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Editorial

IT IS IMPORTANT THAT WE COMMUNICATE

Communication is an art, an integral part of medicine practice that helps a doctor to understand and respond to the totality of the disease process. Various associated problems which directly or indirectly influence the disease process are identified by a good communication.

A good communication bridges the gap between the doctor and patient resulting out of an unknown fear in the mind of the patient. It creates confidence and bonding between them. A frank, sincere, simple confession phased out in a well coordinated and planned manner by a physician or a little effort to describe the steps involved, the likely complications and the alternatives of the procedures available with their concomitant risks and benefits, by a surgeon not only gives transparency to a professional commitment but also saves surgeon and physician from various unforseen dangers that may arise lest some complications occurred. In the face of overwhelming patient load and low staff strength which is most often than not the case, we should still remember that a consistent counselling definitely helps provided we accept these limits.

Emotions and the feeling elements are vital in treating patients. To feel with the distressed, to be sensitive to their subjective and objective needs, understand their body language, read between their verbal expressions is as important as been purely scientific and experimental driven by fascinating theory. After all we are treating human beings and mind and body are inseparable.

Teaching of communication skills should be initiated from undergraduate curriculum and modules should be prepared that includes participatory learning in the form of role plays on rapport building, active listening, responding to emotions, skills in reaching communication ground, right from the start of clinics. A well communicated patient faces one’s own problem with self confidence, self reliance and dignity.

Rekha Das
Editor
THE LOST GODHOOD

Bernard Shaw told once “We have not lost faith; we have just shifted it from god to medical professionals”. The healers have been always found a special place in society. From time immemorial they are respected as messengers of God, the creator. Voltaire said “Men, who are occupied in the restoration of health to other men, by the joint exertion of skill and humanity, are above all the great of the earth. They ever partake of divinity, since to preserve and renew is almost as noble as to create.”

In present context, not only that the profession came to the purview of consumers’ protection act, people at large have lost their heartfelt regards for the medical professionals. Most of our suggestions are interrogated and advice cross checked before someone sticks to them.

Life was never so colorful and living was never so delighted; stimulating people to dream more number of years, and with advancement of medical science and improved affordability of common men no body wants to loose near and dear ones and being custodians of health many times we are targeted for peoples’ suffering and demise.

On the other hand the professional challenges have been multiplied and with growing knowledge, advanced technologies and newer interventions it is humanly a difficult challenge to maintain a balance between scientific advancements in one hand and the human touch on the other. The amount of stress generated in the making of a successful healer in modern medical science, perhaps kills the involved art of humanity and that’s why the patients’ expectation and doctors target are divergent and combination of skill and humanity is many times a rare possibility. Learning the art of healing and to expertise the medical domain is not only a time taking and difficult challenge, but is expensive too. As a professional, sacrificing most productive years of life to master the science and art of Medicine and serving the suffering mass, a doctor has every right to earn from his profession and dream his personal front along with the job.

Materialistic touch has not spared any segment of society and perhaps if not completely, partially it has shadowed our profession too. Disproportionate greed, impossible aspirations, and unethical malpractice by few of the members affect the dignity and reputation of the profession and society at large start loosing the age old trust.

After all we are human beings with a mixture of good and bad in different proportions. It is required that the society places us high to get best out of us for its health and happiness, which in turn help us for a clear conduct and fare approach.

If we are pure in our heart, clear in our conscience, sincere in our efforts, compassionate in our behavior and humanitarian in our approach the lost trust can be bestowed again on us and for times to come we shall be worshipped as “Baidya Narayana Hari” and the profession will get back the glorified godhood.

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ZINC IN HEALTH AND DISEASE

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ABSTRACT

Although the essentiality of zinc for plants and animals has been known for many decades, the essentiality of zinc for humans was recognized only forty years ago. Zinc deficiency was suspected to occur in Iranian patients with growth retardation, hypogonadism in males, hepatosplenomegaly, rough and dry skin, geophagia and severe iron deficiency anemia. Later zinc deficiency was documented in similar patients in Egypt. The diet of these patients consisted of mainly cereal proteins which contained high phytate and this led to decreased availability of iron and zinc. These patients had severe immune dysfunctions, in as much as they died of intercurrent infections by the time they were 25 yr of age. In our studies in experimental human model of zinc deficiency we documented decreased serum testosterone level, oligospermia, severe immune dysfunctions mainly affecting T helper cells, hyperammonemia, neuro-sensory disorders and decreased lean body mass. It appears that zinc deficiency is prevalent in the developing world and as many as 2 billion subjects may be growth retarded due to zinc deficiency. Besides growth retardation and immune dysfunctions, cognitive impairment due to zinc deficiency has also been reported.

The basic mechanisms of zinc action on immune cells have been presented in this paper. Our studies show that the activation of many zinc dependent enzymes and transcription factors are affected adversely due to zinc deficiency. The mechanism of zinc action on Th cells and gene expression of IL-2 and INF-α and NF-κB activation have been presented.

Zinc is also an antioxidant and has anti-inflammatory actions. The therapeutic roles of zinc in acute infantile diarrhea, acrodermatitis enteropathica, prevention of blindness in patients with age related macular degeneration and treatment of common cold with zinc have been presented in this paper. Zinc has been approved by FDA for the treatment of Wilson’s disease and zinc treatment has been shown to be beneficial in sickle cell disease.

Raulin in 1869 first showed that zinc was required for the growth of Aspergillus niger. In 1934 Todd et al. reported that zinc was essential for the growth of the rats. The manifestations of zinc deficiency in animals included growth failure, loss of hair, thickening and hyperkeratinization of the epidermis, and testicular atrophy. Although the essentiality of zinc for animals was established, its ubiquity made it seem improbable that zinc deficiency in humans could lead to any significant clinical problem. During the past 40 years, however, it has been established that deficiency of zinc in humans is quite prevalent. Key Words: Zinc, IL-2, TNF-α, ROS

INTRODUCTION:

During the past four decades, a spectrum of clinical deficiency of zinc in human subjects has emerged. On the one hand, the manifestations of zinc deficiency may be severe; and, on the other end of the spectrum, zinc deficiency may be mild or marginal. A severe deficiency of zinc has been reported to occur in patients with
acrodermatitis enteropathica (a genetic disorder), following TPN (total parenteral nutrition) without zinc, following excessive use of alcohol, and following penicillamine therapy. The manifestations of severe zinc deficiency in humans include bullous pustular dermatitis, alopecia, diarrhea, emotional disorder, weight loss, intercurrent infections due to cell mediated immune dysfunctions, hypogonadism in males, neuro-sensory disorders, and problems with healing of ulcers. If this condition is unrecognized and untreated, it becomes fatal.

The manifestations of a moderate deficiency of zinc include growth retardation and male hypogonadism in the adolescents, rough skin, poor appetite, mental lethargy, delayed wound healing, cell-mediated immune dysfunctions, and abnormal neurosensory changes.

In our studies in the experimental human model in whom only a mild deficiency of zinc in males was induced by dietary means, decreased serum testosterone level, oligospermia, decreased NK cell activity, decreased IL-2 activity of T helper cells, decreased thymulin activity, hyperammonemia, hypogeousia, decreased dark adaptation, and decreased lean body mass were observed. It is, therefore, clear that even a mild deficiency of zinc in humans affects clinical, biochemical, and immunological functions adversely.

Zinc and Immunity

Zinc affects multiple aspects of the immune system. Zinc is crucial for normal development and function of cells mediating innate immunity, neutrophils and natural killer cells. Macrophages are also affected by zinc deficiency. Phagocytosis, intracellular killing, and cytokine production are all affected by zinc deficiency. It has been known for many years that zinc deficiency leads to atrophy of thymic and lymphoid tissue in experimental animals.

A decrease in in vivo generated cytotoxic T killer activity to allogeneic tumor cells in zinc deficient mice and an impairment in cell mediated response to non-H2 allogeneic tumor cells in zinc deficient mice have been reported. Animals maintained on a zinc deficient diet for as little as 2 weeks developed a severe impairment in their ability to generate a cytotoxic response to the tumor challenge. This was totally reversible by zinc supplementation.

Studies of Immune Functions in Experimental Human Model

During our studies in the Middle East, we observed that most of the zinc deficient dwarfs did not live beyond the age of 25 years. The cause of death appeared to be infections. Parasitic infections were common, however, viral and bacterial infections remained undocumented. The possibility that zinc deficiency may have played a role in immune dysfunctions in the zinc deficient dwarfs was considered but lack of proper facilities prevented us from gathering meaningful data on immune functions in those patients in the Middle East.

In our experimental human model studies, when zinc deficiency was very mild (5.0 mg Zn intake during the zinc-restricted period), the plasma zinc concentration remained more or less within the normal range and it decreased only after 4-5 mo of zinc restriction. On the other hand, zinc concentrations in lymphocytes, granulocytes, and platelets decreased within 8-12 wk, suggesting that the assay of cellular zinc provided a more sensitive
criterion for diagnosing mild deficiency of zinc.

We assayed serum thymulin activity in mildly zinc-deficient human subjects (8). Thymulin is a thymus-specific hormone and it requires the presence of zinc for its biological activity to be expressed. Thymulin binds to high-affinity receptors on T cells, induces several T-cell markers, and promotes T-cell function, including allogenic cytotoxicity, suppressor functions, and interleukin-2 (IL-2) production.

As a result of mild deficiency of zinc, the activity of thymulin in serum was significantly decreased and was corrected by both in vivo and in vitro zinc supplementation. The in vitro supplementation studies indicated that the inactive thymulin peptide was present in the serum in zinc-deficient subjects and was activated by addition of zinc. The assay of serum thymulin activity with or without zinc addition in vitro thus may be used as a sensitive criterion for the diagnosis of mild zinc deficiency in humans.

An increase in T\(_{101}\)-, slg- cells, a decrease in the ratio of T4+ to T8+, and decreased IL-2 activity were observed in the experimental human model during the zinc-depletion phase, all of which were corrected after repletion with zinc. We had previously reported that natural-killer (NK)-cells activity was also sensitive to zinc restriction, thus it appears that zinc may play a very important and critical role in the functions of T cells in humans. Our studies in the experimental human model showed for the first time that the production of IFN-\(\alpha\) was decreased, whereas the production of IL-4, IL-6 and IL-10 was not affected due to zinc deficiency\(^5,6\). IFN-\(\alpha\) is known to down regulate the Th\(_2\) clone, and IL-10 may down regulate the Th\(_1\) clone. An imbalance between Th\(_1\) and Th\(_2\) responses in patients with human immunodeficiency virus infection has been implicated in the immune dysregulation in these patients and it has been proposed that resistance to infection and/or progression to acquired immunodeficiency syndrome is dependent on a Th\(_1\) > Th\(_2\) dominance. Our data in experimental human model suggest that cell-mediated immune dysfunctions in human zinc deficiency may be due to an imbalance between Th\(_1\) and Th\(_2\) cell functions.

Th\(_1\) cells are known to promote macrophage activation and production of complement fixing and opsonizing antibodies. IFN-\(\alpha\) is the major component of Th\(_1\) response panel, and it upregulates major histocompatibility complex class I antigen expression. Our studies, therefore, provide a possible mechanism of zinc on cell-mediated immunity.

Several studies have shown the benefits of zinc supplementation on infectious diseases in humans. In double-blind placebo-controlled trials of zinc supplementation, zinc reduced the incidence and duration of acute and chronic diarrhea and acute lower respiratory tract infections in infants and children\(^7,8,9\). Zinc supplementation of sickle cell anemia patients in a placebo-controlled trial resulted in decreased incidence of staphylococcus aureus pneumonia, streptococcus pneumonia tonsillitis, and E. coli urinary tract infections\(^10\).

**Zinc Activates NF-\(\kappa\)B in HUT-78 Cells**

The NF-\(\kappa\)B transcription factor was originally discovered as a kappa immunoglobulin enhancer DNA-binding protein that correlated with gene
transcription\textsuperscript{11, 12}. There are many genes whose expressions are controlled by NF-\(\text{\v{e}}\)B. NF-\(\text{\v{e}}\)B belongs to a family of proteins including members such as Rel A, C-Rel, Rel-B, Bcl-3, p100 and p105. Under non-stimulated conditions, NF-\(\text{\v{e}}\)B consists primarily of the Rel A (p65) and p50 heterodimer associated with cytosolic \(\text{\v{e}}\)B inhibitory protein\textsuperscript{12,13,14}. The current estimate is that over two thousand transcription factors may be zinc dependent\textsuperscript{15}, however, the present dogma is that the amount of zinc required for the integrity of these transcription factors is so small, that in zinc deficient cells one would not see any change.

In as much as zinc deficiency affects IL-2 production and T-cell activation adversely, we have investigated the role of zinc on NF-\(\text{\v{e}}\)B activation in HUT-78, a Th\(_0\) human malignant lymphoblastoid cell line. We showed for the first time that in zinc deficient HUT-78 cells, the activation of NF-\(\text{\v{e}}\)B was adversely affected\textsuperscript{16}.

**Phosphorylation and ubiquitination of \(\text{\v{e}}\)B**

Intracellular zinc concentration was decreased by 40% in zinc deficient HUT-78 cells in comparison to the zinc sufficient cells after 4 days of incubation. In order to examine the effect of zinc on \(\text{\v{e}}\)B (\(\text{\v{e}}\)B inhibitory protein) in HUT-78 cells, we measured phosphorylated \(\text{\v{e}}\)B-\(\alpha\), IKK-\(\alpha\) (\(\text{\v{e}}\)B kinase-\(\alpha\)), and ubiquitinated \(\text{\v{e}}\)B-a in zinc-treated cells.

**Confocal microscopy**

NF-\(\text{\v{e}}\)B is normally held in the cytoplasm as a heterodimer composed of p50 and p65 subunits or comparable related subunits in an inactive form bound to an inhibitory protein, \(\text{\v{e}}\)B. Several types of \(\text{\v{e}}\)B are now recognized (\(\text{\v{e}}\)B-\(\alpha\), \(\text{\v{e}}\)B-\(\beta\), \(\text{\v{e}}\)B-\(\gamma\), BCL-3). NF-\(\text{\v{e}}\)B becomes activated and translocated to the nucleus when \(\text{\v{e}}\)B dissociates from the heterodimer\textsuperscript{17,16}. Phosphorylation of \(\text{\v{e}}\)B by specific kinases, IKK, is followed by attachment of ubiquitin residues and subsequent degradation by the multifunctional proteolytic enzyme proteasome. Dissociation of \(\text{\v{e}}\)B exposes nuclear localization signals on NF-\(\text{\v{e}}\)B molecules resulting in the translocation of both or one component of the heterodimer to the nucleus and binding to DNA. We showed that the phosphorylation of \(\text{\v{e}}\)B and IKK, translocation of NF-\(\text{\v{e}}\)B and its binding to DNA in HUT-78 cells were all zinc dependent\textsuperscript{16}. The activation of NF-\(\text{\v{e}}\)B was considerably reduced in zinc deficient HUT-78 cells. (Figs. 9A, 9B, 9C and 9D).

**Zinc Enhances the Expression of IL-2 and IL-2 Receptors in HUT-78 Cells via NF-\(\text{\v{e}}\)B Activation**

The production of interleukin-2 (IL-2) is a key and early event in the activation of T-lymphocytes. IL-2 triggers peripheral T-lymphocytes to enter the S phase of the cell cycle and to divide. This is probably a result of the suppressive effect of IL-2 on cell cycle inhibitors, which interfere with the activity of cyclin dependent kinases (cdk) at checkpoints of the cell cycle\textsuperscript{18,19}. IL-2 is also involved in the differentiation of thymocytes, peripheral T and B-lymphocytes and other cells of hematopoietic origin\textsuperscript{19}.

A short segment of DNA, 275 base pairs in the promoter area of IL-2 gene, integrates numerous signaling pathways leading to IL-2 synthesis and the activation and proliferation of T lymphocytes\textsuperscript{18}. Both the murine and human IL-2 promoters contain one binding site for genuine Rel/NF-\(\text{\v{e}}\)B factors. The sequence of this site GGGATTCGAC, is identical for both
promoters. NF-κB factors are rapidly induced by a variety of stimuli activating T cells. Almost every stimulus leading to T cell activation also activates NF-κB. Induction of IL-2Rα gene expression is also mediated by the induced nuclear expression of NF-κB.

In as much as, the molecular mechanisms of zinc action on IL-2 production are not known, we have used a human Th0 malignant lymphoblastoid cell line HUT-78, for the study of the effects of zinc on gene expression and production of IL-2, IL-2Rα, and IL-2Rβ. The role of NF-κB in zinc deficient and zinc sufficient cells on the transcriptional activity of IL-2 and IL-2Rα was also determined. We also determined the effect of zinc on IL-4 production, a Th2 cytokine that was not affected by zinc deficiency in our previous studies in human subjects. HUT-78 cells are known to also produce IL-4.

**IL-2 production**

The details of cell culture, zinc assay and other methods have been published elsewhere. We used an ELISA to measure the concentration of IL-2 produced by the cells. HUT-78 cells incubated in zinc-deficient (1 μmol/L zinc) and zinc-sufficient (15 μmol/L zinc) media for 4 days produced very small amount of IL-2: 1 pg/mL vs 16 pg/mL respectively without the PMA/PHA stimulation. However, the IL-2 concentrations in zinc-deficient and zinc-sufficient cells were 468 and 2015 pg/mL, respectively, (P<0.05) at 3 hours and 1701 and 2783 pg/mL, respectively, p<0.05 after 6 h of PMA/PHA stimulation.

**IL-2 mRNA**

The level of IL-2 mRNA was examined by means of Northern-blot analysis. Both zinc-deficient and zinc-sufficient cells produced very small amount of IL-2 mRNA without PMA/PHA stimulation, and we found no significant difference between these two groups of zinc-treated cells. The PMA/PHA stimulation induced the IL-2 mRNA production in both zinc-deficient and zinc-sufficient-HUT-78 cells. However, zinc deficiency decreased 60% at 3 hours and 50% at 6 hours expression of IL-2 mRNA when compared with zinc sufficient cells.

**Results of Nuclear run-on studies**

To determine whether zinc deficiency affected IL-2 mRNA at the transcriptional level, we used a nuclear run-on assay. The relative abundance of newly transcribed IL-2 mRNA was decreased by 50% in zinc deficient HUT-78 cells following PMA/PHA stimulation.

**Total soluble IL-2R production**

The concentration of total sIL-2R was measured by ELISA. The concentrations of total sIL-2R produced by zinc-deficient and zinc-sufficient cells were hardly detected by ELISA, under the unstimulated condition. However, zinc-deficient and zinc-sufficient cells produced (mean 452 and 2022 pg/mL, respectively, P<0.05 total sIL-2R, after 6 hours of PMA/PHA stimulation. Zinc deficiency caused an 80% decrease in total sIL-2R production.

**Zinc and Oxidative Stress**

Role of zinc in modulating oxidative stress has recently been recognized. Oxidative stress is an important contributing factor in several chronic human diseases, such as atherosclerosis and related vascular diseases, mutagenesis and cancer, neurodegeneration, immunologic
disorders, and the aging process\textsuperscript{22-25}. Together O$_2^-$, H$_2$O$_2$ and OH are known as reactive oxygen species (ROS) and these are produced continuously in vivo under aerobic conditions. In eukaryotic cells, the mitochondrial respiratory chain, microsomal cytochrome P450 enzymes, flavoprotein oxidases, and peroxisomal fatty acid metabolism are the most significant intracellular sources of ROS\textsuperscript{22-25}. The NADPH oxidases are a group of plasma membrane associated enzymes, which catalyze the production of O$_2^-$ from oxygen by using NADPH as the electron donor. Zinc is an inhibitor of this enzyme\textsuperscript{26}. The dismutation of O$_2^-$ to H$_2$O$_2$ is catalyzed by an enzyme super oxide dismutase (SOD), which contains both copper and zinc. Zinc is known to induce the production of metallothionein, which is very rich in cysteine, and is an excellent scavenger of OH\textsuperscript{26}. Iron and copper ions catalyze the production of OH from H$_2$O$_2$. Zinc is known to compete with both iron and copper for binding to cell membrane, thus decreasing the production of OH\textsuperscript{26}.

In spite of the known multiple biochemical roles of zinc as an antioxidant, most studies have been done using cell lines or animals and very few studies have investigated the use of zinc in the management of oxidative stress in humans. Most importantly, we are not aware of any study that addresses the protective effect of zinc against oxidative stress in normal healthy humans.

A few investigators have reported that inflammatory cytokines such as TNF-\textsubscript{\alpha} and IL-1\textbeta, generated by activated monocytes-macrophages, are also known to produce increased amounts of ROS\textsuperscript{27,28}. Increases in these cytokines are associated with decreased zinc status in patients with cutaneous leishmaniasis\textsuperscript{29} and increased lipid peroxidation products are associated with decreased zinc status in children with chronic giardiasis\textsuperscript{30}. Although limited information is available on the association of decreased zinc status and in vivo generation of oxidation by-products, the majority of studies reflect disease vs control conditions and do not address the effect of supplemental zinc on these parameters.

NF-\textepsilon B is involved in the expression of a variety of responsive specific genes and is activated by several stimuli such as cytokines, radiation, and oxidative stress\textsuperscript{22-24}. In vitro activation of NF-\textepsilon B by TNF-\textalpha in MNC has been shown to be an excellent model of oxidative stress-sensitive transactivating factor and has been used to evaluate the efficacy of compounds in protecting cells from oxidative stress\textsuperscript{23}. Zinc has been shown to inhibit NF-\textepsilon B activation in prostate cancer cells, thus enhancing anti-cancer therapy\textsuperscript{31}, bovine cerebral epithelial cells\textsuperscript{32} as well as reducing increased levels of activated NF-\textepsilon B in diabetic CD1 mice\textsuperscript{33} and zinc deficient cultured human hepatocellular carcinoma-derived cell line\textsuperscript{34}.

The paradox that zinc can inhibit NF-\textepsilon B activity, i.e. DNA binding and yet is necessary for DNA binding underscores the difficulty in understanding the mechanism of action of zinc as an antioxidant. The induction of NF-\textepsilon B activation pathway appears to be cell specific and is counterbalanced by concomitant activation of NF-B activation inhibitors. One such inhibitor of NF-\textepsilon B activation is A20, a zinc finger-transactivating factor which also binds to DNA producing the A20 protein which
inhibits TNF-α induced NF-êB activation\textsuperscript{35-39}. A20 plays an important role in reducing IL-1β- and TNF-α-induced NF-êB activation\textsuperscript{35-39}.

Our data reported here (Figs.14-17) provide evidence that zinc supplementation to normal healthy subjects a) lowers the oxidative stress-related by-products MDA, HA and 8-OHdG generated by cells and released into the plasma; b) inhibits the induction of TNF-α and IL-1β mRNA in MNCs; and c) exhibits a protective effect against TNF-α induced NF-êB activation in isolated MNCs\textsuperscript{25}. In addition, we provide evidence to show that in the pro-myelocytic leukemia cell line HL-60, which differentiates to the monocyte-macrophage phenotype by PMA, zinc increases the expression of A20 and the binding of A20 transactivating factor to DNA thereby enhancing inhibition of induced NF-êB activation\textsuperscript{25} (Fig. 18).

Recently, in a large study organized by the National Eye Institute, NIH, it was reported that zinc and antioxidants (vitamin C, vitamin E and beta carotene) significantly reduced the odds of developing advanced age related macular degeneration (AMD) and prevented blindness in the high-risk group of elderly subjects\textsuperscript{40}. Although the mechanism of zinc effect was not defined, one may hypothesize that zinc reduced the oxidative stress and was thus beneficial in AMD.

The effect of zinc on NF-êB activation is cell-lineage specific. We have reported that in HUT-78 cells (a Th\textsubscript{0} malignant human lymphoblastoid cell line) maintained under zinc deficient conditions, the activation of NF-êB and the level of newly synthesized IL-2 mRNA were decreased in comparison to the cells maintained under zinc sufficient conditions\textsuperscript{15,21}. We have also demonstrated that in zinc deficient HUT-78 cells, phosphorylated IêB, IKK, ubiquitinated IêB and binding of NF-êB to DNA were all significantly decreased compared to that found in zinc sufficient HUT-78 cells\textsuperscript{15}. We further showed that the binding of recombinant NF-êB (dimeric p50) to DNA in HUT-78 cells was zinc specific\textsuperscript{15}.

Our study showed that in MNC, the TNF-α induced binding of NF-êB to DNA was decreased in the zinc supplemented subjects compared to that in the placebo group, thus demonstrating the protective effect of zinc on TNF-α induced oxidative stress on cells\textsuperscript{25}. We also observed that the expression of genes encoding TNF-α and IL-1β (inflammatory cytokines known to generate ROS) were decreased in zinc supplemented volunteers versus that of placebo supplemented group.

The role of zinc in regulation of the gene expression of IL-1β and TNF-α has not been defined. The zinc finger protein A20 has been shown to inhibit NF-kB signaling by TNF-α and IL-1β via TNF-receptor gene (TRAF pathways) in endothelial cells\textsuperscript{37-39}. A20 is expressed in various types of cells in response to a number of stimuli such as TNF-α, IL-1β, LPS, PMA, Epstein-Barr virus latent membrane protein as well as other stimuli. A20 expression primarily protects cells from TNF-α induced cytotoxicity by decreasing the activation of NF-êB, which leads to decreased IL-1β and TNF-α gene expression as has been demonstrated in endothelial cells. In this study we show that the A20 mRNA increases in zinc supplemented HL-60 cells. The cartoon in Figure 19 presents our hypothesized role.
of zinc in the gene expression of TNF-\( \alpha \) and IL-1\( \beta \). We propose that similar effect of zinc supplementation on the A20 pathway occurs in primary cells. Further studies are on going in our laboratory in order to understand the mechanisms of zinc action.

Evidence is accumulating to indicate that oxidative stress may be an important contributing factor in several chronic human diseases. In view of the fact that TNF neutralization in the treatment of septic shock\(^{41-44}\) and the use of IL-1R\( \alpha \) (IL-1 receptor antagonist) and TNF-\( \alpha \) antibody in the treatment of rheumatoid arthritis\(^{41-44}\) are well known, a trial of therapeutic levels of zinc administration in many chronic diseases in which oxidative stress is known to play an important role may be clinically relevant inasmuch as zinc decrease the gene expression of both TNF-\( \alpha \) and IL-1\( \beta \).

It is evident from the AREDS study\(^{40}\), that in order to achieve antioxidant effect of zinc in vivo, the oral dose of zinc administration must be several times higher than the usual RDA amounts. Clearly, under these situations, one is not attempting to correct a simple zinc deficiency, rather one is using zinc as a therapeutic modality in order to achieve an antioxidant effect. In humans, oral intake of elemental zinc greater than 50 mg daily for more than 12 weeks, most likely will induce copper deficiency\(^{45,46}\). In order to prevent this, in AREDS trial, all subjects were given 2 mg copper orally daily\(^{40}\).

Our study provides molecular evidence for anti-oxidant effect of zinc in human subjects and shows that zinc supplementation in vivo protected MNC against oxidative stress. Although there are several possible biochemical mechanisms by which zinc may decrease oxidative stress in cells, our study shows that zinc negatively regulates gene expression of inflammatory cytokines such as TNF-\( \alpha \), and IL-1\( \beta \), which are known to generate ROS and this may be one additional mechanism by which zinc may be functioning as an antioxidant in humans. Thus our study provides rationale for use of zinc in therapeutic trials either alone or in conjunction with other modalities in chronic diseases including chemoprevention of cancer in which oxidative stress is known to play an important role.

**Therapeutic Uses of Zinc**

In this section, I wish to summarize the therapeutic uses of zinc in humans. These are:

1. Treatment of acute infantile diarrhea with zinc
2. Treatment of accrodermatitis enteropathica with zinc
3. Treatment of Wilson’s disease with zinc
4. Treatment of sickle cell disease with zinc
5. Zinc in the treatment of AMD (age related macular degeneration)
6. Treatment of common cold with zinc

Acute infantile diarrhea is a very serious disorder which affects children of developing countries. The mortality rate of this condition is 60 to 80%. During the past decade, zinc in therapeutic doses has been used to treat these cases. This modality has now reduced the mortality by thirty to forty percent\(^{8,9}\). Also it has been observed that the incidence of pneumonia has been drastically decreased in these patients who received zinc.
Acrodermatitis enteropathica is a relatively rare genetic disorder which affects adversely the absorption of dietary zinc such that the affected individuals become severely zinc deficient. If untreated, the disease becomes fatal. Mutation in the ZIP4 gene (a zinc transporter) is responsible for this disorder. Treatment with therapeutic levels of zinc is highly successful and now these patients survive and lead a normal life.

Wilson’s disease is a genetic disorder in which copper accumulates in liver, kidneys, intestines, brain, and other organs. In our earlier studies we observed beneficial effect of zinc on sickling of deoxygenated sickle cells. Later zinc administration in therapeutic doses (50 to 150 mg zinc as acetate daily orally) was used to treat sickle cell disease patients in order to decrease sickle cell pain crises. We observed that at this level of zinc administration, we induced copper deficiency in our patients. This led us to evaluate zinc as a therapeutic modality for the treatment of Wilson’s disease. Zinc acts by induction of intestinal cell metallothionein in which once induced, has a high affinity for copper and prevents the serosal transfer of copper into the blood. The intestinal cells turn over rapidly and take the complexed copper into the stool where it is excreted. Zinc blocks food copper and endogenously excreted copper via salivary, gastric and other gastrointestinal juices. As a result, zinc produces a chronic negative copper balance.

For maintenance therapy of Wilson’s disease, zinc is the treatment of choice. Zinc has no toxic effects and it can be used for treatment of presymptomatic patients and pregnant women.

Other studies in adult patients with sickle cell disease showed that nearly two-thirds of these patients were zinc deficient. We also related growth retardation, male hypergonadism and immune dysfunction in these patients to zinc deficiency. Zinc supplementation to sickle cell disorder patients in therapeutic doses has shown benefical effects with respect to the above mentioned clinical parameters.

The age-related Eye Disease Study group supported by the National Eye Institute, NIH conducted an 11-center double-masked clinical trial in patients with age-related macular degeneration (AMD). 3640 participants were enrolled. Their ages ranged from 55-80 years and the average follow up period was 6.3 years. Participants were randomly assigned to receive daily oral tablets containing one of the following: 1) antioxidants (vitamin C 500 mg, vitamin E 400 IU; and B carotene 15 mg), 2) zinc 80 mg as zinc oxide and copper 2 mg as cupric oxide, 3) antioxidants plus zinc, or 4) placebo. Copper was added to prevent copper deficiency in the zinc supplemented group.

The group taking the antioxidant plus zinc supplementation reduced the risk of developing advanced AMD by about 25% and the risk of vision loss by about 19%. The group taking zinc alone reduced the risk of developing advanced AMD by about 21% and vision loss by about 11%, whereas the group taking the vitamins alone reduced their risks for developing advanced AMD by about 17% and vision loss by about 10%. No side effects were noted due to therapeutic levels of zinc supplementation. Another interesting observation was reported in that only the zinc supplemented group showed
increased longevity^48.

In order to test the efficiency of zinc acetate lozenges in reducing the duration of symptoms of the common cold, we carried out a randomized, double-blind placebo controlled trial in 50 ambulatory volunteers recruited within 24 h of developing symptoms of the common cold^49. Participants took one lozenge containing 12-8 mg zinc (as acetate) or placebo every 2 to 3 h while awake as long as they had cold symptoms. Subjective symptom scores for sore-throat, nasal discharge, nasal congestion, sneezing, cough, scratchy throat, hoarseness, muscle ache, fever and headache were recorded daily for 12 days.

Compared with the placebo group, the zinc group had shorter mean overall duration of cold symptoms, cough and nasal discharge and decreased total severity scores for all symptoms.

The mechanism by which zinc may affect the common cold is not well understood. It has been suggested that zinc may act as an antiviral agent. Another possibility is that extra cellular zinc ion may exert its antiviral effect by stabilizing and protecting cell membranes. Zinc is known to induce production of interferon and modulate inflammatory cytokines, which in turn may have resulted in beneficial effects on cold symptoms by zinc therapy.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1</td>
<td>T-helper 1</td>
</tr>
<tr>
<td>Th2</td>
<td>T-helper 2</td>
</tr>
<tr>
<td>IL-10</td>
<td>Interleukin-10</td>
</tr>
<tr>
<td>IL-2</td>
<td>Interleukin-2</td>
</tr>
<tr>
<td>TNF-á</td>
<td>Tumor necrosis factor-á</td>
</tr>
<tr>
<td>IL-1â</td>
<td>Interleukin-1â</td>
</tr>
<tr>
<td>NF-êB</td>
<td>Nuclear Factor-êB</td>
</tr>
<tr>
<td>PMA</td>
<td>Phorbol-12 myristate 13 acetate</td>
</tr>
<tr>
<td>PHA</td>
<td>Phytohemagglutinin-p</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>MNC</td>
<td>Mononuclear cells</td>
</tr>
<tr>
<td>ICAM</td>
<td>Intercellular adhesion molecule</td>
</tr>
<tr>
<td>VCAM</td>
<td>Vascular endothelial cells adhesion molecule</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>MDA</td>
<td>Malondialdehyde</td>
</tr>
<tr>
<td>FBS</td>
<td>Fetal bovine serum</td>
</tr>
<tr>
<td>TBA</td>
<td>Thiobarbituric acid</td>
</tr>
<tr>
<td>HAE</td>
<td>4-hydroxyalkenals</td>
</tr>
<tr>
<td>8-OHdG</td>
<td>8-hydroxy deoxyguanine</td>
</tr>
</tbody>
</table>

**ACKNOWLEDGEMENT**

I wish to gratefully acknowledge the help and support of Dr. Frances W.J. Beck and Dr. Bin Bao. I would also like to thank Diane Snell and Sally Bates for their technical and clerical assistance.

**REFERENCES**

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CD73 (ecto-5'-nucleotidase in the CD8+ subset is associated with zinc deficiency in human patients. J Lab Clin Med 1997;130:147-156.


BIOCHEMICAL PROFILE IN NAFLD - A PRELIMINARY STUDY

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1 - SCB Medical College & Hospital, Cuttack, Orissa. 2 - Beam Diagnostics, Cuttack, 3 - A.H. Regional Cancer Centre, Cuttack

ABSTRACT:

Eighty menopausal women in the age range (45-73) were exposed to the study in between December 2002 to June 2003. Their Bone Mineral Density was assessed by Achilles Express Bone Ultra Densitometer. Their average BMD was calculated according to T-score by using WHO guidelines for classification into Normal, Osteopenic and Osteoporotic. Findings were statistically analysed and the results were compared with the work done by other authors. It was observed that the incident of osteopenia and osteoporosis was high in post menopausal women as compared to normal. Even though menopause is the leading cause of osteoporosis in this age group, it can be improved by slight modification of the diet and lifestyle.

Key words: ALT, HOMA, Insulin resistance, NAFLD activity score (NAS).

INTRODUCTION:

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver injuries that occur in the absence of significant alcohol consumption.¹ It can extend from simple hepatic steatosis to cryptogenic cirrhosis.² Non-alcoholic steatohepatitis (NASH) is an advanced form of NAFLD in which fatty change is associated with inflammation, hepatic injury and/or hepatic fibrosis.³

Most cases of NAFLD occur in patients with obesity (60-95%), type 2 diabetes (28-55%) and hyperlipidemia (27-92%).⁴ However, insulin resistance is the key denominator in all these conditions. NAFLD patients with the metabolic syndrome (insulin resistance syndrome or syndrome X) have a higher prevalence and severity of fibrosis, compared to subjects with pure fatty liver.⁵

NAFLD and NASH are emerging as a common cause of chronic liver disease in industrialized countries where the reported prevalence of NAFLD is 17-33% and that of NASH is 5.7-17%.⁶ However, due to changes in lifestyle trends the prevalence rate seems to be increasing in developing countries;⁷ one of our studies revealed a prevalence rate of 24.5% in coastal Orissa.⁸

The prevalence of NAFLD and NASH are obviously dependent on the accuracy of diagnosis. Although liver biopsy is considered to be the gold standard for diagnosis,⁹ performing liver biopsies as a screening test in population based studies is not feasible. Consequently hepatic imaging and serum liver function tests have been used as indirect or
surrogate tests to estimate the prevalence of NAFLD and NASH. A number of studies have reported that NAFLD is the most common cause of chronically elevated enzymes (ALT, AST, GGT) of unexplained etiology. On the other hand, some published literature also suggest that LFT abnormalities do not correlate with the degree of steatosis or fibrosis.

With this background, the present study was designed to evaluate the different biochemical parameters in patients with NAFLD and to correlate these parameters with the NAFLD Activity Score (NAS).

MATERIAL AND METHODS

Patients:

NAFLD was diagnosed by liver biopsy in 24 patients attending the gastroenterology department at SCB Medical College, Cuttack from November 2005 to June 2006. The patients included 21 men and 3 women between the age group of 27-55 years. History of alcohol consumption was elicited by independent interviews with the patients and their family members. In none of them there was history of significant alcohol consumption (> 20g/d for > 5 yrs). All patients had negative serology for HBV, HCV and HIV. No patient had conditions related to secondary NAFLD like use of drugs producing steatosis (corticosteroids, tamoxifen, amiodarone), previous gastrointestinal surgery, total parenteral nutrition, etc. Other liver diseases like chronic viral hepatitis, auto immune hepatitis, primary biliary cirrhosis and metabolic liver diseases were excluded by relevant serology and biochemical tests as indicated. The body mass index (BMI in Kg / m²) was calculated in all the patients. The patients were classified on the basis of their BMI as normal (BMI 18.5-24.9), over weight (BMI 25-29.9) and obese (BMI > 30). The patients were assigned the diagnosis of diabetes mellitus if there was documented use of oral hypoglycemic agents or insulin, or FPG was >125 mg% and/or 2hr PGPG > 200 mg%. Hyperlipidemia was diagnosed when fasting serum cholesterol was > 200 mg/dl and/or fasting serum triglyceride was above 150 mg/dl.

Histology: A liver biopsy was performed in every patient at the baseline for the diagnosis of NAFLD and before the initiation of treatment. The necroinflammatory grade and stage of fibrosis were assessed according to the method proposed by Kleiner et al. Each biopsy was analyzed and graded by two pathologists without knowledge of the patient’s clinical or laboratory data. Scores for steatosis and lobular degeneration were assigned 0-3 each. For ballooning the scoring was performed in the scale 0-2. Fibrosis was assessed and scores assigned in the scale 0-4. However, fibrosis was excluded while grading.

The cases were graded basing on the NAFLD activity score (NAS) into grade I, II and III. Cases with NAS 0-2 were classified as grade I, NAS 3-4 as grade II and NAS 5-8 as grade-III. Prognostically grade I would correspond to mild degree of injury, grade II to moderate degree of injury and grade III to severe degree of hepatic injury.
Laboratory investigations:

The laboratory investigations included liver function tests (AST, ALT, AST:ALT ratio and serum bilirubin), fasting plasma glucose, 2 hours post glucose blood sugar, fasting insulin, and total serum cholesterol and triglyceride levels. Standard biochemical tests were performed by a multi-channel autoanalyser. Plasma insulin was measured by chemiluminescence technique. Insulin resistance (IR) was calculated by homeostasis model assessment (HOMA). \( \text{HOMA}_{IR} = \frac{\text{fasting sugar (mg/dl)} \times \text{fasting insulin (\( \mu \text{U/mL} \))}}{405} \). As reported in the earlier studies, patients were deemed to be insulin resistant when they had a HOMA \(_{IR} \) index >1.64.\(^{15,16}\)

Ultrasonography:

Abdominal ultrasonography was performed to assess the presence of fatty liver by two separate experienced ultrasonologists.\(^{17}\)

Statistical analysis:

Statistical analysis was performed using student’s ‘t’ test. The data were expressed as mean ± SD. Results were considered significant when p value was <0.05. All data were analysed by the statistical software SPSS, 10.5.

RESULTS:

The diagnosis of NAFLD was made in all 24 patients histologically. Of these 7 were classified as grade-I (NAS score, 0-2), 11 as grade II (NAS score 3-4) and 6 as grade III (NAS score 5-8) [Table-1]. The data were analysed to see if there was any correlation between the various grades of NAFLD and the following clinical variables: age, sex, BMI, serum bilirubin (total), AST, ALT, serum cholesterol, serum triglyceride, FPG, 2 hr PGPG, serum insulin and HOMA\(_{IR}\).

Most of the patients were males (87.5%) with grade II histological changes, and their mean age was 40.6 (27-55) years. The mean BMI was 25.4 (19-31) and there was no correlation between the values of BMI and the NAFLD grades (Table 1). All our patients showed fatty liver ultrasonographically.

FBS, 2hr PGBS and serum insulin were normal in most cases. Insulin resistance (HOMA-IR) was more than 1.64 in 75% of cases. The mean values of HOMA were on the higher side in all grades of NAFLD (Table 2).

The serum triglyceride level was raised above normal in 21 cases (87.5%); it showed a rising trend with increasing grades of NAFLD. The mean serum cholesterol was normal in NAFLD grade I and III but was on the higher side in grade II (Table 3).

The mean serum bilirubin level was within normal limit, where as AST (SGOT) and ALT (SGPT) were raised above normal. The AST (SGOT) was raised in 10 cases (41.6%) where as the ALT (SGPT) was raised in 15 cases (62.5%) and there was a gradual rise of ALT levels with increasing grades of NAFLD. Mean ALT: AST ratio was more than one in all grades (Table 4).

DISCUSSION:

We attempted to find whether there was any correlation between the various biochemical parameters and the grades of
NAFLD and NAFLD Activity Score (NAS). As diabetes mellitus, insulin resistance, hyperlipidemia and abnormal liver enzymes are commonly associated with NAFLD, we attempted to correlate these values with the NAS score.

All the patients in our study were in the age range 27-55 years with a mean age of 40.6 years, and the majority were males (87.5%). The mean BMI was 25.4 (19-31). These observations were similar to those reported by Madan et al.\textsuperscript{16}

One of our previous study\textsuperscript{17} had shown that ultrasonography is a simple, safe and non invasive procedure without any discomfort to the patient and can be used to study the prevalence of fatty liver in the general population. This was also demonstrated by Nomura et al\textsuperscript{24} earlier. During the present study all our patients demonstrated fatty liver ultrasonographically.

We found that while most of our patients were non-diabetic, the insulin resistance as calculated by HOMA (HOMA\textsubscript{IR} > 1.64) was present in 75% of our patients which is consistent with the values reported from Northern India by Madan et al\textsuperscript{16} and Duseja et al\textsuperscript{18} who observed insulin resistance in 80% and 100% of their NAFLD patients respectively. Way back in 1999, Marchesini et al, had also observed that the HOMA\textsubscript{IR} was nearly doubled in 46 NAFLD cases compared to the 92 matched controls.\textsuperscript{19} Chitturi et al too have observed that insulin resistance is often associated with NAFLD.\textsuperscript{20}

For assessing serum hyperlipidemia we measured two parameters, serum cholesterol and serum triglyceride levels. Serum cholesterol was normal in grade I and III patients in our series, whereas serum triglyceride levels were raised compared to normals in the majority. The serum triglycerides levels also showed a rising trend with increasing grades of NAFLD (Table-2). However this rise was not statistically significant and this may be due to the small number of patients.

Analyzing the LFT values, we found raised ALT levels in most of our cases and the values correlated with the underlying histological scoring of NAFLD. Although some authors have observed similar findings\textsuperscript{10,21}, others\textsuperscript{22} have reported that the enzyme values were within the normal range despite advanced liver disease.\textsuperscript{22} In our patients the mean value of serum AST was found to be raised. A comparison of the biochemical parameters of our patients with that of Agarwal et al\textsuperscript{23} showed similar abnormalities in LFT (Table-5).

In summary, the present study compared the different biochemical parameters among different histopathological grades of 24 NAFLD patients. Their ALT and serum triglyceride levels showed a steady rise with increasing grades of NAFLD. Insulin resistance was present in 75% of our cases. To conclude serum ALT, triglyceride and insulin resistance (HOMR\textsubscript{IR}) together with ultrasonography can be taken as non-invasive predictors for the diagnosis of NAFLD and the necroinflammatory grade.

However, further studies with greater number of patients will shed more light on the subject.
### Table - 1

**Age, Sex, and BMI in different grades of NAFLD**

<table>
<thead>
<tr>
<th>NAS Grade (Score)</th>
<th>No. of Cases</th>
<th>Age(Yrs) Range Mean</th>
<th>Sex</th>
<th>BMI Range mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (0-2)</td>
<td>7</td>
<td>32-51 (40)</td>
<td>6</td>
<td>21-28 (24.2)</td>
</tr>
<tr>
<td>II (3-4)</td>
<td>11</td>
<td>31-53 (41)</td>
<td>9</td>
<td>19-31 (24.6)</td>
</tr>
<tr>
<td>III (5-8)</td>
<td>6</td>
<td>27-55 (41)</td>
<td>6</td>
<td>22-31 (27.3)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>27-55 (41)</td>
<td>21</td>
<td>19-31 (25.4)</td>
</tr>
</tbody>
</table>

### Table - 2

**Blood Sugar, serum Insulin and HOMAIR in different grades of NAFLD**

<table>
<thead>
<tr>
<th>NAS Grade</th>
<th>No. of Cases</th>
<th>FBS mg/dl Range mean ± SD</th>
<th>2hr PPBS (mg/dl) Range mean ± SD</th>
<th>S. Insulin (µU/ml) Range mean±SD</th>
<th>HOMAIR Range mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>75-134, 93±20</td>
<td>110-240, 142±44</td>
<td>7.2-22.8, 12±5.4</td>
<td>1.33-4.67, 2.6±1.2</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>71-140, 93±22</td>
<td>94-250, 144±53</td>
<td>5.3-18.2, 8.16±4.8</td>
<td>0.95-3.19, 2.0±0.7</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>87-245, 111±64</td>
<td>100-265, 155±67</td>
<td>6.5-15.1, 10±3</td>
<td>1.4 - 9.13, 3.2 ± 3</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>71-245, 98.6±36</td>
<td>94-265, 146±52</td>
<td>5.3-22.8, 9.8±4.9</td>
<td>0.95 - 9.1, 2.4±1.6</td>
</tr>
</tbody>
</table>

### Table - 3

**Serum lipids in different grades of NAFLD**

<table>
<thead>
<tr>
<th>NAS Grade</th>
<th>No. of Cases</th>
<th>Serum TG (mg/dl) Range, Mean±SD</th>
<th>Serum TC (mg/dl) Range, Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>168-317 (213.7 ± 60.5)</td>
<td>144-214 (180.5 ± 23.5)</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>85-360 (215 ± 85.4)</td>
<td>140-303 (209.7 ± 43.4)</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>164-378 (260 ± 85.8)</td>
<td>173-208 (191.5 ± 12.6)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>85-378 (226 ± 78.3)</td>
<td>140-303 (196.6 ± 34.1)</td>
</tr>
</tbody>
</table>
Table - 4
Liver Function Test values in different grades of NAFLD

<table>
<thead>
<tr>
<th>NAS Grade</th>
<th>No.of Cases</th>
<th>S. Bilirubin Total (mg/dl) Range Mean ±SD</th>
<th>AST (IU/L) Range Mean ±SD</th>
<th>ALT(IU/L) Range Mean±SD</th>
<th>ALT/AST Ratio Range Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>0.6-1.2, 0.8 ± 0.2</td>
<td>22-55, 32 ± 12</td>
<td>22-64, 38 ± 16</td>
<td>0.9-1.4, 1.16</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>0.5-1.1, 0.7 ± 0.2</td>
<td>17-99, 41 ± 27</td>
<td>19-83, 45 ± 23</td>
<td>0.83-1.3, 1.13</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>0.5-1.3, 0.8 ± 0.3</td>
<td>28-75, 49 ± 17</td>
<td>29-114, 70 ± 33</td>
<td>0.92-2.5, 1.45</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>0.5-1.3, 0.7 ± 0.3</td>
<td>17-99, 41 ± 21</td>
<td>19-114, 50 ± 27</td>
<td>0.8-2.5, 1.24</td>
</tr>
</tbody>
</table>

Table - 5
Comparison of Biochemical parameters

<table>
<thead>
<tr>
<th>Biochemical Parameters</th>
<th>Normal Value</th>
<th>Present Study 2006 (n = 24)</th>
<th>Agarwal et al 2001 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGPT (IU/L) (ALT)</td>
<td>5-40</td>
<td>49.71, 19-114</td>
<td>96, 53-159</td>
</tr>
<tr>
<td>SGOT (IU/L) (AST)</td>
<td>5-40</td>
<td>40.83, 17-99</td>
<td>53, 30-212</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>1.0</td>
<td>1.24, 0.83-1.52</td>
<td>1.85, 0.38-2.6</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>50-150</td>
<td>196, 140-303</td>
<td>155, 70-1018</td>
</tr>
</tbody>
</table>

REFERENCES:

5. Dixon JB, Bathal PS, Orien PE. Non-alcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the


ABDOMINAL RECTOPEXY WITH POLYPROPYLENE MESH IN COMPLETE RECTAL PROLAPSE - OUR EXPERIENCE

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1 - SCB Medical College, Cuttack, 2 - Shanti Hospital, Cuttack

INTRODUCTION:
Rectal prolapse is defined as a protrusion of a part or all the layers of the rectum through the anal orifice. Partial prolapse involves the anal and distal rectal mucosa usually < 4cm beyond anal verge where as in complete rectal prolapse or procidentia, all the layers of the rectum extrude through the anal verge, usually > 4cm.

The definite cause of rectal prolapse is not known although a number of physiological and anatomical abnormalities associated with the rectal prolapse are well recognized. It is not yet clear whether these abnormalities are primary or secondary to the prolapse.

The diagnosis of complete rectal prolapse is straightforward and based upon history and evaluation of the anorectal area. It is often associated with myriad of functional disturbances significantly altering the patients qualities of life. Women are six times more often affected than men.

The surgical management has evoked considerable controversies and both the patient and the surgeon are too often dissatisfied because of persistent incontinence, bowel management problems and recurrences.

OBJECTIVE OF THIS STUDY:
The objectives of the present study is to determine that the polypropylene mesh repair in complete rectal prolapse is a safe feasible and single stage option for the management of complete rectal prolapse.

MATERIALS & METHODS:
Twenty five cases of complete rectal prolapse out of 1200 cases of anorectal problems admitted in surgical wards in the Dept. of General Surgery, S.C.B. Medical College & Hospital and Shanti Hospital, Cuttack during the period from Jan. 2004 to Dec. 2005, were enrolled in the present study.

Only those cases, which were confirmed to have complete rectal prolapse on clinical examination and investigation and posted for elective surgery were included in our study. All the patients underwent thorough clinical examination with history. Digital rectal examination was done with palpation of the prolapse, tone of anal sphincter and presence of any ulcer. Routine blood examination, proctoscopy, sigmoidoscopy and colonoscopy were done to exclude associated pathologies. USG abdomen
and pelvis were done to rule out any abnormalities.

Patients having associated systemic disorders were treated according to their problems. The hemoglobin levels were corrected by preoperative blood transfusion. Other infections if any detected were tackled with. The nutritional status of the patients was improved by giving a mixture of vitamins, minerals, carbohydrates, lipids and proteins. Patient with cardiac problems were treated as per cardiologists advice. The diabetic status were checked and corrected.

Preoperatively all the patients were immunized with tetanus toxoid and TIG. Patients were kept on IV fluid on the morning of surgery with one dose of cefuroxime, metronidazole and pantoprazole iv. Shaving of the abdomen and perineal area was done on table. Bladder was catherised with no. 16 foley’s catheter.

Depending on the fitness of the patients general or spinal anaesthesia was given. Patient was positioned supine with moderately steep trendelenberg tilt. Skin was prepared with povidone iodine. Lower midline incision was preferred.

After excluding any co-existent large bowel disease, the rectum was mobilized posteriorly, laterally and anteriorly with special care taken not to injure the inferior mesentric vessels and pre-sacral plexus. The posterior plane of separation was followed from the sacral promontory by the side-to-side sweeping movement of surgeon’s right index finger as far down as possible nearing the pelvic floor. The polypropylene mesh was fixed to the sacrum with non-absorbable prolene stitches in the midline and folded around the rectum to cover all except the anterior one fourth to one fifth of its circumference and was secured by three or four seromuscular stitches with prolene 2-0 uniting its lateral margins to the bowel wall. Finally pelvic peritoneum was reconstructed by suturing the flaps in front. Closed suction drain was given in the pelvis. Abdomen was closed in layers.

**OBSERVATION**

The patients were observed post operatively, monthly, three monthly, six monthly, after one year and after two years for bowel dysfunction, disturbances of micturition, disturbance of sexual function, mesh rejection, recurrence as given in the following table.

**TABLE 1**

<table>
<thead>
<tr>
<th>Age Group in yrs.</th>
<th>Sex</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>Nil</td>
<td>Nil</td>
<td>-</td>
</tr>
<tr>
<td>11-20</td>
<td>Nil</td>
<td>Nil</td>
<td>-</td>
</tr>
<tr>
<td>21-30</td>
<td>F(4) M(3)</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>31-40</td>
<td>F(4) M(3)</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>41-50</td>
<td>F(3) M(1)</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>51-60</td>
<td>F(2) M(1)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>61-70</td>
<td>F(1) M(1)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>F(1) M(1)</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal anorectal surgery</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal Hernia Repair</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Spinal Laminectomy</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
### TABLE 3
Symptoms & Signs:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients</th>
<th>%</th>
<th>Signs</th>
<th>No. of Patient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducible mass protuding per anum</td>
<td>25</td>
<td>100</td>
<td>Prolapse on straining</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Mucous discharge</td>
<td>20</td>
<td>80</td>
<td>Enlarged anal orifice</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>Bleeding per anum</td>
<td>10</td>
<td>40</td>
<td>Ulcer in prolapsed mucosa</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Pruritus ani</td>
<td>10</td>
<td>45</td>
<td>Concealed hemorrhage detected by proctoscopy</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Pain</td>
<td>10</td>
<td>40</td>
<td>Decreased tone of anal sphincter and levator ani</td>
<td>23</td>
<td>92</td>
</tr>
<tr>
<td>Sense of incomplete evacuation</td>
<td>12</td>
<td>48</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>5</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenesmus</td>
<td>3</td>
<td>12</td>
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</tbody>
</table>

### TABLE 4
Post Operative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Total No. of cases</th>
<th>Nature of Operation</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mesh</td>
<td>Others</td>
</tr>
<tr>
<td>Early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>02</td>
<td>-</td>
<td>02</td>
</tr>
<tr>
<td>Chest infection</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transient paralytic ileus</td>
<td>02</td>
<td>-</td>
<td>02</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infection around</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prosthesis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal impaction</td>
<td>01</td>
<td>01</td>
<td>-</td>
</tr>
<tr>
<td>Incontinence</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disturbances of micturition</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### TABLE 5
Final Outcome

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of cases</th>
<th>Nature of Operation</th>
<th>Surgical Outcome</th>
<th>Success rate in percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mesh</td>
<td>Others</td>
<td>Mesh</td>
</tr>
<tr>
<td>Mass protruding per anum</td>
<td>25</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mucous discharge per anum</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bleeding per anum</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pruritus ani</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pain and discomfort</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
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<tr>
<td>Sense of incomplete evacuation</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tenesmus</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Over all success rate approximately 97 100

### TABLE 6
Return to Active Life

<table>
<thead>
<tr>
<th>Post operative period</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3\textsuperscript{rd} week (15\textsuperscript{th} day to 21\textsuperscript{st} day)</td>
<td>01</td>
<td>04</td>
</tr>
<tr>
<td>4\textsuperscript{th} week (22\textsuperscript{nd} day to 28\textsuperscript{th} day)</td>
<td>09</td>
<td>36</td>
</tr>
<tr>
<td>5\textsuperscript{th} week (29\textsuperscript{th} day to 35\textsuperscript{th} day)</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>6\textsuperscript{th} week (36\textsuperscript{th} day to 42\textsuperscript{nd} day)</td>
<td>03</td>
<td>12</td>
</tr>
</tbody>
</table>

### TABLE 7
Follow-up

<table>
<thead>
<tr>
<th>Follow up time</th>
<th>Total cases</th>
<th>incontinence</th>
<th>Constipation</th>
<th>Recurrence</th>
<th>Mesh rejection</th>
<th>Disturbance of micturition</th>
<th>Disturbance of Impotency</th>
<th>Morbidity %</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} Month</td>
<td>25</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>08</td>
<td>0</td>
</tr>
<tr>
<td>2\textsuperscript{nd} Month</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3\textsuperscript{rd} Month</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4\textsuperscript{th} Month</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At 1 Year</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
RESULTS:

The incidence of prolapse rectum in relation to total hospital admission is 0.07% and in relation to number of surgical admission is only 0.5%.

* Out of the 20 patients we have studied 17 patients (68%) were male, 8 patients (32%) were female. The rectal prolapse is not confined to elderly female patients. The youngest was 22 years and the oldest was 77 years. Thus 56% of the patients were in 21-40 years age range and 8% were between 61-70 years. 16% and 12% were distributed in 41-50 years and 51-60 years age range.

* 24% were malnourished at the time of admission, 60% were average body build and 4% obese.

* 50% of the patients were multiparous and 25% childless.

* 32% of female patients were having uterine and rectal prolapse for which they have undergone Colpoperineorrhaphy.

* 4% of patients had a past history of trauma to rectum due to sexual abuse for which they had undergone perineal surgery.

* 4 patients were having chronic constipation following previous perineal surgery.

* 4 patients had history of protracted diarrhea before admission to the hospital.

* 2 female patients had undergone hysterectomy previously.

* 1 patient was psychotic with neurological disorders.

* 1 patient had undergone spinal laminectomy.

* 2 elderly patients had chronic obstructive pulmonary disease.

* 3 patients were IDDM.

* 3 patients were hypertensive on antihypertensive drugs.

* 1 patient was a psychotic on psychiatric drug.

* 1 patient had undergone inguinal herniorrhaphy for inguinal hernia.

* 5 patients had uncomplicated prolapse for very long period (5 years).

* 8 patients had problems for 2-5 years

* Majority of 12 patients had prolapse for 0-2 years.

All the 25 (100%) patients presented with reducible mass protruding per anum as the chief complaint. Other complaints like mucous discharge was present in 20 (80%) patients; bleeding per anum in 10 patients (40%), sense of incomplete evacuation in 12 patients (48%), constipation in 8 patients (32%) incontinence in 5 patients (20%) and tenesmus in 3 patients (12%).

Only 2 cases (8%) developed wound infection and 2 patients (8%) developed transient paralytic ileus.

One patient (4%) who was a daily wager had resumed his normal activity on 21st day at the end of 3rd week. 9 patients (36%) resumed their normal activity during 4th week while 12 patients (48%) resumed in 5th week. 3 elderly patients (12%) resumed their normal activity during 6th week.

Only 2 cases (4%) who developed fecal impaction and constipation post
operatively were cured after conservative treatment at the end of 2nd month. There
were no incontinence, recurrence, mesh rejection, disturbance in micturition,
impotency or mortality reported during the period of follow-up. The over all success
rate for mesh rectopexy was 97%. The 2nd year follow-up is ongoing.

DISCUSSION

Complete rectal prolapse can be a distressing condition for the patient.
There should be two primary objectives in treating these patients. The first is to carry
out a procedure that safely corrects the prolapse with minimal morbidity and without
any mortality. The second is to cure or significantly improve the associated
incontinence and the underlying defecatory disorder. The advantages of
sacral rectopexy are, rendering the patient continent and minimising recurrence rates.
In our study during Jan 2004 to Dec 2005,
the observations made were analyzed and
compared with the works of previous
studies. Between 1970 to 1985, at the St.
Marks Hospital and the London Hospital;
only 66 patients of complete rectal prolapse was reported by Mann C. V. et.
al. This study did not define the exact incidence of rectal prolapse, however the
incidence of rectal prolapse in this region is relatively high, which may be attributed
to illiteracy, poor bowel habits, and suffering of the patients from chronic
dysentery due to poor sanitary conditions. We have recorded the male predominance
in our series with a male to female ratio of
2:5:1. The female patients were evenly
distributed throughout age range. Hughes2
(1949) in his series at St. Mary's Hospital
had reported 84% of the patients to be
women; most of them in 5th or subsequent
decades of life, and the male patients were
mostly in their 2nd and 3rd decades. P. B.
Chakraborty3 (1982) has reported in his
study; the male to female ratio of 3:1 with
most of the patients in 31 to 40 years age
group. The higher incidence amongst
Indian males might be due to the fact that
females in this part of the world are
inhibited to undergo examination and
treatment.

Survey elicits 24% patients to be
malnourished; 60% of average body built
and 16% patients obese. Bachoo P. et. al.4
(2001) attributed debility as a cause of
rectal prolapse in low socio-economic
status.

Our series is comparable to
Carrasco (1934) and Gabriel5 (1984) who have also recorded the predominance in
women who have suffered the strain of
parturition than in those who have not.

In our present series, 16% patients
were chronic constipators, 16% patients
had protracted diarrhoea or dysentery, 4%
patients had previous h/o trauma to
rectum. 8% patients had undergone
hysterectomy, 4% patients suffered from
chronic obstructive pulmonary disease
(COPD), 4% patients had past h/o spinal
injury and 4% patients had neurological
disorder. COPD which leads to increased
intra abdominal pressure has a definite
relation as reported by Lynn K. Flowers5
preponderance of rectal prolapse in
patients suffering from mental disease
particularly amongst the inmates of
asylum. Our findings corroborated with
above literature except in Diabetics and
Hypertensive, which had higher
representation in our series. As Diabetes
and Hypertension doesn’t have any direct
association within the etiology of the
disease, this figure may probably be
chance association.
Mann & Hoffmann\(^1\) (1991) reported out of 66 patients in their series 11 had undergone hysterectomy, 4 had repair for uterine prolapse, 4 had pelvic floor surgery, 17 had various forms of anorectal surgery, 1 had total colectomy and 1 patients had spinal laminectomy. The result observed in our study is fairly comparable to other workers.

Our series corroborates well with the works of J.K. Elvarasi et. al.\(^8\) (1998) reported mass protruding per anum in 100% cases, mucous discharge in 70% cases, blood discharge in 23% cases, pruritus ani 9% cases and constipation in 2% cases.

All the patients in our series had prolapse on straining. 92% patients had decreased tone of anal sphincter and levator ani, 56% had enlarged patulous anal orifice, 40% had ulcers in the prolapsed mucosa and only 12% patients had concealed haemorrhage detected by proctoscopy. 80% patients had a length of the prolapse between 5 to 7 cm and rest 20% between 7 to 10 cm. Goligher et. al.\(^9\) (1975) have also noted patulous anus, atony of sphincters and levator ani, superficial ulceration on the prolapsed mucosa in their patients of incomplete rectal prolapse. R.C.G. Russell et. al.\(^10\) (2004) had noted complete rectal prolapse are usually more than 5 cm in length. Our series is comparable to the findings of other workers.

We have used prolene mesh for sacral rectopexy in majority of 80% cases. G.S. Duthie et. al.\(^11\) (1991) have opined suture rectopexy as the easiest of the abdominal procedures and have tended to reserve it for elderly patients because of its simplicity.

We have observed that only 8% patients developed wound infection 4% patients developed fecal impaction. There was no case of incontinence, infection around prosthesis and disturbance of micturition. There was no mortality. Novell JR et. al. (1994) has reported 8.5% incidence of postoperative paralytic ileus and 100% improvement in constipation.

As shown 8% patients who developed fecal impaction and constipation after mesh rectopexy was cured after conservative treatment for 2 months during follow up. There were no reports of recurrence. Neither there were any report of incontinence, mesh rejection, disturbance in micturition, impotence. There was no mortality. Donal G. Kim\(^12\) (ASCRS) 2000 reported faecal impaction in 7% cases, which fairly resembles with our study. It was also comparable to G.S. Duthie et. al.\(^11\) (1991). Khanna AK et. al.\(^13\) (1996) & Bakshi G. et. al.\(^14\) (2004) have reported 0% recurrence rate which corroborates well with the excellent results of our series.

**CONCLUSION :**

Following conclusions can be derived after observing the results of this study.

Complete rectal prolapse is a disease of younger age group in this part of the world as compared to western population. Males showed greater incidence of disease than females in contrast to western population. The overall success rate for mesh sacral rectopexy was 97% approximately. The net result of operative management is that operation can be done in short duration with minimum blood loss, shorter hospital stay, lesser morbidity and no mortality and no recurrence.
REFERENCES :


5. Carasco & Gabriel - 1939 - Pralapus due d Rect. Moss on


12. Donal G. Kim. MD, FACS, ASCRS - Core subjects ; Prolapse and Intussusception.


INDUCTION CHEMOTHERAPY FOLLOWED BY RADIATION IN TREATMENT OF LOCOREGIONALLY ADVANCED CARCINOMA OF LARYNX AND HYPOPHARYNX

Pattanayak L, Singh DN, Senapati SN, Samanta DR, Kakkar S
A.H. Regional Cancer Centre, Cuttack

ABSTRACT:

Aim - A prospective study was designed to assess the response and toxicity to neoadjuvant chemotherapy followed by radiotherapy in locoregionally advanced carcinoma larynx and hypopharynx.

Material & Method - 42 patients with histopathologically proven, locoregionally advanced squamous cell carcinoma larynx, hypopharynx (T3, T4), who reported at Department of Radiation Oncology, A.H. Regional Cancer Centre, Cuttack between Jan 2005 to Jul 2006 were enrolled. All eligible patients received three cycles of neoadjuvant chemotherapy (cisplatin plus fluorouracil) followed by radiotherapy. Chemotherapy protocol consisted of cisplatin 30mg/m² and fluorouracil 600mg/m² on days 1 to 3 administered at three weeks intervals. Two weeks after the 3rd cycle, all patients were treated with external beam radiotherapy (shrinking field technique) with conventional fractionation schedule, 66Gy in 33 fractions, 2Gy/fraction. Most of the patients developed G2 and G3 acute toxicity like mucositis, dysphagia and dermatitis which was managed conservatively.

Observation & Results - After completion of all cycles of chemotherapy, 1 patient had complete response, 31(74%) had partial response and 7(16.6%) had no response. 6 weeks after completion of radiotherapy, 23(54.7%) patients showed complete response (CR) and 19(45.2%) had partial response (PR). For all stages & sites combined, the complete response was better in stage III disease (69%) as compared to stage IV (31%). The complete response rate was better for laryngeal primary i.e. 69% as compared to 37.5% in hypopharyngeal primary.

Conclusion - Neoadjuvant chemotherapy followed by radiotherapy has shown favorable results in terms of complete response and locoregional control in advanced carcinoma larynx and hypopharynx with manageable toxicities.

KEY WORDS: Larynx, hypopharynx, head and neck carcinoma, neoadjuvant chemotherapy.

INTRODUCTION:

Head and Neck malignancies are estimated to be the sixth most common cancer worldwide, encompassing a lifetime risk of 2% in men and 0.6% in women¹. In addition to concerns about survival, the side-effects of treatment also affect function and quality of life (QOL).

The past two decades have witnessed a paradigm shift in the treatment of squamous cell carcinoma of head and neck. Data from randomized trials have confirmed that the addition of chemotherapy to curative treatment improves clinical outcomes in patients with advanced disease, demonstrating significant benefit in organ preservation, longer time to disease progression, better locoregional control, fewer distant
metastasis, and longer overall survival times\textsuperscript{2,3,4,5,8}. The combination of a platinum agent and 5-fluorouracil has been used as the standard neoadjuvant treatment and has shown to permit organ preservation in operable patients by inducing tumor reduction before definitive local therapy is performed.\textsuperscript{7,8}

**AIMS & OBJECTIVES:**

1. To evaluate the response of locoregionally advanced head and neck cancer to induction chemotherapy followed by radiation.
2. To assess the toxicity profile of the study group.
3. To compare the results with published literature.

**MATERIAL & METHOD:**

Patients who attended AHRCC, Cuttack and satisfied the eligibility criteria during the study period Jan. 2005 to July, 2006 were enrolled.

**INCLUSION CRITERIA:**

- Histopathologically proven T2, T3, T4 squamous cell carcinoma of larynx and hypopharynx.
- Any nodes without evidence of distant metastasis.
- No prior radiotherapy, chemotherapy or surgery of the neck.
- Age between 20 and 80 years with normal biochemical parameters.
- ECOG performance status scale 0, 1, 2.\textsuperscript{9,10}
- Patient willing to fulfill study requirements signed the informed consent.

**TREATMENT PROTOCOL:**

The study was designed as random. After proper patient selection, neoadjuvant chemotherapy consisting of CDDP 30mg/m\textsuperscript{2} and 5FU 600 mg/m\textsuperscript{2} on days 1 to 3 was administered at 3 weekly intervals for 3 cycles. 2 weeks after the 3\textsuperscript{rd} cycle chemotherapy, external beam radiation therapy (shrinking field technique) with conventional fractionation schedule was delivered to a dose of 66 Gy in 33 fractions.

**RADIATION THERAPY:**

All eligible patients underwent simulation and radiation portals were planned according to site & extent of disease. Conventional fractionated radiotherapy was delivered using megavoltage equipment (Telecobalt unit) at 200c Gy/fraction, 5 fractions per week up to 44 Gy followed by off cord, giving a CTD of 66Gy in 6-7 wks. Patients were evaluated weekly for acute radiation morbidity during radiotherapy using RTOG Toxicity Criteria\textsuperscript{11,12,13}.

**EVALUATION OF RESPONSE:**

Tumour response was first evaluated 12 wks from the end of RT and quantified using UICC Response Criteria\textsuperscript{14}:
- Response was categorized as Complete Response (CR), Partial Response (PR), No Response (NR) or Progressive Disease (PD).

**OBSERVATION AND RESULTS:**

42 patients of locally advanced carcinoma of laryngopharynx who satisfied the eligibility criteria were accrued during the study period Jan 2005 to July 2006 in the Dept. of Radiotherapy, AHRCC, Cuttack. The following observations were made.
TABLE - 1

Patient characteristics

<table>
<thead>
<tr>
<th>AGE</th>
<th>Range</th>
<th>Median Age</th>
<th>30-75yrs</th>
<th>60 yrs</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>32(76%)</td>
<td>10(24%)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SEX</td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SITE</td>
<td>Larynx</td>
<td></td>
<td>26(62%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypopharynx</td>
<td></td>
<td>16(38%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAGE</td>
<td>III</td>
<td></td>
<td>29(69%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td></td>
<td>13(31%)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE - 2

Response rate as per site and stage category

<table>
<thead>
<tr>
<th>Site and Stage</th>
<th>(n)</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>20</td>
<td>14(48.27%)</td>
<td>6(20.68%)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>9</td>
<td>3(10.34%)</td>
<td>6(20.68%)</td>
</tr>
<tr>
<td>Larynx</td>
<td>6</td>
<td>4(30.76%)</td>
<td>2(15.38%)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>7</td>
<td>3(23.07%)</td>
<td>4(30.76%)</td>
</tr>
</tbody>
</table>

TABLE - 3

Acute toxicities during RT

<table>
<thead>
<tr>
<th>Group</th>
<th>Grade – 1</th>
<th>Grade – 2</th>
<th>Grade – 3</th>
<th>Grade – 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>8 (19.04%)</td>
<td>14(33.33%)</td>
<td>18(42.8%)</td>
<td>2(4.7%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>7(16.7%)</td>
<td>13(40.6%)</td>
<td>16(38.09%)</td>
<td>6(14.28%)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4(9.52%)</td>
<td>17(40.47%)</td>
<td>18(42.85%)</td>
<td>3(7.14%)</td>
</tr>
</tbody>
</table>

Majority of the patients (57.1%) presented in the 6th decade and have a median age of 60 years at presentation. 76% patients were males and laryngeal lesions were the commonest site of involvement i.e. 62%. Out of the patients enrolled 69% had stage III and 31% presented with stage IV disease (Table1). The tumor response was first assessed after completion of the last cycle of
chemotherapy and revealed CR in 2.3% of patients while 73.8% patients had PR. On evaluating the response 12 wks after completion of RT, it was inferred that 48.27% patients of stage III carcinoma larynx and 10.34% patients of carcinoma hypopharynx had CR. 30.76% patients of stage IV carcinoma larynx and 23.07% patients of carcinoma hypopharynx had CR. (Table2).

The acute radiation toxicity was scored as per RTOG toxicity criteria for mucositis, dysphagia and skin reactions. Majority of the patients developed G2 and G3 toxicities which was observed during 4th to 5th week of RT. (Table3). 86.13% of the patients developed G2 and G3 mucositis while 78.69% developed G2 and G3 dysphagia. 40.4% patients developed G2 dermatitis and 42.85% patients developed G3 dermatitis, which were managed conservatively. Out of the study group, 36 patients were evaluated for late effects. 20 of them developed subcutaneous fibrosis, 2 patients suffered from airway obstruction and only 1 patient had cartilage necrosis. Most of the patients (78.57%) completed the treatment as per protocol i.e. 50 days. In 14.2% patients treatment was prolonged by 7 days and in the rest it was delayed by 7 to 10 days.

**DISCUSSION**:

The study evaluating the response of induction chemotherapy in locoregionally advanced carcinoma larynx and hypopharynx was undertaken in the Department of Radiation Oncology, AHRCC, Cuttack with patient accrual from January 2005 to July 2006.

The present study has been compared with few landmark studies in head and neck malignancies.

**TABLE - 4**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>n</th>
<th>Median follow-up (yrs)</th>
<th>CR (NACT + RT) %</th>
<th>CR (RT alone) %</th>
<th>OS (NACT) %</th>
<th>OS (RT alone) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALCSG 5</td>
<td>332</td>
<td>33</td>
<td>mths</td>
<td>-</td>
<td>-</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Lefevre et al¹⁵</td>
<td>EORTC H &amp; N Coop. Group</td>
<td>202</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>44 mths (med duration of surv)</td>
<td></td>
</tr>
<tr>
<td>Forastiere A et al¹⁶</td>
<td>RTOG 9111</td>
<td>547</td>
<td>3.8</td>
<td>86.7</td>
<td>85.5</td>
<td>55 (5 yr)</td>
<td>55.56 (5yr)</td>
</tr>
<tr>
<td>Lewin et al¹⁷</td>
<td></td>
<td>461</td>
<td>4.5</td>
<td>48</td>
<td>39</td>
<td>0.3 prob of surv</td>
<td>0.3 prob of surv</td>
</tr>
<tr>
<td>Present Study</td>
<td></td>
<td>42</td>
<td>1</td>
<td>54.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In a large multicentric trial, Lewin et al¹⁷ reported the median age of presentation of carcinoma laryngopharynx to be 62yrs. Spector et al¹⁸ reported the median age of hypopharyngeal tumors from 60 to 65 yrs which correlates with the study literature showing median age at presentation as 60yrs. Lewin et al reported sex ratio of male:female of 2.9:1 in 2001 which correlates with the present series of
3.2:1.62. According to Jemal et al\textsuperscript{18} 9500 persons in the U.S. are diagnosed of carcinoma larynx. In our series 62\% of patients had larynx as the primary site as compared to 38\% incidence of hypopharyngeal malignancy. According to spectors et al\textsuperscript{19} 87\% of patients with pyriform sinus cancer reported in stage III / IV and 82\% of patients with pharyngeal wall cancer presented in stage III disease. Majority (69\%) of the patients in our study population presented with stage III disease. In the multicentric trial by Lewin et al\textsuperscript{17}, 48\% patients had CR and 23\% patients had PR after completion of induction chemotherapy followed by radiotherapy. The present study shows CR in 54.7\% and PR in 45.2\% for all stages and sites combined. As per toxicity, the study revealed that most of the patients developed G2 and G3 acute toxicities like mucositis, dysphagia and dermatitis in 42.8\%, 38.09\% and 42.85\% of the patients respectively. 78.57\% patients received the scheduled radiation dose within the planned overall treatment time i.e. 50 days.

The Veterans Affairs Laryngeal Cancer Study Group\textsuperscript{20} after 2 yrs of follow up reported an overall laryngeal preservation rate of 64\%. Lefebvre et al\textsuperscript{15} reported a 3 year estimate of retaining a functional larynx in 42\% patients. With a median duration of follow up 12 months, 52.4\% patients of carcinoma larynx and hypopharynx are surviving without disease, 23.80\% of patients are the surviving with disease, 7.14\% of patients have developed distant metastasis, 9.5\% patients were lost to follow up and 4.7\% patients of carcinoma larynx and hypopharynx died due to disease.

**CONCLUSION :**

Induction chemotherapy followed by radiotherapy provides better complete response and locoregional control rates in advanced carcinoma larynx and hypopharynx as compared to conventional fractionated radiation. There are no increased acute toxicities with induction chemotherapy followed by radiation as reviewed from the present literature. The preliminary results of this study shows that larynx preservation appears to be feasible in 52.4\% patients with a median duration of follow up of 12 months in patients with locoregionally advanced carcinoma larynx. With small number of patients enrolled and median duration of follow up of 12 months, the study needs more number of patient accrual and prolonged follow up to recommend this protocol as a standard modality of treatment in locoregionally advanced carcinoma of larynx and hypopharynx.

**REFERENCES:**


NEONATAL HEMOCHROMATOSIS – A RARE CASE REPORT
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Deptt. of Pathology
S.C.B. Medical College, Cuttack, Orissa

ABSTRACT:

Neonatal hemochromatosis is a rare and fatal disorder of unknown origin. Till date less than 250 cases have been reported in literature. Two and half months old male boy presenting with jaundice and ascites from birth died at the age of 3 months. Two siblings died with similar illness around 3 months of age. Post mortem liver biopsy showed features of hemochromatosis. We report this case because of its rarity.

Keywords: Mixed Lineage Leukemia, Immunophenotyping

INTRODUCTION:

Neonatal hemochromatosis or neonatal iron storage disorder, is a rare and often fatal disorder which causes either death in utero or acute liver failure in the neonatal period.1 The cause is not known. It has been observed in siblings and has an autosomal recessive mode of inheritance. In medical literature fewer than 250 cases have been reported.2 4

CASE SUMMARY

A male child aged two and half months presented with yellow discoloration of the skin and passage of yellow coloured urine for last one & half months. It was associated with progressive swelling of the abdomen.

Family history – The mother was G3P3A0L0. TORCH panel test indicated all the parameters to be negative except herpes simplex virus. Two siblings died with similar illness within 3 months of birth. No family history of such attacks within the paternal or maternal relatives could be obtained

The child was normal at the time of birth and upto 13 days of life. After 15 days, the child gradually developed anorexia, vomiting. At 1 month, jaundice was evident with yellow coloration of urine. On physical examination, pallor was ++, jaundice ++, hepatosplenomegaly with liver enlarged 6 cms below the costal margin and spleen 3 cms without any lymphadenopathy. Routin investigation showed his Hb% to be 6.4 gm%, total platelet count was 25000 /cmm of blood. Liver function test showed both direct and total serum bilirubin levels to be raised to 4.5 mg/dl and 9.4 mg/dl respectively. The serum levels of SGOT, SGPT were also raised. Ultrasonography revealed hepatosplenomegaly with ascites.

The baby developed convulsion during hospital stay and was on ventilator. He died at the age of 3 months and 5 days. The clinical diagnosis was neonatal hepatitis. Postmortem liver biopsy was done. Histopathological examination revealed complete loss of lobular architecture with fatty change evident in
some hepatocytes. Scattered brownish pigment was seen inside the hepatocytes. (Fig. 1) Kupffer cells were normal in number and morphology without containing any pigment. Focal areas of necrosis could be appreciated around portal triad. The brownish granules stained positively with Perl's stain. (Fig. 2)

![Fig. 1 - Photomicrograph showing enlarged hepatocytes with fatty change & presence of brownish pigment. (H&E stain, 400X)](image)

![Fig. 2 - Photomicrograph confirming the presence of iron pigment (Perl’s stain, 400X)](image)

**DISCUSSION**

Idiopathic hemochromatosis refers to a genetic defect in iron storage that results in increased storage and damage to the heart & liver as well as other organs. A disease of similar name seen in the neonates (neonatal hemochromatosis) bears little resemblance to its adult namesake aside from the accumulation of iron. Neonatal hemochromatosis or neonatal iron storage disease is a rare disorder characterized by severe hepatic insufficiency of intrauterine onset and marked iron deposition in multiple organs including liver. The outcome is always fatal. The present case is a baby of two and half months presenting with features of acute hepatic failure. Since it is a postmortem study and clinically the suspicion of neonatal hemochromatosis was not made, other organs were not sent for histopathological evaluation. It is a hereditary condition and clinical manifestation was also observed in two other siblings of the patient. Even many times the disease is unrecognized unless a sibling was similarly affected. Although neonatal iron storage disease and hereditary hemochromatosis are different diseases, the striking similarity is that iron deposition is found in parenchymal cells rather than in reticulo-endothelial cells. Here, also the iron granules were seen exclusively in hepatocytes and the kupffer cells were uninvolved. Fibrosis develops in the late stage of disease and the serum levels of transaminases decrease. In the said case both the findings were absent probably due to absence of chronicity. Because of the presence of sibling history, fatalness of the disease in the neonatal period, acute hepatic failure and presence of Perl’s stain positive granules inside the hepatocytes, we have finally diagnosed this case as neonatal haemochromatosis or neonatal iron storage disease.

Liver failure due to iron storage disorder may respond to iron chelation (desferroxamine), prostaglandine E, and
antioxidant, but sometimes the results have been disappointing. Liver transplantation, therefore remains the real therapeutic option in the presence of liver failure.

REFERENCES:


HYPERTENSION: PERTINENT TO PRACTITIONERS

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HISTORY OF HYPERTENSION

Stephen Hales, an English clergyman and scientist, first measured blood pressure in mares in 1733. The mercury sphygmomanometer was invented by Riva Roci an Italian physician in 1896 long after the invention of stethoscope by Laennec, a French physician in 1816.

As BP measurement became commonplace it was observed that some people have BP levels distinctly above the average value of general population. Absence of symptoms combined with lack of knowledge about long-term sequel of persistent hypertension led to the belief that probably the high BP was a physiologically appropriate for the individual concern and therefore, regarded as 'essential' (the term is now used to describe primary hypertension).

But sooner the belief gave way to recognition that high BP is associated with disease. Advantages of lowering BP were convincingly reported by several authors in the 1960s. The veterans administrative cooperative study groups, the Framingham study and the Massachusetts study have produced landmark trials regarding benefits of treating hypertension. Treatment of hypertension evolved gradually. Methyldopa and reserpine used in the 1960s through the 1970s gave way to β-blockers and Ca blockers in the 1980s. 1990s saw the use of a plethora of drugs like ACE inhibitors, AT II receptor blockers and newer dihydropyridine Ca channel blockers that made the choice for individual patients not only effective but also acceptable and safe.

How to measure BP

* Measure after the patient sits for about 5 minutes in a quiet room.
* Patient should refrain from smoking, chewing tobacco (paan/guthka) and taking caffeine (cold cures, coffee) at least 30min prior to measurement.
* Measure in either supine or sitting posture. In sitting posture the back should be supported and feet rested on floor.
* Keep the cuff at heart level irrespective of position of the patient.
* Measure in both arms on first visit, BP varies within 10mm of Hg in either arm. Use the arm which records higher BP for subsequent measurements.
* Measure at least twice in 1-2 min interval, repeat measurements if the difference is high.
* Standard bladder (the inflatable rubber bag inside the cotton cuff) is 12-13cm long and 35cm wide. One should have a bigger bladder for obese people and a smaller one for thin people. The smaller one should be used in
children. Width of bladder should be 40% of arm circumference and length should be enough to wrap more than 80% of arm without overlapping. Relatively smaller cuff overestimates and larger cuff underestimates BP.

* Place the cuff in such a manner that the midline of the cuff is aligned to brachial artery. Wrap the cuff closely around the arm which should be bare. Keep the lower edge of the cuff 2 cm above the antecubital fossa. Loose application of cuff causes overestimation of BP.

**Which instrument to use**

Mercury sphygmomanometer is the gold standard for BP measurement and is most accurate. Aneroid manometers should be calibrated with a mercury manometer every six months, otherwise they may be erroneous. Automated digital device are now more frequently used for home measurement, an accurate, validated according to international standard protocols and well maintained device should be used. Home measurements of BP are generally lower than clinic measurement, which should be remembered while considering home measured values of BP.

**Normal level of BP**

For all 18 years old and above the normal BP is less than 120/80 mm of Hg. Old concept of age+100 as normal systolic BP is history now. Note that normal BP is less than the said value. How much less in not defined, it is lower the better. Systolic BP less than 100 mm of Hg when chronically present is sometimes referred to as 'low BP' which is actually normal. Those persons having the so called low BP are actually blessed for longevity. Some non-specific symptoms in these individuals should not be attributed for lower BP.

**Definition of Hypertension**

Hypertension is defined as systolic BP 140 or more and/or diastolic BP of 90 or more. Between 120 to 139 systolic and 80 to 89 diastolic it is known as 'pre hypertension'. The term pre hypertension is introduced to emphasize the importance of lifestyle modification in these individuals as many of them are going to develop hypertension in future. So that development of hypertension can be delayed or prevented in them. Depending on level of BP it is classified as given in table.1.

**TABLE 1**

**Classification of Hypertension.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>(Mild)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>(Moderate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III*</td>
<td>≥ 180</td>
<td>≥ 110</td>
</tr>
<tr>
<td>(Severe)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stage III is omitted in a recent guideline for treatment of hypertension*

Normally BP varies in a wide range between measurements. It has a diurnal variation. BP is highest after getting up from bed in the morning and gradually falls as day passes. It is lowest during sleep. It is physiological for BP to rise during physical activities, emotional outbursts, anger and mental stress. Therefore one should not be diagnosed as hypertensive on basis of a single measurement. Hypertension should be confirmed on the basis of average of several recordings over several days. Confirmation should be done earlier when the risk level is higher.
In some, apprehension in the clinic setting causes BP to shoot up resulting in a record of high BP by the doctor in an otherwise normotensive. Such a condition is known as 'white coat hypertension' or 'isolated clinic hypertension'. Here, 'white coat' refers to a doctor. The diagnosis of white coat hypertension can only be made by 24 hour recordings by a special device known as ambulatory BP monitoring (ABPM). At times in elderly individuals, a stiff brachial artery may require high cuff pressure for its compression during BP measurement, as a consequence high BP is recorded in spite of normal intra-arterial pressure known as 'pseudo-hypertension'. Pseudo-hypertension is suspected when one can palpate the brachial artery after the pulse is obliterated by inflation of arm cuff (positive Osler sign).

**Consequences of hypertension**

Hypertension is asymptomatic. Studies show that symptoms attributed to hypertension like dizziness, headache etc are equally prevalent in non-hypertensives. Longstanding hypertension selectively damages certain organs of the body called 'target organs damage' (TOD). The target organs are:

1. Eyes
2. Heart
3. Kidneys
4. Brain
5. Aorta and peripheral arteries.

Although clinically there are five target organs, hypertension is a systemic disease with involvement of the endothelium in general. The endothelial dysfunction is the basic mechanism manifested as target organ damage.

Hypertensive retinopathy is well known, when advanced, it may lead to blindness. Very high BP may lead to papilledema. When papilledema is present it is referred to as 'malignant hypertension'. In the heart, long standing hypertension produces myocardial hypertrophy leading to abnormal systolic and diastolic function. It promotes coronary arterial plaque formation that leads to different types of coronary arterial disease from stable angina, myocardial infarction to sudden cardiac death. Cerebro-vascular accident (both ischemic and hemorrhagic stroke) is a common sequel to hypertension. Ischemic stroke are usually due to plaque formation in carotid arteries and hemorrhagic strokes are due to arteriolar damage in the brain itself. Hypertensive nephropathy leads to chronic renal failure.

Adequate treatment of hypertension can largely prevent all these complications. 70 percent of stroke and 40 percent of myocardial infarctions can be prevented by treatment of hypertension.

**Orthostatic hypotension**

Normally assumption of upright posture from supine causes a sudden fall of BP due to pull of gravity, but in healthy individuals it is quickly corrected by reflex mechanisms mediated by pressure receptors on blood vessels. These reflexes become abnormal or slow in certain neuropathies, particularly diabetic neuropathy when there occurs postural fall of BP known as orthostatic hypotension. If the systolic BP is less than 20 mm of Hg after 2 min of standing, orthostatic hypotension is diagnosed. It should be a routine to measure standing BP in all diabetics and in those having symptom of postural dizziness. Orthostatic hypotension was a common side effect of drugs that were used previously to reduce BP, but presently used antihypertensive
drugs has largely eliminated this side effect. Alpha adreno-receptor blockers like prazosin more commonly produce orthostatic hypotension than any other drugs.

**Treatment of hypertension**

Steps in the treatment of hypertension are

1. Confirm hypertension
2. Exclude secondary cause
3. Stratify the risk level
4. Implement life style measures
5. Start drug treatment
6. Consider use of statin and aspirin when the risk of cardiovascular disease is high.
7. Achieve target level of BP
8. Follow up for compliance of treatment, maintenance of BP at or below target value and look for development of target organ damage.

If the BP is very high (more than 180/120) treatment should be started immediately, but mild to moderate elevation needs to be confirmed by multiple recordings on multiple occasions. After confirmation of hypertension a few investigations are done on a routine basis to assess for TOD, to exclude secondary cause (seen in only 5 percent of cases) and to know about presence of other coronary risk factors.

History and clinical examination assess presence of other risk factors and give clue to presence of TOD and secondary causes. Presence of renal bruit and brachio-femoral delay suggests renal artery stenosis and coarctation of aorta respectively. Endocrine causes like Cushing's syndrome and thyroid disorders are apparent on clinical examination. Blood sugar, lipid profile, electrolyte estimation (Na+, K+), routine and microscopic examination of urine and an ECG are sufficient enough to see for TOD, risk factors and secondary causes. An abdominal ultrasound, chest X-ray and echocardiography may be done but are optional tests.

After clinical and laboratory assessment the individual patient is risk categorized. When there is TOD, diabetes mellitus, past history of stroke, established coronary artery disease or more than 2 coronary risk factors, he/she is categorized to high risk. When the patient has 2 or less risk factors, no established coronary artery disease, is a non-diabetic and has no TOD then he/she is attributed to low risk category. The purpose of risk stratification is not to consider BP as a barometric value but to reduce risk of cardiovascular disease as a whole.

There are two ways to reduce BP, one is life style changes previously known as non-pharmacological treatment and the other is drug treatment. Drug treatment should always be given along with life style measures. Life style measures are

1. Physical activity, most effective is brisk walking for 30 min a day. Jogging, cycling, swimming are also equally effective.
2. Salt restriction by avoiding table salt and salty food.
3. High dietary fibre and potassium intake in the form of vegetables, fresh fruits and whole grains.
4. Lower intake of saturated and trans fats by avoiding food from animal sources except fish. Animal source
includes milk and other dairy products although they are considered as vegetarian food.

5. Avoidance of tobacco in any form.

6. Limitation of alcohol intake to not more than 21 units in week in males and 14 units in female.

Very effective and safe drugs are available now to reduce BP. The classes of drugs now available are generally referred to A,B,C and D

A. Angiotensin converting enzyme inhibitors (ACEI): Enalapril, Lisinopril, Ramipril and Angiotensin receptor blockers (ARB) Losartan, Telmisartan, Olmesartan, Irbesartan, Valsartan.

B. Beta blockers (BB): Atenolol, Metoprolol, Nebivolol, Bisoprolol, Carvedilol.

C. Ca+ Channel blockers (CCB): Nifedipine, Amlodipine, Felodipine.

D. Diuretics: Hydrochlorothiazide, Indapamide, metolazone.

Alpha blockers like prazosin, sympatholytic drugs like methyldopa, clonidine and vasodilators like hydralazine are also available and are used as add on to above drugs or when multiple drugs are not tolerated or contraindicated.

There is no definite rule to start any particular class of drug in any particular individual. It is the level of BP achieved than the class of drug used which is more important. Any class may be given as first line drug. However, one should look for any compelling indication for any particular drug as for example, ACEI or ARB should be given in diabetic hypertensives as first line, BB is drug of choice in hypertension associated with coronary artery disease. In uncomplicated hypertension, in those who are younger ACEI or ARB should be used as first line and in those who are elder CCB or diuretics may be given as first choice. BB has been used for long in uncomplicated hypertensive. But use of BB is now not generally preferred as a first line drug in elderly individuals. Fixed dose combination of various drugs are available which may also be started if BP is moderate to severe. In some cases 3-4 drugs may also be started initially. If there is no sign of acute target organ damage, one should weight for 3-4 weeks for full effect of the drug before increasing the dose or switching to other class. When one is taking adequate doses of three drugs that includes a diuretic but yet the BP is not at target level, it is known as 'resistant hypertension'. Non-compliance is the commonest cause for resistance; other causes are intake of NSAID, alcohol abuse, supervening secondary cause, excess salt intake and physical inactivity.

Two common but benign side effects encountered are ACEI induced dry cough and CCB induced ankle edema which may require substitution of the offending drug. Combination f BB and thiazide diuretic should be aided because that increases the chance of new onset diabetes. Diuretics should be avoided in those having gout. In hypertension with pregnancy ACEI and ARB are contraindicated and therefore should not be given to young women who are likely to be pregnant. Methyldopa is the drug of choice in pregnancy associated hypertension. CCB may also be used in hypertension with pregnancy.

Lipid lowering drug of statin class (Atorvastatin, simvastatin) and low dose aspirin (75-160mg) should be used unless contraindicated in all high risk patients irrespective of baseline lipid levels.
How much to reduce

Generally the target is to keep BP less than 140/90 in uncomplicated cases. When there is diabetes, target is less than 130/80 and when there is renal insufficiency the target is still lower, if there is proteinuria > 1 g/day the target is less than 125/75.

Lower the BP better is the prognosis. Therefore BP should be reduced as much as possible. The systolic pressure is targeted usually. It is more difficult to reduce systolic pressure than diastolic.

Hypertensive crisis

When BP is more than 180/120, it is severe hypertension. Treatment of severe hypertension is dictated by presence or absence of acute TOD. When there is acute TOD as for example abrupt onset of hemiplegia, acute myocardial infarction, acute pulmonary edema, papilledema, dissection of aorta etc, BP should be lowered immediately to prevent further organ damage which is achieved by parenteral drugs. Such a situation is known as 'Hypertensive Emergency'. When there is acute intracranial complication, BP should not be brought to normal immediately. Chronic hypertension causes shift to right of cerebral auto-regulation curve, by quickly reducing BP to normal may compromise cerebral perfusion that will aggravate the clinical situation. When BP is very high but patient has no acute TOD, they are usually cases of uncontrolled or poorly controlled chronic hypertension. Here BP should be lowered quickly over few days by oral drugs. These cases are known as 'Hypertensive Urgency'.

In both hypertensive emergency and urgency sublingual nifedipine is contraindicated. It may produce a precipitous fall of BP which may be difficult to rise endangering the life of the patient. Safe and effective parenteral drugs are available (table 2) which should be given in hypertensive emergencies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frusemide</td>
<td>20-40mg IV in 1-2 min.</td>
<td>5-15min</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.25-10 µg/kg/min as IV infusion</td>
<td>Immediate</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>5-100 µg/kg/min as IV infusion</td>
<td>2-5min</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.25-5mg IV every 6 hr</td>
<td>15min</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10-20mg IV</td>
<td>10-20min</td>
</tr>
<tr>
<td></td>
<td>10-50mg IM</td>
<td>20-30min</td>
</tr>
<tr>
<td>Esmolol</td>
<td>200-500 µg/kg/min IV for 4min then 50-300µg/kg/min IV.</td>
<td>1-2min</td>
</tr>
</tbody>
</table>

CONCLUSION

Hypertension is a highly prevalent disease with devastating consequences. It is not difficult to diagnose neither to follow up. No sophisticated instrumentation or any specialized skill is required in the majority of patients. Fortunately very safe and effective treatment is available now to prevent these adverse complications. But regrettably most hypertensives are undiagnosed till they develop complications and most of those who are known to have...
hypertension are under-treated. Increased awareness of hypertension amongst the general population, perseverance for lifestyle measures, compliance for treatment and to achieve target BP can prevent hypertension related diseases to keep the population healthy and productive.

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LEARNT FROM OWN MISTAKE

Prafulla Kumar Das
Asst professor, Department of Surgical Oncology,
Acharya Harihar Regional Cancer Center, Cuttack-753007

Forty-two years Hindu Male presented with vomiting, dyspepsia, heartburn for last 3 months. There was no history of yellow discoloration of conjunctiva or urine in the past, and he took occasional alcohol for last 10 years. Clinical examination revealed average built, no pallor, or icterus, or supraclavicular lymphadenopathy. Per abdominal examination revealed neither hepatomegaly nor any mass in any quadrant of the abdomen. The digital rectal examination was normal. The upper gastro intestinal endoscopy detected an ulceroinfiltrative disease in the prepylorus and the adjacent lesser curve of the stomach. The histopathological study of the biopsy material gave a diagnosis of invasive adenocarcinoma of stomach. Hence a diagnosis of carcinoma stomach was made.

An ultrasonology of abdomen and pelvis was done to assess the extent of the disease and opined to have a mass in pylorus with some perigastric nodes enlargement. There was no para aortic adenodepathy or ascites. The PA view of x-ray chest was normal.

His hemoglobin level was 11.2 gm% with PCV 39%. The LFT and the kidney function test was normal. Lower radical partial mastectomy was done and post operative period was uneventful.

On the 3rd postoperative day the hb level was tested and found to be 9.8 gm % with PCV being 34%. The author advised not to give any blood transfusion. But the relative of the patient were very much keen to go for the blood transfusion for the simple reason that they got the rare B negative blood with much difficulty and did not want to go it waste. The pressure from them was so much that the author was bound to agree for it coupled with the logic that it was a borderline level to decide yes or no for such transfusion.

The histopathology revealed a low risk malignancy without any lymph node metastasis. On 9th day the patient was discharged with advice of follow ups every 3 months. The first 3 month follow up was uneventful but in the 2nd 3rd month follow-up the SGPT level LFT was 90 u/ml which was higher than the normal range but the serum alkaline phosphatase was normal. The serum HbsAg was negative but the antibody for the Hepatitis C virus was found positive. This was attributed to blood transfusion 6months ago during postoperative period.

Now retrospectively the author analyzed his own strategy of management regarding postoperative blood transfusion. In the above case, in the 3rd postoperative day when the hb level was 9.8 gm% with PCV level 34%, the author decided not to go for any transfusion knowing very well that blood transfusion could transmit many blood borne diseases from donor to recipient and therefore the benefits & risks should be weighed and a logical and rational approach should prevail over other factors. A through post event research revealed that post operative transfusion could have been avoided in the presence of hb =/> 8gm% and PCV level 25%.

Thereby the author learnt a lesson from his own mistake.
The inauguration and installation ceremony of IMACON-2007 is on 28th December 2007, where the veteran IMA leader of our State Dr. M. Abbas will be sworn as National President of IMA.

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IMA House, North Ambazari Road, Nagpur - 440010 (MS)

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E-mail: imacon 2007@gmail.com
Website: www.imanagpur.com
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(27th - 29th December, 2007)

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E-mail:

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Delegate Fee

Spouse Fee

Total Amount

Registration Fees

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Request for Cancellation:
- Before 31st Nov. 2007 : 25% Deduction
- 31st Nov. 2007 onwards : No Refund request will be entertained.
Refund will take at least 30 working days after the conference is over.

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THE PTI WORKSHOP ON HIV AIDS HAVE BEEN CONDUCTED BY THE FOLLOWING LOCAL BRANCHES UNDER ORISSA STATE BRANCH IMA.

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<th>St. No.</th>
<th>Name of Branch</th>
<th>Date of Workshop</th>
<th>No. of Participants attended</th>
<th>Trainer I</th>
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