>
<thead>
<tr>
<th>Name/author of study</th>
<th>Trial</th>
<th>Primary outcome</th>
<th>Study population</th>
<th>Hazard ratio (Confidence Interval)</th>
<th>Interpretation of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHS</td>
<td>Vitamin E (600 IU every other day) and aspirin (100 mg every other day) vs placebo</td>
<td>Incidence of chronic lung disease</td>
<td>38,597 women aged ≥45 without chronic lung disease followed for 10 years</td>
<td>Chronic lung disease: 0.90 (0.81-0.99) vitamin E vs placebo</td>
<td>Vitamin E supplementation lead to reduction in risk of chronic lung disease</td>
</tr>
<tr>
<td>Lykkesfeldt et al.</td>
<td>Vitamin cocktail containing vitamin C (272 mg), α-tocopherol acetate (31 mg), and folate acid (400 μg) vs placebo for 3 months</td>
<td>Plasma antioxidant status</td>
<td>37 smokers and 38 nonsmokers with self-reported low fruit and vegetable intake</td>
<td>-</td>
<td>Ascorbic acid was depleted in smokers, and increased after supplementation.</td>
</tr>
<tr>
<td>De Benedetto et al.</td>
<td>NAC (600 mg) vs placebo for 12 months</td>
<td>H₂O₂ content in the exhaled air condensate (EAC)</td>
<td>55 males and females, aged, 47-75 years, non-smokers/ex-smokers for at least 5 years, and affected by moderate COPD</td>
<td>-</td>
<td>NAC decreased oxidant stress in airways, as indicated by H₂O₂ content in EAC</td>
</tr>
</tbody>
</table>

References


52) Ametov AS, Barinov A, Dyck PJ, Hermann R,


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Sexual Selection is Safe Selection

Why are the women more attracted to slimmer and fitter men? If you accept Darwin’s ideas, it is due to sexual selection: certain bodily or facial features are indicators of better health and better genes. The findings of a new study published in American Journal of Human Biology (news release, Feb. 18, 2014), apparently supports this. The study, which the authors claim to be the first of its kind, was carried out in University of Wroclaw in Poland, on 90 healthy men and 103 healthy women. Nose and throat swabs were collected from them to find out who among them were colonised by six potentially harmful bacterial species including staphylococci and streptococci. It was found that men with lean body mass and low fat content were less likely to be colonised by bacteria than their fatty cohorts. They were not only carrying less fat but also less germs. The authors feel that the lean, fit men are likely to be more immunocompetent. However, similar association was not observed in women.


- Dr. K. Ramesh Rao
Management of Severe Traumatic Brain Injury in Adults

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Abstract

Head injury is a major cause of mortality and morbidity in India and responsible for two lakh deaths each year. In addition, over ten lakh people require rehabilitation services each year. The management of head injury has been revolutionised through the introduction of evidence based recommendations by the Brain Trauma Foundation. This article is broadly based around these recommendations and deals with the emergency room, anaesthetic and intensive care management of head injured patients. It recommends the introduction of protocols by each and every institution dealing with head injured patients in order to streamline their management.

Key words: Head injury, Intracranial haematoma, Glasgow coma scale, Intracranial pressure.

Introduction

India has unenviable distinction of having the highest rate of Traumatic Brain Injury (TBI) in Asia from road traffic accidents and falls. Approximately ten lakh people suffer from severe TBI out of which nearly 2 lakh die. Over ten lakh people require rehabilitation services each year. 60% of TBI are due to road traffic accidents. Falls are responsible for 20 – 25% of cases and occur predominantly in children and elderly. Violence results in 10 % of cases. Alcoholic intoxication is present in 15 – 20% of patients suffering from TBI. 40% of cases are seen in the age group of 21 – 35 years, 20% under 15 years of age and 5% over 65 years. 80% of cases are seen in males. 66% of cases occur in the evening and nights. 71% of cases of TBI are mild, 15% of cases are moderate and 13% of cases are severe. The major behavioural factors responsible for TBI are non-usage of helmets, alcohol influence, over-speeding, dangerous overtaking and careless crossing of roads.

Intracranial injuries may be classified into diffuse and focal injury. Diffuse brain injury consists of brain concussion or diffuse axonal injury. Concussion is definite retrograde and post traumatic amnesia, even if it is for a few minutes. Diffuse axonal injury is diagnosed on the basis of radiological imaging and should be suspected in coma lasting for more than 6 hours. Focal brain injury consists of brain contusion (coup or contre coup injuries), extradural haematoma, subdural haematoma and intracerebral haematoma (usually located in the frontal or temporal lobes). Subarachnoid haemorrhage is also seen in many cases. (Fig 1 - 4).

Pathology of TBI

Primary injury is the damage produced by the direct mechanical impact and acceleration deceleration stress on the skull and brain tissue. Skull fractures occur over the cranial vault and may be depressed fractures compressing the underlying brain. Fractures involving the skull base result in blood and cerebrospinal fluid leakage into the nose, pharynx or external auditory meatus. Periorbital haematomas (raccoon / panda sign) and retro-auricular haematomas (battle sign) are also seen in base of skull fractures.
In gunshot injuries to the head, the predominant components are subdural and intra cerebral haematoma and cerebral oedema. High velocity injuries are more difficult to treat due to the cavitation effect of the bullet compared to low velocity injuries (bullet velocity less than 360 metres sec\(^{-1}\)) which inflict less damage on the parenchyma.

A lucid interval may occur in extradural and subdural haematomas. An acute subdural haematoma is usually associated with raised intracranial pressure (ICP). A subdural haematoma is acute if the patient becomes symptomatic within 72 hours, sub-acute if between 3 – 15 days and chronic after 2 weeks.

In secondary injury, cerebral hypoxia induced by the primary injury leads to brain swelling which causes the ICP to rise and further worsen the cerebral hypoxia. This vicious cycle is exacerbated by a number of factors whose avoidance will result in a more favourable outcome (Table – 1). All these factors should be diagnosed and treated on an emergency basis in order to limit or prevent secondary brain injury.

Pre-Hospital management of TBI

The main goals of emergency therapy in the field and emergency department are to prevent and treat all systemic (extracranial) and intracranial insults that cause secondary neuronal injury and ultimately improve outcome in patients with severe TBI. The severely brain injured patient (GCS of 8 or less) should be immediately transported to a centre with round the clock CT scanning facility, operation theatre facility, neurosurgical care and the ability to monitor ICP and treat intracranial hypertension in an intensive care setup. Earlier evacuation of intracranial haematomas when and if indicated has a more favourable outcome. If the airway is compromised, it should be secured at the scene of accident itself. Controlled trials are underway in various developed countries to determine whether the presence of a physician at the scene of accident will decrease morbidity and mortality from TBI.

Emergency department management of TBI

Neurological assessment should ideally be done before endotracheal intubation. The Glasgow Coma Scale (Table – 2) was proposed by Teasdale and Jennet in 1974\(^1\). The aim was to allow comparisons between various head injury units. The responses are associated with a points system which gives a classification of the degree of impairment. The lower the score, the more severe the impairment. The minimum score is 3 and the maximum score is 15.
Mild TBI – GCS of 14 to 15. Loss of consciousness if present is less than 5 minutes. These cases require close neurological monitoring but not intensive care.

Moderate TBI – GCS of 9 – 13. These patients have a mixed prognosis.

Severe TBI – GCS of 8 or less persisting for 6 hours or more. Virtually all these patients require ICU admission and ICP monitoring.

Pupillary size, any inequalities, reflex response to light and accommodation should also be assessed along with symmetry of motor function in the extremities. Injuries to other organ systems should then be assessed. Intra-thoracic and intra-peritoneal injuries should be treated without delay. Management of bleeding causing haemorrhagic shock takes precedence over neurosurgical procedures.

Brain herniation syndromes are due to mechanical compression by an accumulating mass or a diffusely increased ICP. Almost all cases present with progressive somnolence and the Cushing’s reflex (hypertension & bradycardia). The following herniation syndromes are described (Figure-5):

A. In **Trans-calvarial herniation**, the brain protrudes through a defect in the skull. This is often worsened by raised ICP.

B. In **Subfalcine herniation**, the cingulate gyrus of the frontal lobe is pushed under the falx cerebri. Clinical signs include increased tone or paresis in the contralateral leg.

C. In **Uncal herniation**, there is displacement of the medial edge of the uncus and the hippocampal gyrus medially and over the ipsilateral edge of the tentorial foramen causing compression of the midbrain. The ipsilateral or contralateral occulomotor nerve may be stretched or compressed. Initially there will be asymmetric pupillary dilatation (anisocoria) which will progress to ipsilateral pupillary dilatation and contralateral hemiparesis.

D. **Upward cerebellar herniation** is uncommon and is usually due to upward herniation of vermis and cerebellar hemispheres through the tentorial foramen due to infratentorial mass lesions. Radiology usually reveals effacement of the superior vermic cistern, compression of the fourth ventricle, upward and forward displacement of the quadrigeminal plate, mesencephalon and cerebral aqueduct causing supratentorial hydrocephalus. If left untreated, there will be medullary compression leading to bradycardia and ventilatory arrest.

E. **Tonsillar herniation** is due to a supra or infra tentorial mass lesion and is a rapid and often fatal event unless recognized immediately and treated. The cerebellar tonsils descend through the foramen magnum compressing the lower brain stem resulting in ventilatory arrest. Of all the herniation syndromes, this one has the narrowest window of intervention to prevent death.

F. **Cerebral transtentorial herniation** is characterised by displacement of the cerebral hemispheres and basal ganglia downwards while the diencephalon and adjacent midbrain are pushed through the tentorial notch. This is usually due to lesions occupying the intracranial vertex or frontal-occipital poles. Clinical presentation will be an impairment of vertical gaze and bilateral extensor posturing.

**Tracheal Intubation** – Tracheal intubation is indicated in all cases with a GCS of 8 or less. All head injured patients should be considered as having a full stomach. Many of them have an associated cervical spine injury. Rapid sequence intubation with manual in line stabilization (MILS) is preferred in haemodynamically stable patients. The patient is pre-oxygenated with 100 % oxygen and anaesthesia is induced with Thiopentone 3 – 4 mg Kg⁻¹ or Propofol 1 – 2 mg Kg⁻¹. Succinyl Choline 1.5 mg Kg⁻¹ is then administered and the trachea intubated. Applying cricoid pressure if a cervical spine injury is not ruled out is controversial. One recommendation would be to apply cricoid pressure after placing the posterior part of the Philadelphia hard collar.

Routine intravenous induction is carried out in a patient without full stomach and stable haemodynamics by titrating the Thiopentone or Propofol dosage to minimize hypotension. Rocuronium 0.6 - 1.0 mg Kg⁻¹ may be used to facilitate endotracheal intubation since

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**Table 2: Glasgow Coma Scale (Adult)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening</td>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>To verbal command</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Best verbal</td>
<td>Oriented, conversing</td>
<td>5</td>
</tr>
<tr>
<td>response</td>
<td>Disoriented, conversing</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No verbal response</td>
<td>1</td>
</tr>
<tr>
<td>Best motor</td>
<td>Obeys verbal commands</td>
<td>6</td>
</tr>
<tr>
<td>response</td>
<td>Localizes to pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Withdrawal</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Abnormal flexion (Decorticate)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Extension (Decerebrate)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No motor response (Flaccid)</td>
<td>1</td>
</tr>
</tbody>
</table>
it has no effect on cerebral dynamics. Lignocaine 1.5 mg Kg\(^{-1}\) given 90 seconds before laryngoscopy will blunt any haemodynamic response and attenuate any rise in ICP. A small dose of propofol or fentanyl or a short acting beta-blocker like esmolol may also be used to blunt the laryngoscopic response.

Ketamine is contraindicated in the routine management of TBI since it elevates the ICP. However, it may have a small role to play in inducing patients in haemorrhagic shock. Midazolam at 0.2 mg Kg\(^{-1}\) may be used for induction. It has minimal haemodynamic effects and hence the cerebral circulation is usually not disturbed. It however interferes with neurological assessments. Fentanyl produces minimal to moderate decreases in MAP and CPP at a dose of 2 – 4 mcg Kg\(^{-1}\). It increases the ICP to a moderate extent\(^{\text{4}}\). When larger doses are used, measures to maintain systemic BP may be required.

If facial fractures and soft tissue oedema prevent direct visualization of the larynx, a fibre-optic intubation or intubation over an illuminated stylet may be tried. Avoid nasal intubation if a base of skull fracture is suspected to avoid intracranial placement of the endotracheal tube or introduction of contaminated material into the brain. Nasal intubation should also be avoided in the presence of severe facial bone fractures or a bleeding diathesis. Instruments for an emergency tracheostomy should be available. Once the airway is secured, insert an oro-gastric tube to decompress the stomach.

Antibiotics should be administered at the time of intubation to reduce the incidence of pneumonia. However, prophylactic antibiotic use for ventricular catheter placement to reduce infection is not recommended\(^{\text{21}}\).

After securing the airway, mechanical ventilation is initiated and the respiratory rate and tidal volume are adjusted to maintain a PaCO\(_2\) of 35 mm Hg. Hyperventilation to a PaCO\(_2\) of 30 mm Hg is indicated only if transtentorial herniation is suspected. Propylactic hyperventilation to a PaCO\(_2\) of less than 25 mm Hg is not recommended. Hyperventilation is used only as a temporary measure to reduce ICP and should ideally be avoided during the first 24 hours after injury. If hyperventilation is used, jugular venous oxygen saturation or brain tissue oxygen tension should be monitored. The Fraction of inspired oxygen (FiO\(_2\)) and positive end expiratory pressure (PEEP) are adjusted to maintain a PaO\(_2\) of 100 mm Hg. Hypoxaemia (PaO\(_2\)< 60 mm Hg or SpO\(_2\) < 90 %) should be avoided\(^{\text{5}}\). A PEEP level upto 12 cm H\(_2\)O is safe in head injury and does not raise the ICP\(^{\text{6}}\). Use a fibreoptic bronchoscope to suction out aspirated material from the bronchi.

**Fluid resuscitation and haemodynamic stabilization**

Fluid resuscitation should be guided by systemic blood pressure, urine output and central venous pressure. Sympathetic over activity in patients with severe TBI along with a reflex response to raised ICP often maintains the blood pressure at normal levels. Induction of anaesthesia in these patients often unmasks hypovolaemia and precipitates hypotension.

Total osmolality is the most important factor that determines the formation of cerebral oedema. Normovolaemia should be maintained in these patients using isotonic and hypertonic solutions. Plasma total osmolality should however be maintained at less than 320 mosm Kg\(^{-1}\). When large volumes of crystalloid are required, use an isotonic solution like Normal saline (308 mosm L\(^{-1}\)). Hypertonic saline (3 %) can be beneficial in severe TBI. In addition to being a useful resuscitation fluid, hypertonic saline reduces cerebral oedema and ICP. A rebound phenomenon is not seen following the use of this solution. The dose is 125 to 250 ml every 6 hours. It may also be used as a continuous infusion at 0.5 – 1.0 ml Kg\(^{-1}\) hour\(^{-1}\). Stop hypertonic saline once the serum sodium concentration reaches 160 mEq L\(^{-1}\). Potential adverse effects include central pontine myelinolysis, seizures, congestive heart failure, hypokalemia, hyperchleraemic acidosis and coagulopathy.

Hydroxy Ethyl Starch (HES) and albumin have also been used for resuscitation. The maximum dose of HES is 20 ml / Kg. HES can worsen coagulopathy which is seen in approximately 20 % of patients with TBI. Dextran should be avoided because of their effect on platelet function.

Blood should be transfused to maintain a haematocrit over 30 % while blood products may be needed to correct coagulation defects such as disseminated intravascular coagulation (DIC) induced by the release of brain thromboplastin.

Ringer’s Lactate is hypotonic (273mosmKg\(^{-1}\)) and will result in an increase in cerebral oedema and ICP as well as contribute to lactic acidosis in ischaemic areas of the brain. Dextrose containing solutions should be avoided because hyperglycaemia is associated with a poorer neurological outcome. In addition, the free water load left after the glucose is metabolised will cause a reduction in plasma osmolality and worsen cerebral oedema.

If the blood pressure and cardiac output cannot be restored to normal through fluid resuscitation alone, inotropes may have to be administered. An infusion of dopamine or phenylephrine is preferred over other inotropes.

**Radiological Evaluation**

CT scanning remains the radiological investigation of choice for evaluating TBI. Indications for scanning TBI patients may be according to the Canadian criteria\(^{\text{7}}\) or New Orleans criteria\(^{\text{8}}\). Brain imaging helps to distinguish cases that require immediate surgical intervention from those that do not and may also identify those whose protracted recovery requires early tracheostomy and feeding gastrostomy.

Indications for early surgical intervention based on CT findings include open depressed skull fractures with dural laceration and various haematomas. An extra dural haematoma with a volume of over 30 ml should be evacuated regardless of GCS. An acute EDH should be evacuated if associated with a GCS of 8 or less and unequal pupils\(^{\text{9}}\). One however has to keep in mind that the acute EDH may be just an incidental finding and not
contributing to the low GCS. The neurosurgeons clinical judgement and wisdom also plays a role before taking up the patient for haematoma evacuation. An acute SDH of less than 10 mm thickness or associated with a midline shift of over 5 mm should be evacuated. An acute subdural haematoma of over 10 mm thickness or taking up the patient for haematoma evacuation. An clinical judgement and wisdom also plays a role before evacuation.

Diffuse Axonal Injury (DAI) is a diffuse nonfocal pattern of injury for which surgical treatment is not indicated unless intractable intracranial hypertension develops. The Marshall classification of initial CT scan appearance categorizes patients with DAI (Table – 4). CT scan appearance in mild DAI includes loss of grey white differentiation, ventricular compression and intra-ventricular blood. Severe high velocity injuries may be associated with multifocal contusions, oedema, effacement of basilar cisterns and brain stem compression. Magnetic Resonance Imaging (MRI) is better than CT scan in revealing the diffuse nature of the injury. Findings include punctate haemorrhages in the peri-ventricular white matter, corpus callosum and brain stem, traumatic sub-arachnoid haemorrhage, intraventricular haemorrhage and tissue tear haemorrhages.

<table>
<thead>
<tr>
<th>Injury Grade</th>
<th>CT Appearance</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal CT scan</td>
<td>9.6 %</td>
</tr>
<tr>
<td>II</td>
<td>Cisterns present - shift &lt; 5 mm</td>
<td>13.5 %</td>
</tr>
<tr>
<td>III</td>
<td>Cisterns compressed / absent – shift &lt; 5 mm</td>
<td>34 %</td>
</tr>
<tr>
<td>IV</td>
<td>Cisterns compressed / absent – shift &gt; 5 mm</td>
<td>56.2 %</td>
</tr>
</tbody>
</table>

Anaesthetic management of TBI

The main goals of anaesthetic management are the optimization of cerebral perfusion and oxygenation, prevent secondary injury and provide good surgical conditions. There is no single way of anaesthetising these patients and the suggested management is what is being generally practiced by the author. General anaesthesia is preferred since it facilitates good control of the ventilatory and circulatory systems. Many patients reach the operation theatre with an endotracheal tube in-situ. In patients who are yet to be intubated, anticipate a full stomach, a contracted intravascular volume due to bleeding elsewhere and a possible cervical spine injury.

Cannulate the radial or dorsalis pedis artery for direct blood pressure monitoring before induction. The arterial BP transducer should be zeroed at the level of the circle of Willis (external auditory meatus). Hypertension should be treated cautiously because it may be a compensatory hyperactivity of the sympathetic nervous system in response to raised ICP (Cushings reflex). Assess adequacy of volume replacement, analgesia, ventilation and oxygenation. If necessary, treat hypertension with a beta-blocker like esmolol which has a minimal effect on cerebral dynamics. The cerebral perfusion pressure (CPP) is maintained over 60 mm Hg. A higher CPP may be required in hypotensives, elderly patients and those with cerebrovascular disease. A head up tilt of 10 – 30 degrees should be used to facilitate venous return and CSF drainage. Any rotation or flexion of the head and neck for surgical positioning should not obstruct venous return from the cranium.

The ideal agent for maintenance of anaesthesia should reduce ICP, protect the brain against any ischaemic or metabolic insults and maintain adequate oxygen supply to the brain tissue. Thiopentone infusions decrease CBF, cerebral blood volume and ICP. They protect against focal brain ischaemia. They can however depress the cardiovascular system which can result in systemic hypotension and worsening of cerebral ischaemia. Prolonged infusions can result in persistent sedation. The cerebral haemodynamic effects of propofol are similar to thiopentone. One advantage of propofol is that emergence from anaesthesia is rapid even after a prolonged infusion. Hypotension during a propofol infusion may be attenuated by correcting any hypovolaemia before starting it. Patients receiving propofol infusions have a reduced incidence of postoperative nausea and vomiting. Prolonged infusions of propofol at high doses can produce significant morbidity. Etomidate is similar to thiopentone in reducing CBF, CMRO2 and ICP with better cardiovascular stability. Prolonged usage may however cause adrenocortical suppression.

Inhalational agents decrease CMRO2 through direct action and increase CBF by causing cerebral vasodilatation. Concentrations of less than 1.0 MAC should be used. It is advisable to avoid volatile agents in patients with raised ICP altogether and use an intravenous technique instead. It is the author’s practice to maintain anaesthesia with an infusion of propofol till the dura is opened. Isoflurane is a potent depressant of CMRO2 and increases CBF only over 1.0 MAC concentration. Sevoflurane has a lesser effect on cerebral haemodynamics than isoflurane. Sevoflurane is however metabolized to Compound A on contact with soda lime in the closed circuit and this substance may achieve toxic levels during prolonged anaesthesia with low flows. Desflurane at higher concentrations increases CBF and ICP. Both Sevoflurane and Desflurane are much more expensive than Isoflurane.

Table 3: Computed Tomography scanning rules for minor head injury

<table>
<thead>
<tr>
<th>Canadian Criteria</th>
<th>New Orleans Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Persistent anterograde amnesia with GCS of 15</td>
</tr>
<tr>
<td>GCS &lt; 15 at 2 hours after injury</td>
<td>Intoxication (Alcohol / Drugs)</td>
</tr>
<tr>
<td>Suspected open / depressed skull fracture</td>
<td>Physical evidence of trauma above the clivices</td>
</tr>
<tr>
<td>Any sign of base of skull fracture</td>
<td>Age &gt; 60 years</td>
</tr>
<tr>
<td>More than one episode of vomiting</td>
<td>Seizures (witnessed or suspected)</td>
</tr>
<tr>
<td>Age over 64 years</td>
<td>Headache</td>
</tr>
<tr>
<td>Medium Risk</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Amnesia before impact of &gt; 30 minutes</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>High risk mechanism of injury</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Marshall Classification of initial CT scan appearance in patients with Diffuse Axonal Injury

<table>
<thead>
<tr>
<th>Injury Grade</th>
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<td>IV</td>
<td>Cisterns compressed / absent – shift &gt; 5 mm</td>
<td>56.2 %</td>
</tr>
</tbody>
</table>
Nitrous Oxide also dilates cerebral vessels and increases ICP. In addition, it should be avoided if a pneumocephalus is demonstrated on CT scan of the brain as it diffuses into the air space increasing its volume and pressure.

Muscle relaxants facilitate IPPV and reduce ICP. Coughing and straining, which can increase ICP may be avoided with their use. Vecuronium has no effect on ICP, systemic blood pressure or heart rate. Cis-Atracurium has little effect on ICP and does not depend on the liver or kidneys for elimination. It does not release histamine like atracurium. Rocuronium is useful for intubation because of a rapid onset of action and lack of any effect on the ICP.

Local anaesthetics should be infiltrated at the site of skin incision and skull pin insertion to prevent systemic and intra-cranial hypertension.

Acute brain swelling and protrusion through the craniotomy should be treated by adjusting the ventilation, oxygenation, depth of anaesthesia [Bolus dose of Thiopentone (15 – 30 mg Kg-1), osmotic diuretics and muscle relaxants. CSF drainage (10 – 20 ml) through an intraventricular catheter may also be used to immediately reduce the ICP.

Monitoring – Routine monitoring includes ECG, noninvasive BP, invasive BP, pulse oximetry, end tidal CO₂, temperature, urine output, central venous pressure, neuro-muscular blockade, arterial blood gases and laboratory investigations like haematocrit, serum electrolytes, plasma glucose and serum osmolality. Some of the methods of monitoring described are not available in the author’s institution and are mentioned only for the sake of completion.

ICP Monitoring – The ICP should be monitored as a guide to therapy and also to assess the response to therapy and determine the prognosis. It should ideally be monitored in all salvageable patients with a GCS of 8 or less and an abnormal CT Scan (one that reveals a haematoma, contusion, swelling, herniation or mass effect). The ventricular catheter connected to an external transducer is the most accurate and reliable monitor of ICP and allows easy calibration and drainage of CSF to reduce ICP. CPP can be calculated easily (MAP – ICP). Treatment is initiated if ICP is persistently elevated over 20 mm Hg12. ICP can also be measured from epidural, subarachnoid and intraparenchymal locations (Figure-6).

ICP monitoring is usually done from the supratentorial region of the cranium. Intraventricular catheter placement may be difficult if the ventricle is compressed due to high ICP. They have been associated with a higher incidence of infection and a greater potential to cause brain tissue injury during placement. Monitoring ICP from subarachnoid, subdural and epidural locations are less accurate than intraventricular catheters. Fiberoptic ICP monitoring systems may be placed in the parenchyma, subdural or intraventricular compartment. They are expensive, prone to drift, cannot be calibrated in vivo and fragile. Micro-pressure transducer ICP monitoring systems do not have the disadvantages of the fiberoptic systems.

Transcranial doppler – High values for flow velocity may indicate vasospasm or hyperaemia. Values over 120 cm sec-1 in the middle cerebral artery correlates with angiographically demonstrated vasospasm and values over 200 cm sec-1 indicates severe vasospasm. TCD also helps to assess CO2 reactivity, auto-regulation, response to treatment and also helps to estimate CPP.

Brain Tissue Oxygen Tension (BTOT) – This is measured using a probe placed in the cerebral parenchyma. A BTOT of lesser than 15 mm Hg for over 30 minutes is associated with increased mortality13. The main disadvantage of BTOT monitoring is that it gives only a focal picture.

Near Infrared Spectrometry – Oxy-haemoglobin and deoxy-haemoglobin are strong absorbers of light in the near infrared spectrum. Differences in their absorption spectra allows the measurement of oxygen saturation in cerebral blood under the sensor through the skull bone. This is an indirect indicator of adequacy of CBF.

Monitoring for air embolism – Posterior fossa procedures in the sitting position carry the highest risk of venous air embolism. Methods for the detection of venous air embolism are listed in Table – 6 (from the most sensitive to the least sensitive).

Recovery from Anaesthesia and Postoperative management - Patients who had a good GCS preoperatively and have undergone an uneventful surgery may be awakened and extubated in the operation theatre. This facilitates early neurological assessment. Avoid systemic hypertension and
coughing while emerging from anaesthesia as they are predisposed to cerebral oedema, raised ICP and haematoma formation. If the level of consciousness is depressed preoperatively, ventilate the patient electively in the postoperative period. Poly trauma patients and patients who are hypothermic should also be ventilated electively in the post-operative period. Causes of delayed awakening in the operation theatre include a low preoperative GCS score, elevated ICP, residual drug effects, metabolic and electrolyte disturbances, hypothermia and seizures.

### Intensive care management of the TBI patient

The indications for monitoring ICP have been listed in the previous section. An intraventricular catheter is preferred since it provides accurate readings and allows therapeutic drainage of CSF. Loss of autoregulation induced by TBI will result in the CBF becoming dependent on the mean arterial pressure (MAP). Reductions in MAP will then cause cerebral ischaemia while increases in MAP result in hyperaemia, cerebral oedema and rise in ICP. The Lund approach to treat raised ICP works on the assumption that the integrity of the BBB for salts is lost following TBI. The goal of management is to limit the resulting oedema and ICP elevation by using osmotic diuretics and maintaining an ICP of less than 20 mm Hg.

The CPP should be maintained between 50 and 70 mm Hg to maximize brain tissue oxygenation. Arterial hypotension (SBP < 90 mm Hg) should be avoided. The systolic BP should be maintained between 90 and 160 mm Hg. Adequate MAP is maintained by infusing isotonic fluids to maintain euolaema or slight hypervolaemia. Intravascular volume status can be assessed by monitoring the CVP and urine output, respiratory variation in the arterial pulse pressure and ultrasonographic assessment of inferior vena cava size changes with different phases of breathing.

### Management of raised ICP

CPP is the difference between MAP and ICP and should be maintained over 60 mm Hg. A head up tilt of 10 – 30 degrees should be used to facilitate venous return and CSF drainage.

The head and neck should be maintained in a neutral position so that venous return from the cranium is not obstructed. Tight endotracheal tube ties should not be used for the same reason. Incremental drainage of CSF through an intraventricular catheter (15-20 ml) will bring down the ICP immediately.

Mannitol and Frusemide may be used as diuretics. Mannitol 0.25 – 1.0 gm Kg⁻¹ is administered over 10 – 20 minutes and repeated every 3 – 6 hours. A larger dose of 1.0 – 1.5 gm Kg⁻¹ is used if transtentorial herniation is suspected. It is recommended to restrict usage of mannitol, prior to monitoring ICP, to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes. The serum osmolality should be monitored and maintained at less than 320 mosm Kg⁻¹. Frusemide prevents the rebound phenomenon seen with mannitol. Infusions of hypertonic saline and glycerol are also being used in the management of raised ICP.

Mechanical ventilation should be adjusted to maintain a PaCO₂ of 35 mm Hg. Lower levels of 30 mm Hg is indicated only if impending herniation is suspected and is used as a bridge to surgical decompression. Levels below 30 mm Hg can produce vasoconstriction and aggravate cerebral ischaemia. Once hyperventilation is instituted, other measures to reduce ICP should be introduced and the PaCO₂ allowed to normalize as soon as possible.

### Decompressive Craniectomy

Decompressive craniectomy is a controversial line of management and is practiced in certain centres only. Post surgical quality of life should be considered before planning this procedure. Decompressive craniectomy decreases ICP and improves outcome in young patients who deteriorate within 48 hours of TBI. It should be considered prior to initiating barbiturate therapy (< 55 years of age is a relative indication). It should be considered in all cases of non-fatal primary brain injury associated with asymmetric or focal brain swelling on CT scan who have refractory intracranial hypertension which has failed to respond to maximal medical therapy, with or without CSF drainage.

### Barbiturates

Barbiturates have cerebral protection and ICP lowering effects and must be considered in severe TBI cases in which raised ICP is refractory to medical and surgical management. Barbiturate therapy should be initiated only after the patient is haemodynamically stable. Clinical trials have however not revealed any clear benefit or improved outcome associated with the use of high dose barbiturate therapy for refractory intracranial hypertension. High dose barbiturate therapy is indicated in haemodynamically stable salvageable patients who have raised ICP refractory to the previous steps. Barbiturates reduce ICP by decreasing CBF in parallel with CMRO₂. Thiopentone is administered in a loading dose of 15 mg Kg⁻¹ followed by an infusion of 0.2 mg Kg⁻¹min⁻¹. Thiopentone infusions are associated with haemodynamic instability, prolonged recovery after stopping the infusion and difficulty in neurological assessment. Prophylactic administration of barbiturates to induce burst suppression in head injured patients is not recommended.

### Hypothermia

Mild hypothermia (34 – 36 degrees) has been demonstrated to markedly attenuate ischaemic cerebral injury in animal models. The mechanism may be due to a reduction in metabolic demand, free radical formation and oedema formation. Adverse side effects of hypothermia include hypotension, cardiac arrhythmias, coagulopathies and infection. Rewarming
should be carried out gradually. Studies indicate that there is a greater reduction in mortality risk when hypothermia is maintained for more than 48 hours\textsuperscript{16}. Hypothermia is not routinely used in clinical practice.

\textbf{Steroids –} The CRASH trial which studied the effect of early administration of methyl prednisolone on outcome after TBI in 10008 patients revealed a higher risk of death within two weeks of injury in the group receiving steroids than in the group receiving placebo\textsuperscript{17}. There was also a higher risk of subsequent death or severe disability. The trial investigators concluded that corticosteroids should not be routinely used in the treatment of TBI. Besides steroid administration also causes hyperglycaemia and is associated with an increased risk of gastrointestinal haemorrhage.

\textbf{Anticonvulsants –} Administration of phenytoin to severe TBI patients prevents early onset seizures, but has no effect on late post traumatic seizures. Seizure prophylaxis is recommended during the first week after TBI. Phenytoin at a loading dose of 15 mg Kg\textsuperscript{-1} week after TBI. Phenytoin should be infused at a rate of less than 50 mg min\textsuperscript{-1} in adults to avoid cardiovascular depression. Indications for seizure prophylaxis include a GCS of less than 10, cortical contusions, depressed skull fracture, intracranial haematoma, penetrating head injury and seizures occurring during the first 24 hours after TBI. Seizure prophylaxis is recommended during the first week after TBI. Phenytoin at a loading dose of 15 mg Kg\textsuperscript{-1} over 20 minutes followed by 5 – 7 mg Kg\textsuperscript{-1} day\textsuperscript{-1} or Fosphenytoin 15 – 20 mg Kg\textsuperscript{-1} loading dose followed by 4 – 6 mg Kg\textsuperscript{-1} day\textsuperscript{-1} is used. A multicentre prospective study has recently concluded that there is no statistically significant difference between levetiracetam and phenytoin in early TBI seizure prophylaxis\textsuperscript{18}.

\textbf{Nutrition -} Nutritional support should be initiated as soon as possible. Full nutritional support should be achieved by the seventh post injury day. 15 % of total calories should come from proteins. Enteral feeding is preferred and a naso-jejunal tube should be placed to protect against aspiration and gastric intolerance. Stress ulcer prophylaxis is indicated with a H2 inhibitor or proton pump inhibitor (PPI). At least two studies have shown that neurological outcome is poorer if the plasma glucose levels are over 200 mg dl\textsuperscript{-1} and hypertonic saline. Mild cases are treated with water restriction and loop diuretics which impair the ability of the kidneys to concentrate urine (Furosemide 10 – 20 mg every 6 hours). In severe cases where the serum sodium level is less than 125 mEqL\textsuperscript{-1}, infuse hypertonic saline at 1-2 ml Kg\textsuperscript{-1} hr\textsuperscript{-1} for 2 to 3 hours. Correct serum sodium at a rate of 0.5 mEq L\textsuperscript{-1} hr\textsuperscript{-1} to avoid central pontine myelinolysis.

\textbf{Complications of TBI}

\textbf{Neurogenic Pulmonary Oedema –} The aetiology of neurogenic pulmonary oedema is massive transient central sympathetic discharge due to raised ICP following severe TBI and is particularly associated with hypothalamic lesions. It may rapidly progress to death or resolve completely within a few hours to days. There is systemic vasoconstriction, redistribution of blood from the systemic to the pulmonary circulation, left ventricular failure, pulmonary venoconstriction and increased pulmonary capillary permeability. The treatment is to decrease ICP, reduce systemic blood pressure using diazoxide (1-3 mg IV) every 5 minutes up to 150 mg or phenoxybenzamine (1 mg Kg\textsuperscript{-1} as an infusion over 2 hours to a maximum of 4 mg Kg\textsuperscript{-1} day\textsuperscript{-1}), IPPV to support ventilation and inotropes to support the circulation if needed.

\textbf{Syndrome of Inappropriate ADH secretion – SIADH} causes water retention along with continued excretion of sodium. This causes dilutional hyponatraemia, decreased serum osmolality, increased urine osmolality and decreased urine output. Water retention and serum hypo-osmolality cause nonspecific signs of water intoxication like nausea, vomiting, headache, irritability, disorientation, seizures and coma. Treatment consists of water restriction, loop diuretics and hypertonic saline. Mild cases are treated with water restriction alone (1-1.5 L day\textsuperscript{-1}). More severe cases are treated with water restriction and loop diuretics which impair the ability of the kidneys to concentrate urine (Frusemide 10 – 20 mg every 6 hours). In severe cases where the serum sodium level is less than 125 mEqL\textsuperscript{-1}, infuse hypertonic saline at 1-2 ml Kg\textsuperscript{-1} hr\textsuperscript{-1} for 2 to 3 hours. Correct serum sodium at a rate of 0.5 mEq L\textsuperscript{-1} hr\textsuperscript{-1} to avoid central pontine myelinolysis.

\textbf{Diabetes Insipidus –} DI is less commonly seen in TBI. It develops 12-24 hours after injury and lasts for a few days. A decrease in ADH levels results in the excretion of large volumes of dilute urine (4-14 L day\textsuperscript{-1}) that results in dehydration, hypernatremia, increased serum osmolality (over 320 mosmKg\textsuperscript{-1}), decreased urine osmolality (less than 200 mosmKg\textsuperscript{-1}) and decreased urine specific gravity (< 1.005). Serum sodium levels are often elevated (> 145 mEqL\textsuperscript{-1}). Signs of hypernatremia include decreased level of consciousness, muscle weakness, irritability, spasticity, confusion, ataxia, seizures and coma. Treatment of DI is
by calculating the free water deficit using the formula

\[(\text{serum sodium} - 140) \times \text{body weight (Kg)} \times 0.6 / 140\]

and replace it with a hypotonic solution like 0.45 % saline or Ringers Lactate. Desmopressin (DDAVP) is used to treat DI. The intravenous or subcutaneous dose is 0.3 mcg Kg \(^{-1}\) day \(^{-1}\) in two divided doses. The oral dose is 0.05-1.2 mg day \(^{-1}\) in three divided doses. The intranasal dose is 10-40 mcg day \(^{-1}\) in three divided doses. Once the intravascular volume is restored, persistent hyponatremia may be treated using Hydrochlorothiazide 50-100 mg day \(^{-1}\) IV.

Cerebral salt wasting – CSW is caused by increased secretion of atrial natriuretic peptide, brain natriuretic peptide and c-type natriuretic peptide. Natriuresis, diuresis and vasodilatation occur due to the suppression of aldosterone synthesis by these peptides. Excessive loss of sodium in urine (150-200 mEq L \(^{-1}\)) causes hyponatremia. Sodium should be replaced in these cases along with fluid administration. Hypertonic saline may be infused in these patients with close monitoring of serum sodium levels. The rate of correction should not exceed 0.5 mEq L \(^{-1}\) hr \(^{-1}\).

**Conclusion**

The management of head injury is multidisciplinary and is a team effort involving the emergency room physician, the neurosurgeon, the neuro-anæsthetist and the intensivist. Each and every institution dealing with these cases should evolve protocols based on their needs and availability of resources to achieve the best possible results. However it should be understood that these are purely guidelines that may have to be customised to suit the individual patient and the individual consultant at that point in time. This approach has led to an improvement in the management of these cases with a reduction in mortality and morbidity.

**Acknowledgement**

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**References**


Industrial Toxins and Brain development

Increasing incidence of autism, attention deficit hyperactivity disorder and dyslexia among children has prompted some to claim that toxic chemicals might be triggering a "silent pandemic" of neurodevelopmental disabilities. In a report published online on February 15, 2014 in Lancet Neurology, researchers from Harvard and Mount Sinai have identified six more chemicals as "developmental neurotoxicants: manganese, fluoride, chlorpyrifos and DDT (pesticides), tetrachloroethylene (a solvent), and the polybrominated diphenyl ethers (flame retardants). Manganese is associated with diminished intellectual function and impaired motor skills; solvents are linked to hyperactivity and aggressive behaviour; and certain types of pesticides may cause cognitive delays. Controlling the pandemic is difficult as the usage of most of the industrial chemicals are poorly regulated and requires international cooperation. The authors justly call for an international action. (Philippe Grandjean, Philip Landrigan. Neurobehavioral effects of developmental toxicity. Lancet Neurology, February 2014 DOI: 10.1016/S1474-4422(13)70278-3)

- Dr. K. Ramesh Rao

Reality And Delusion

Most of us humans are not delusional because our brain screens the conclusions we draw from our experiences through "reality testing": we discard those ideas which are not supported by evidence as unreal. For example, when we get headache, we may briefly consider brain tumour as its cause until that idea gets tested as unreal and is rejected. But delusional people cling on to their ideas even when incontrovertible evidence shows their ideas to be unreal. In a new study published in Frontiers in Psychology, Professor Philip Gerrans of University of Adelaide, claims that persistent delusions are the result of problems with "reality testing". People with "reality testing" problems find it difficult to break free from illogical ideas and suffer from severe mental health issues that may prove a threat to themselves or others. Understanding the mechanism of "reality testing" may help in providing relief to these sufferers. It would be interesting to find out if "reality testing" is functional in highly religious people and fan boys! (Philip Gerrans. Pathologies of Hyperfamiliarity in Dreams, Delusions and Déjà Vu. Frontiers in Psychology, 2014 (in press) DOI: 10.3389/fpsyg.2014.00097)

- Dr. K. Ramesh Rao
Introduction

Male factor infertility is an important cause of a barren marriage. Semen abnormalities constitute the most important cause of the same. These could be abnormalities in sperm concentration, motility or morphology. Several medical and surgical methods have been introduced in the past and several more are currently being tried to improve the sperm abnormalities. These methods have not yielded much benefit except in established cases of obstruction. To evolve methods to improve sperm abnormalities, a proper understanding of sperm physiology and a deeper perspective of pathophysiology of sperm abnormalities are important. The paper describes the current role of nutraceuticals in male infertility. Nutraceuticals are widely used in an attempt to combat the effect of free radicals in male reproductive system.

Nutraceuticals

Nutraceuticals is a portmanteau of the words Nutrition and Pharmaceuticals. Stephen Defelice in 1989, first coined the word ‘Nutraceuticals’, from the two words nutrition and pharmaceuticals. He was the founder and chairman of the Foundation for Innovation of Medicine, (FIM) in New Jersey. According to him, nutraceutical can be defined as “a food or a part of food that provides medical or health benefits including the prevention and or treatment of a disease”6. The term indicates several products like isolated nutrients, dietary supplements, herbal products, specific diets, genetically modified food, processed foods such as cereals, soups and beverages2.

While nutrition plays a crucial role in health and disease, it is not exactly clear what role nutraceuticals play. Nutritional deficiencies have been implicated in the pathogenesis of several diseases. For example, deficiencies in Vitamin C, Vitamin B and Vitamin D give rise to scurvy, beriberi and rickets, respectively. Although there seems to be no clear association between nutritional deficiency and infertility, inadequacy of certain nutrients such as folic acid, L-carnitine and selenium have been claimed to cause infertility3-4.

Spermatogenesis

Nutrition plays an important role in spermatogenesis. There is a definitive role of micronutrients such as zinc, folate and antioxidants for the normal maintenance of spermatogenesis and sperm maturation, DNA synthesis, repair and transcription. However, knowledge about the effect of paternal malnutrition on sperm aneuploidy is scarce. Environmental factors such as exposure to pesticides and chemotherapy have been associated with aneuploidy in spermatozoa of humans5.

Nutraceuticals commonly used are:

1) Nutritional factors: Arginine, VitB 12, Folic acid
2) Motility enhancers: L-carnitine, Acetyl carnitine, Co enzyme Q10
3) Antioxidants: Vit C, Vit E, Glutathione, Lycopene, Selenium, Zinc

Male infertility

Infertility affects 15% of the married, eligible couples. Male factor accounts for about 50% of the cause for infertility. Nutraceuticals, which are readily available in the market, offer an easy alternative to the couples against Assisted Reproductive Technologies. These include those that offer improvement in sperm function, semen parameters, sexual function and erectile function. However, there is no clear evidence that support these claims. The benefits of nutraceuticals in male infertility are yet to be proven. More importantly, the side effects of these supplementations are unknown and very often used by common population as a substitute for lack of nutrition in the diet.

Free radicals in health and disease

Oxidative metabolism in all the cells, tissues and organs leads to the production of free radicals - reactive oxygen species and reactive nitrogen species. These molecules have an unpaired electron in the outer orbit. They are unstable and very reactive. Free radicals are effectively counteracted by several natural antioxidants6.
Free radicals also serve a physiological function. Reactive oxygen species (ROS) are produced during a variety of biological processes. These molecules in small concentrations are essential for cell growth, differentiation or proliferation. They are involved in physiological processes such as signal transduction, regulation of protein kinases or transcription factors. They also regulate redox balance, immune responses, activate macrophages and neutrophils. Cell adhesion and relaxation of smooth muscle are controlled by free radicals. Reactive Oxygen species are essential for apoptosis. These molecules are very important for the correct function and life of the cell. Oxidative stress in male reproductive system

The cells in the male reproductive system are vulnerable to the effects of free radicals like any other cell in the body. The male reproductive system has an inherent antioxidant system to protect the cells from the detrimental effects of free radicals and ROS. In addition to enzymes, substances such as zinc and carnitine make up the antioxidant system.

The spermatozoan has high content of polyunsaturated fatty acids (PUFA) in its plasma membrane and is highly susceptible to oxidative damage. Thus to maintain viable reproductive ability, a protective mechanism against oxidative stress is of importance. Although the body employs a number of mechanisms to minimize ROS induced damage, antioxidants in seminal plasma provide substantial protection to spermatozoa against ROS insult starting from spermiogenesis (during the loss of cytoplasm).

This is now considered to be the underlying pathological consequence. A wide range of conditions including testicular torsion and diabetes, may ultimately lead to the production of free radicals. Excessive amounts of free radicals may cause peroxidative damage to the spermatozoa, however the amount at which free radicals can cause damage is unknown.

Deficiency of these substances may lead to a reduction in the sperm quality and it is yet to be answered if antioxidants need to be supplemented to treat this condition. As discussed earlier, ROS also has physiological role. In reproduction they are involved in vascular tone regulation, gene regulation, fertilization, sperm capacitation, hyper-activation, motility and acrosome reaction. Free radicals act as signals for various physiological processes. It is unclear as to whether ROS present in excess in the body is physiological or pathological.

Antioxidants in the male reproductive system

Antioxidants, which can be enzymatic or non-enzymatic, prevents or delays the oxidation of the substrate, which can be any molecule found in any biological material.

Seminal plasma also contains several naturally occurring antioxidants like catalase, glutathione peroxidase, superoxide dismutase, beta-carotene, ascorbate, etc. They are involved in continuously inactivating the reactive oxygen species leaving behind a small physiological level of reactive oxygen species to maintain normal cell function. It is possible that free radicals are associated with several disease states without being causative.

Nutraceuticals in male infertility

Nutraceuticals are a group of substances, which are claimed to improve sperm parameters. Commonly used nutraceuticals in male infertility are:


Treatment with nutraceuticals is widespread for a variety of conditions like atherosclerosis. The efficacy of nutraceuticals in the treatment of these conditions has not been proved. Folic acid seems to have an apparent benefit in reducing aneuploidy in spermatozoa.

Normal and abnormal semen

Attempts to define normal semen have been recent. The first world report from World Health Organization (WHO) was available in 1980. Four further editions have been published. Each new edition have been redefining and down staging normal parameters and the current WHO manual does not even call it normal parameters but as Reference values or Standard
parameters\textsuperscript{12}. There are too many parameters listed. We will confine this paper to concentration, motility and morphology.

**Azoosperma**

Azoosperma defined as absence of spermatoza in the ejaculate, both in a neat semen sample and in a centrifuged resuspended semen sample. This may be obstructive or non obstructive\textsuperscript{13}. Obstructive azoosperma requires surgical correction or sperm retrieval techniques. Nutraceuticals are of no value.

In non-obstructive Azoosperma - gonadotrophins are of immense value in hypogonadotrophic hypogonadism. Nutraceuticals have been tried with no proven benefit. Anti oxidants are the primary group of drugs used in other non-obstructive azoosperma patients. The results are conflicting. Significant number of men with non-obstructive azoosperma have chromosomal anomalies or Y chromosome micro deletions. It is unlikely that nutraceuticals would be of any value to these patients.

**Oligoasthenoteratozoosperma**

These conditions are difficult to define except in the total state as in Total asthenozoosperma. The definition of these conditions have been changed 5 times in the last 30 years .For example the lower reference limit for normal morphology is 4\% ( WHO 2010 ) which has come down from 80.5\% while the motility has come down from 60\% to 40\% (WHO 1988). It is not clear if the increased DNA fragmentation and increased ROS levels found in some of these men is the cause or consequence of the sperm abnormalities\textsuperscript{9}.

**Risks of antioxidants**

Treatment with antioxidants is not required in all situations. Antioxidants do not seem to have any short-term risks. The long-term risks are unknown. Some studies found that cancer patients who took antioxidants had worse outcomes\textsuperscript{13}. Fertility treatment studies show that 40\% of men seeking fertility treatment are fertile and devoid of sperm oxidative damage. Supplements given to improve fertility may cause harm than cause good which is the actual purpose they are taken for. For example, selenium given alone or in combination with other antioxidants reduces the number of motile spermatoza. Vitamin-C and Vitamin-E supplementation causes an increase in DNA damage and plasma membrane damage of spermatoza\textsuperscript{14}. There are a large number of studies which emphasise on the beneficial effect of antioxidant supplementation and an equal number of studies which say that there is no effect,\textsuperscript{15} the duration of therapy, dose, and long term side effects needs to be established by larger studies before implementation of nutraceutical supplementation as a routine in male infertility treatment.

**Conclusion**

The role of nutraceuticals in sperm abnormalities is not clear. A recent Cochrane study on Antioxidants in male infertility concluded that a well-designed large randomized placebo controlled trials are needed to confirm the usefulness of antioxidants in male infertility\textsuperscript{16}. It may be prudent not to empirically use nutraceuticals in sperm anomalies except in a double blind randomized clinical trial setting. If clinical exigencies demand the need for a drug, folic acid may be used. Clinically randomized studies based on scientific evidence are required to standardize therapies with antioxidants. Currently, many drugs are used with minimal data showing any beneficial effect. A definitive conclusion cannot be drawn from the existing heterogeneous literature: Further randomized, controlled, clinical trials are needed to be able to fully understand the efficacy and safety of antioxidants and propose proper protocols for their use.

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Diagnose the condition

50 year old female presented to emergency with palpitation and breathlessness. Her ECG was taken.

- Dr. M. Chokkalingam, Consultant Cardiology, CSSH.

Answer in page: 147

Walk a Lot, to Keep Walking!

Walking briskly for about four hours a week apparently preserves your bone health and the muscle tone, and prevents hip fractures. That is the conclusion of a longitudinal study conducted at Brigham and Women’s Hospital on 36000 men over a period of 24 years. The study relied on answers to questionnaires that the participants filled up once in every two years. The questions were designed to obtain information about how they spent their time in various activities including sitting, walking, playing, swimming etc. Information was also collected about the serious skeletal injuries suffered by the participants during that period. The results of the study suggest that the more a person walked, and more vigorously he walked, the lower the risk for hip fracture as he aged. To keep your bone healthy, just brisk walking is enough; no need for any strenuous exercise. The study is published online in Feb. 13th issue of the American Journal of Public Health.

- Dr. K. Ramesh Rao
Case Report

An Innovative Combined Three Dimensional Augmentation of Alveolar Ridge using Titanium Mesh, PRF and Autogenous Bone Graft with Implant Placement

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Dr. Vinayak S Gowda completed his under graduation from VS Dental College and Hospital, Bangalore in 1997 and post graduation from SDM Dental College and Hospital, Dharwad in 2002. He completed his Diploma in Implantology from ICOI. He did his Fellowship in implants from International Institute of Implantology, Nuremberg under Professor Dr. Manfred Lang in 2006. He has many publications in national and international journals to his credit. He has given guest lectures in many implantology conferences and conducted preconference programmes. His area of interest is periodontal regeneration, implantology and peri-implantitis.

Abstract

Alveolar bone augmentation is mandatory in deficient ridges prior to implant placement but ridge defects require regenerative membranes and bone grafts to achieve and particularly vertical bone augmentation which still remains a challenge to be proven. The aim of this case report is to propose a treatment modality for three dimensional augmentation of alveolar ridge using autogenous symphseal graft, PRF membrane, Titanium mesh and bone morselizer.

Key words: Ridge augmentation, PRF, Titanium mesh, autogenous graft.

Introduction

Alveolar bone augmentation for dental implant rehabilitation is one of the greatest challenges. In order to place the implant in ideal anatomic position, adequate alveolar ridge dimensions should be present. Alveolar ridge defects are most commonly seen after periodontal infection and tooth extraction. Placement of implants in such defective sites could compromise the functional and aesthetic results. However, adequate bone quality and quantity is mandatory prior to implant placement1 because patients with loss of alveolar bone height or width may require reconstructive procedures including vertical ridge augmentation which remains a challenge in the reconstruction of the atrophic maxilla and mandible4.

The use of barrier membranes along with bone grafts and bone substitutes has been proposed and tested for the partial and full augmentation of the alveolar process prior to implant surgery3. The use of titanium mesh for reconstruction of the atrophic alveolus was first introduced by Dr. Philip Boyne et al. in 19854,5. The use of titanium mesh along with bone grafts has been shown to be successful in both vertical and horizontal bone defects. The combination of rigid osteoconductive scaffold (titanium mesh) along with autogenous bone grafts would increase the possibility of vertical augmentation and esthetic results and decrease the post operative morbidity.

Platelet Rich Fibrin contains high concentration of platelets and growth factors which is found to stimulate the osteoblasts and periodontal ligament cells which fastens the wound healing and repair of the ridge defects6. The aim of this case report is to present a combined surgical approach for a three dimensional augmentation of alveolar ridge using titanium mesh, Platelet rich fibrin and autogenous graft prior to implant placement.

Case Report

A 23 year old female patient reported to the Department of Periodontics with the chief complaint of loose upper front tooth for the past 3 months. Patient also had a complaint of sensitivity in upper front & lower back teeth for 2 days. Patient underwent scaling 2 years before she reported as she had severe bleeding from gums.

Clinical examination: Extraorally no abnormality was detected. The gingiva was erythematous, soft and edematous in consistency which was generalized and diffuse, with loss of stippling in attached gingiva (Fig 1). Generalised enlargement of marginal gingiva and interdental papilla and bleeding on probing was present. Periodontal examination revealed the presence of generalized periodontal pocket. Grade II mobility was seen in 21 and 11 with pathologic migration and exudation in relation to 21. There was no discoloration of the involved teeth. Bimaxillary protrusion of teeth was present. Blood investigations were normal.

Radiographic Interpretation: Generalised horizontal bone loss extending till the junction of middle third and apical third and vertical bone loss extending till the apical third was observed in 21 and 11 (Fig 2 & 3).
Autogenous bone graft was harvested from mandibular symphysis using trephines (Fig 5) and the harvested bone was triturated using bone morselizer (Fig 6). The triturated bone was mixed with blood. The donor site was decorticated using round bur to induce bleeding. The titanium mesh of thickness 0.5 mm was contoured around the alveolar ridge so that there was a gap of 2mm above the crest of the alveolar ridge and sharp edges were removed. The mesh was adapted on both the buccal and lingual aspects of the ridge. The titanium mesh was stabilized using titanium screws (Fig 7). The morselized bone blend was placed under the mesh (Fig 8).

**Management:** Scaling, root planing and curettage was carried out initially to reduce the inflammation. The patient was recalled after a month and periodontal flap surgery was carried out to control the inflammation and to prevent bacterial translocation in the defect area where the ridge augmentation was planned. In the maxillary anterior teeth, sulcular incisions followed by vertical incisions were placed distal to the line angles of 11 and 21. The flap was elevated and extraction of 21 was carried out as there was increase in the grade of mobility and pathologic migration of the teeth. The area was thoroughly debrided. Ridge mapping was at 3mm and 6mm away from the crest of the ridge which revealed a ridge width of 4 mm approximately. The vertical defect area was measured corresponding to the CEJ of the adjacent tooth using UNC 15 probe (Fig 4).

PRF was prepared following the protocol developed by Choukroun et al.8. The procedure of PRF preparation consisted of withdrawing 10 ml of intravenous blood from the antecubital fossa. The blood was transferred into 10 ml sterile tube without anticoagulant and immediately centrifuged at 3000 rpm for 10 minutes. Fibrin clot formed in between the acellular plasma on top and the red blood cells at the bottom was separated using sterile tweezers and scissors. The PRF membrane is placed over the titanium mesh and black silk 3-0 sutures were placed. (Fig 9 & 10)

The titanium mesh was removed at the end of 4 months as there was a slight exposure of the mesh. A crestal incision was placed and the buccal and lingual flaps were elevated. Then the screws were loosened and the titanium mesh was removed from the bone. There was an increase in a ridge width of 2 mm and height by 4-5 mm(Fig 11 & 12). The flap was sutured after removal of the mesh. At the end of six months the patient was recalled and subsequently 11 was also extracted and implants of dimension 3.25 X 13mm was placed in relation to 11, 21(Fig 13). PRF was placed subsequently around the implants to enhance the regeneration (Fig 14) and sutures were placed.

Subsequently healing collars were placed after 6 months. After obtaining a sufficient emergence profile, impressions were made and the final prosthesis was given.(Fig 15)

Vertical and horizontal bone augmentation can be successfully performed to gain bone height and width that is essential for ideal implant positioning and esthetic outcomes using variety of techniques.

Titanium mesh has some distinct advantages as a barrier membrane. Its rigidity resists deformation by the overlying soft tissue. Because it is non-resorbable it is present throughout the healing phase of the graft. Last, it causes little soft tissue reaction even when it is exposed. This is important because all membranes can become exposed during healing, and this can be especially common for titanium mesh. A layer of pseudo periosteum is constantly observed under the mesh. Though titanium mesh exposure was reported in 51.11%, the success of bone grafting was not reduced, owing to the success rate of 97.72%.

In this patient, though the prognosis was hopeless in both 21 and 11, initially only 21 was extracted, as the bone loss was maximum around 21 and required augmentation. The titanium mesh can be beneficial only in isolated areas of ridge defects than wide defects.

In the present case there was titanium mesh exposure at the end of 4 months and hence the decision to remove the mesh was made. Von Arx, et al. reported 10 out of 20 patients had exposure of the mesh. Of those patients only three had less than 10% of the graft volume lost. However, implants were successfully placed in 19 of the 20 patients.

In the present case we used Platelet rich fibrin to prevent the mesh exposure.

Currently, PRF has been successfully tested in a number of procedures including maxillofacial surgery, periodontal surgery, and implantology. In a previous study, the authors were able to demonstrate that PRF could stimulate new bone formation in areas that were previously deficient of the amount of bone required for implant placement. The biomaterial acts by releasing high-concentration growth factors to the wound site, thereby stimulating healing and new bone formation.

A clinical and radiographic study demonstrated significant bone regeneration with mean horizontal and vertical augmentation of 3.71±1.24mm and 4.16±0.59 mm respectively. Histologic studies have demonstrated the presence of woven bone adjacent to lamellar which is indistinguishable from normal bone architecture.

Conclusion

The case report illustrated the successful combined surgical approach for three dimensional augmentation of alveolar ridge using autogenous bone graft, titanium mesh and Platelet Rich Fibrin prior to implant placement.

Discussion

The use of barriers made of titanium macro-mesh in combination with bone grafts and bone substitutes has been proposed and tested for the partial and full augmentation of the alveolar process in implant surgery. The regeneration of localized alveolar ridge following extraction of chronic defects has been the goal of clinicians and researchers. Bone loss occurs in chronic inflammation, and in post extraction cases where no socket preservation procedure was attempted which results in difficulty for patients wearing a conventional prosthesis or being restored with dental implants. Severe alveolar bone loss can result in malnutrition, poor self-esteem, multiple dental visits for failed prosthesis, and jaw fracture.
Informed Consent

According to a report published in the February 20 issue of the New England Journal of Medicine (NEJM), the leading experts on bioethics are of the opinion that the full informed consent is not required for certain types of health research. They have argued that the time consuming process is not only unnecessary for patient protection but may even be harmful if it acts as a hindrance to gaining the new knowledge that might benefit the patient. They have suggested that the inclusion of patients in large numbers on the Ethics committees. The two situations where the experts feel informed consent is unnecessary are: 1) research that is determined to have no negative effects on clinical or other outcomes or values that matter to patients and will proceed without consent but with “public notification” to the patient community in the healthcare system; 2) research determined to have minor but still meaningful effects on patients’ interests, will proceed with specific notification to affected patients, who will have an option to decline participation. (http://www.news-medical.net/news/20140221/Informed-consent-is-not-required-for-certain-health-research-saybioethics)

- Dr. K. Ramesh Rao
From the Pages of History

HARVEY CUSHING (1869 – 1939)

Dr. V.G.Ramesh, Professor and HOD, Dept. of Neuro Surgery, Chettinad Hospital and Research Institute, Chennai, India
Chettinad Health City Medical Journal 2013; 2(4): 142

Father of Modern Neurosurgery, a great medical scientist, a gifted author – all-in-one – is what Harvey Cushing can be described in a single sentence. He was an extraordinary human being who by his untiring work, established Neurosurgery as a separate specialty, brought new concepts in the practice of medicine in general. He authored enormous amount of literature, in an era when modern medicine was just establishing itself.

Harvey Williams Cushing was born in Cleveland, Ohio, on April 8th, 1869. He came from a family of physicians. Harvey Cushing went to school in Cleveland and then to Yale where he received his A.B. degree in 1891. At the Harvard Medical School he gained his A.M. and M.D. cum laude in 1895. From this time he served for one year in surgery in the Massachusetts General Hospital and then, in 1896, he was appointed to the house-staff in surgery under Dr. Halsted at the Johns Hopkins Hospital, Baltimore where he remained until 1900 as resident in surgery. He learned meticulous surgical technique from Halsted while modeling his intellectual pursuits after William Osler, who at that time was chairman of the Department of Medicine. In 1900, he went to Berne, Switzerland along with Kocher and Kronecker, began his work in experimental neurology. Later he was associated with Sherrington in Liverpool. On his return, at the age of 32, he was made Associate Professor of Surgery at Johns Hopkins Hospital, and at the hospital was placed in full charge of cases of surgery of the central nervous system. In 1911, he was appointed Surgeon-in-Chief at the Peter Bent Brigham Hospital in Boston. He became a Professor of Surgery at the Harvard Medical School starting in 1912. During 1917-1919, he was director of U.S. Base Hospital attached to the British Expeditionary Force in France. In 1918, he was made Senior Consultant in Neurological surgery for the American Expeditionary Forces in Europe during World War I. He served in the U.S. Army Medical Corps, attaining the rank of Colonel. After the war he returned to Boston and continued until 1932. Next year, in 1933, he went to Yale as Sterling Professor of Neurology, a position which he held until 1937. Cushing died on October 7, 1939 in New Haven, Connecticut, from complications of a myocardial infarction. He was interred at Lake View Cemetery in Cleveland. Interestingly, an autopsy performed on Cushing revealed that his brain harbored a colloid cyst of the third ventricle.

Contributions to Medicine in general

1) As a medical student, he developed the first continuous record for recording pulse and respiration during surgery in 1895, which forms the basis for present day anesthesia records.
2) Cushing was involved in the introduction of X-ray technology into the clinical realm at Massachusetts General Hospital and Johns Hopkins Hospital after its discovery by Roentgen.
3) He did the first human experimentation with nerve block anesthesia for operation using cocaine.
4) He was the first to use blood pressure monitoring during surgery.
5) He studied typhoid disease and developed a pioneering approach to surgical management of perforations of the esophagus due to typhoid infection.
6) He showed that the gut can be sterilized by fasting and this has formed the basis for pre-operative bowel preparation.
7) He predicted the routine use of positive-pressure endotracheal anesthesia twenty years before it was used routinely.
8) He was the first to describe the tolerance of the heart to surgical manipulation, which was accepted only twenty years later.

Contributions to Neurosurgery

1) He established the safe surgical method of removing intracranial tumors with meticulous surgical technique.
2) He was the first to establish the basic techniques in Neurosurgery like finger pressure for haemostasis of scalp; waxing the bone edges; haemostatic clips; motor driven suction during surgery, etc. He brought down the surgical mortality after neurosurgical procedure from over 50% to less than 20%.
3) He invented the electro-surgical cautery along with Bovie.
4) He was the first to map human cerebral cortex with faradic stimulation in conscious patients.
5) He did the first surgery for acromegaly (1909).
6) He described Cushing’s law and Cushing’s triad in relation to raised intracranial pressure.
7) He described the C.P.Angle syndrome and advocated intracapsular excision of acoustic neurinoma.
8) He described the Cushing’s syndrome due to excess adrenal corticosteroids.
9) He described the Cushing’s ulcers – the gastric ulcers due to raised intracranial pressure.
10) He was the first to classify brain tumours along with Percival Bailey.

Contributions to Medical Literature: He has authored several medical books. He won the prestigious Pulitzer prize for his biography book “Life of Sir William Osler” in 1926.

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Answer to : Diagnose the condition

The ECG shows wide QRS tachycardia with varying R-R interval with no definite P waves. There is left axis deviation with poor R wave progression in the anterior chest leads.

Diagnosis: Atrial fibrillation with fast ventricular rate with LAHB. The ECG is showing atrial fibrillation with interventricular conduction defect most probably in the left anterior fascicle. The left axis deviation with poor R wave progression and wide QRS denotes LAHB(left anterior hemi block) pattern. The irregularity and the absence of capture, fusion beats and AV dissociation differentiates this from Ventricular tachycardia.

- Dr. M. Chokkalingam, Consultant Cardiology, CSSH.
Thank You reviewers!

The success of a journal depends on the authors and the quality of the papers they submit. Equally important is the immense contribution from the peer reviewers. They voluntarily, freely provide their time and expertise to critically evaluate the articles and contribute to their improvement with their valuable comments and suggestions. The following scholars have kindly reviewed the articles for our journal. Chettinad Health City Medical journal gratefully acknowledges their help and support for the journal.

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