JOURNAL
OF THE
DOW UNIVERSITY OF HEALTH SCIENCES
JDUHS

Recognized by PMDC
Indexed in IMEMR, PakMediNet and Global Health

Volume 2, Issue 3
September - December 2008
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Indexed in IMEMR, PakMediNet and Global Health
The JDUHS is published 4 monthly by the Dow University of Health Sciences
Editorial correspondence should be addressed to: The Editor-in-Chief, JDUHS, Dow University of Health Sciences,
Baba-e-Urdu Road Karachi-74200, Pakistan. Tel: 9215754-57 Fax: 9215763
E-mail: jduhs@dugh.edu.pk, Website: www.dugh.edu.pk
Annual subscription rates: In Pakistan: Rs. 450, Bangladesh & India: Rs. 600, UK: £ 15, USA and other countries: US$ 15
Published by: The Registrar, Dow University of Health Sciences (DUHS), Karachi-74200, Pakistan
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EDITORIAL

GENOME-WIDE ASSOCIATION STUDIES IN GENOMIC MEDICINE - ARE WE THERE YET?

M. Ilyas Kamboh

Almost all human diseases have a genetic component, small in some and larger in others. Rare disorders like cystic fibrosis or sickle cell disease are largely determined by single gene mutations with high penetrance. On the other hand, common diseases like coronary heart disease or type 2 diabetes result from a complex interaction of multiple genes and environmental factors where individual genes contribute small but cumulative effects to disease susceptibility. Identification of underlying genes for these diseases is a critical first step towards devising potential therapeutic and preventive measures.

Traditionally, geneticists have used two main approaches to identify genes for complex diseases: family-based linkage studies or case-control association studies. In linkage studies, coinheritance of the disease is traced with chromosomal regions among family members using highly polymorphic genetic markers. In association studies, cases and controls are used to find differences in frequencies of genetic variants between the two groups. Linkage studies have proved to be a bonanza for identifying the genetic basis of a number of rare single gene disorders because of the large contribution of a given gene to a phenotype. However, linkage studies lack the power to detect genes with modest to weak effects, which are responsible for common diseases. Genetic association studies are more powerful than linkage studies to detect modest effect sizes. The added advantage is that a large number of unrelated cases and controls can be collected with relative ease compared to family samples. Moreover, for late-onset diseases, such as Alzheimer’s disease, it is not feasible to collect samples from older family members who have already succumbed to the disease. In the past researchers have tried the ‘candidate gene’ approach (biologically plausible genes or genes located under linkage peaks, called positional candidate genes) where they looked for associations between single nucleotide polymorphisms (SNPs) and various common diseases. This approach has produced, for the most part, dismal results partly because most of the efforts for identifying genes were focused on screening a few SNPs per candidate gene. However, this approach is inadequate as it fails to cover the entire variation in a gene. The recent efforts by the Human Genome Project and the International HapMap Project to provide a dense SNP map of genes have provided the opportunity to thoroughly examine the role of biological or positional candidate genes. However, a mere focus on known candidate genes would not capture the full spectrum of variation responsible for a common disease because of the potential existence of yet to be discovered biological pathways for a given disease. For this reason, a new approach was envisioned where an association study would be carried on hundreds of thousands of SNPs covering the entire genome, giving the concept of genome-wide association studies (GWAS). This approach is hypothesis free and conceptually would identify all known and unknown causative genetic variation underlying a disease.

The new era of gene hunting began in 2005 when a GWAS reported the identification of a new gene for age-related macular degeneration using a chip array consisting of about 100,000 SNPs. Since then, a plethora of GWAS have identified many new genes for several common and complex diseases, especially over the last two years. A ground-breaking large GWAS was reported in 2007 by a consortium of more than 50 British groups, called the Wellcome Trust Case Control Consortium (WTCCC), where they used a panel of 500,000 SNPs to genotype 17,000 subjects for seven common diseases: bipolar disorder, coronary heart disease, Crohn’s disease (the most common form of inflammatory disease), hypertension, rheumatoid arthritis, and type 1 & type 2 diabetes. They used 2,000 cases for each disease and 3,000 shared controls for each disease and identified strong statistical evidence of association with 24 variants. Several GWAS on additional diseases have been reported in 2008, including among others systemic lupus erythematosus, lung
cancer, prostate cancer, colorectal cancer, breast cancer and schizophrenia (http://www.genome.gov/26525384). The published GWAS available at the afore-mentioned site also include studies on continuous traits, such as plasma lipid and glucose levels, body mass index, hair color, skin pigmentation and height.

Thus, the initial GWAS are providing important information about the complex genetic architecture of common diseases as well as continuous traits and revealing potential novel biological pathways for new drug targets. This success is culminated by several factors, notably the availability of dense SNP maps, the use of state-of-the-art hardware and software in manufacturing the SNP chip arrays, the availability of large and well characterized clinical samples for a number of diseases and improved statistical tools for data analyses. Since the ultimate purpose of genetic research is to translate the discoveries from bench to bedside, an obvious question arises about the clinical implications of new discoveries discerned by GWAS. Could this information be used in ‘personalized genomic medicine’ in order to lower the disease risk through therapeutic or preventive measures or tailor the drug therapy based on particular genetic background (pharmacogenomic) or used as a diagnostic tool? Although some genome companies like deCODEme, 23andMe, Knome and Navigenics have already started offering some of the new genetic tests directly to the public, most researchers feel that it is premature, at least now, to use this information because much more needs to be learned about how these genetic variants cause disease and how they interact with each other and environmental factors to modify disease risk. Furthermore, the variants identified thus far may not be functional and, more importantly, they account for only a fraction of the total variation responsible for a given disease because the currently used SNP panels have used far less coverage of the human genome compared to the HapMap-based estimates. It has been suggested that less common variants (frequency <5%) will have a larger effect on the disease outcome as compared to the identified common variants having modest effects (odds ratios ranging from 1.2 to 1.5). Since the commercially available genotyping arrays do not carry less common or rare variants, a concerted effort is needed to identify these variants by deep sequencing. The recently announced 1000 Genomes Project is precisely aimed towards achieving this goal where 1000 individuals will be sequenced as part of an international collaborative effort to produce a comprehensive catalog of human genetic variants occurring at a frequency of 1% or higher. The new DNA sequencing technologies are being built to reduce the cost and time of sequencing such that the initial sequencing cost of about US$1 million over a few months for an individual genome would be cut down to US$1,000 over a few hours, in the not too distant future. This is evident from two recent individual genome sequences that were completed for a cost of US$ 250,000 and US$ 500,000, respectively, but would cost less than half if done today. When a more complete picture emerges about the causative common and rare functional variants it will not only increase their predictive power of the disease outcome, but will also help to understand the disease mechanisms underlying the associations.

Finally, in order to translate the GWAS discoveries into clinical practice it would also be necessary to carry out large scale, prospective, population-based cohort studies in order to evaluate the predictive and diagnostic values of new genetic variants and how they interact with environmental factors to modulate the disease risk. Manipulation of the modifiable environment of genetically susceptible individuals for common diseases offers the best opportunity to intervene for prevention of disease process.

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ORIGINAL ARTICLE

EFFECTS OF α-TOCOPHEROL ON LIPID PROFILE IN PRIMARY HYPERLIPIDEMIA

Muhammad Farooq Alam Siddiqui,1 Fauzia Imtiaz,2 Rukhsana Rubeen,2 Mahayrkh Asif,1 Zeba Haq,2 Musarrat Nafees.3

ABSTRACT

Objective: To determine the antihyperlipidemic effects of α-tocopherol in primary hyperlipidemia.
Design: An analytical cohort study
Patients and Methods: This study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute of Jinnah Postgraduate Medical Center, Karachi, from February to April 2001. Newly diagnosed and un-treated primary hyperlipidemic persons of either gender between the ages 17 to 70 years were initially enrolled in the study for a 12 weeks (90 day) trial with fortnightly follow up visits. The selected patients were divided into 2 groups. The first group (Group-I) was treated with diet restriction and exercise only. The second group (Group-II) was treated with diet restriction, exercise and α-tocopherol. Results were compared using paired t-test.
Results: There were 35 patients in all. After treatment with α-tocopherol, cholesterol reduction was highly significant (p<0.01). Triglyceride reduction was significant (p<0.05). Increase in HDL-c level was highly significant (p<0.001). The LDL-c reduction was statistically highly significant (p<0.001). VLDL reduction was also significant (p<0.01).
When compared between the Groups I and II, the reduction in cholesterol was moderately significant (p<0.01), LDL-c reduction was found to be markedly significant (p<0.01). HDL and VLDL reduction was also found to be significant (p<0.05). In comparison there was no significant change in triglyceride level.
Conclusion: Diet restriction and exercise had significant beneficial effects on lipid profile. When supplemented with α-tocopherol, there was a highly significant beneficial effect on lipid profile.
Keywords: Lipid Profile, α-Tocopherol, exercise, diet

INTRODUCTION

It was in 1913 that Antischkoff (cited by Boyd, 1980), first succeeded in producing lesion in the rabbit aorta, which resembled those in humans by means of a cholesterol rich diet.1
Hyperlipidemia is the major cause of coronary heart disease (CHD) and atherosclerosis.2 3 More than 650,000 people die every year of coronary heart disease in the United States alone. In 1984 the link between serum cholesterol level and risk of CHD was demonstrated for the first time. A 1% drop in serum cholesterol reduces the risk for CHD by 2%.4
There exist many demographic and socio cultural differences between countries but one factor that relates most closely to CHD is the median cholesterol of middle-aged population. In a country such as Japan, where the average serum cholesterol level is low, other coronary risk factors do not seem to operate and hence CHD is relatively uncommon even in cigarette smokers and persons with Diabetes mellitus and hypertension.5
A major lipid soluble free radical scavenger α-tocopherol
is transported in low-density lipoprotein and decreases the oxidation of LDL. The biological membrane has poly-unsaturated fatty acids (PUFA) as a part of membrane phospholipids. Vitamin E is distributed in lipid phase of membrane contributing to the structure and stability of the membranes. Living cells have been vulnerable to be attacked by spontaneously formed free radicals either formed endogenously or exogenously, chemicals, toxins, radiation etc. The α-tocopherol as an anti-oxidant, breaks the free radical chain reaction. Transportation of α-tocopherol, in circulation, is in chylomicrons (CMs). In blood, the α-tocopherol in CMs rapidly equilibrates with other plasma lipoproteins and the bulk is formed in the low density lipoproteins. Subsequently, it becomes associated with plasma B-lipoprotein.

Low-density lipoprotein (LDL) is a contributory factor for oxidation of atherogenesis. The oxidized LDL is taken up by the LDL macrophages affecting the vascular endothelial lining and producing vasoconstriction. Pharmacological doses of vitamin E appear to protect LDL from oxidation. Serum high-density lipoproteins (HDL) cholesterol is also increased via vitamin E supplementation. Supplemental doses of vitamin E above the usual intake afford protection from various chemical toxicants. These include metals, such as silver, mercury, lead, selenium as well as hepatotoxic compounds such as carbon tetrachloride, Benzene, Cresol and several drugs.

Though the antioxidant role of α-tocopherol is well established, there is sparse published data available regarding the lipid lowering effects of α-tocopherol. The objective of this study was to determine the antihyperlipidemic effects of α-tocopherol in primary hyperlipidemia.

**PATIENTS AND METHODS**

This study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Science Institute (BMSI), Jinnah Postgraduate Medical Center (JPMC), Karachi from February to April 2001. Thirty five patients with primary hyperlipidaemia were enrolled in this study. Patients selected were newly diagnosed untreated primary hyperlipidemic of either gender between 17 to 70 years. Those with normal lipid profile were selected for control group. After explaining the complete project, consent was obtained from all participants before they were enrolled in the study. The study period consisted of 3 months with fortnightly follow up visits. The required information such as name, age, gender, occupation, address, previous medication, date of follow up visit laboratory investigation etc. of each patient were recorded on a performa especially designed for this study.

The selected patients were divided into 2 groups. Group-I (n=15) had fifteen primary hyperlipidemic patients according to the criteria mentioned above. They were advised an isocaloric weight maintaining diet (as percent calories) consisting of carbohydrates 50-60%, proteins 10-20%, total fats less than 30% and cholesterol less than 300 mg/day. Diet was adjusted according to body weight and physical activity. This weight maintaining dietary programme was followed throughout the study period. This group was also advised exercise of 15-30 minutes daily (brisk walking). In group-II (n=20), hyperlipidemic patients with same criteria were given α-tocopherol acetate 400 mg once daily, alongwith diet control and exercise of same duration for 12 weeks.

Initially a detailed medical history and physical examination of all patients were carried out. All the baseline assessments took place on the day of inclusion (day 0) in the study and a similar assessment was done on day 45 and day 90 of research design. After the baseline measurement (day 0), patients were given α-tocopherol acetate as per schedule of the groups for 12 weeks. During this period patients were treated with individualized weight maintaining diets with caloric content adjusted to the patient’s age, body weight and physical activity under supervision of a dietician. All patients were fully inquired about compliance and side effects of the treatment at each fortnightly visit.

Blood samples were drawn from each patient on the morning of day0, day45 and day 90, after an overnight fast of 12-14 hours.

All the laboratory tests were done in the National Institute of Cardiovascular Diseases and the reference values used were: (cholesterol < 200 mg/dl, triglyceride < 159 mg/dl, HDL > 40 mg/dl, LDL< 120 mg/dl). Serum total cholesterol, serum triglycerides and serum HDL-cholesterol were estimated by the enzymatic method, using Kit provided by Eli Tech Diagnostic, France. LDL-cholesterol was calculated according to formula given by Beamount et al. VLDL-cholesterol was calculated according to the formula, proposed by Wilson (cited by Delong et al.).
RESULTS

The observations of all the treatment groups were recorded on day 0, day 45 and day 90 on various parameters. The mean serum total cholesterol level of group I patients reduced gradually from 211.9 ± 3.7 mg/dl on day 0 to 199.9 ± 3.0 mg/dl on day 90. This reduction was not statistically significant when compared with day0 and day45 or day 45 and day 90, but was significant when evaluated between day 0 and day 90 (p<0.05). The average percentage changes being 5.6%. In group II patients, mean serum total cholesterol level decreased from 247.3 ± 6.4 mg/dl to 210.5 ± 8.0 mg/dl, on day-0 to 183.8 ± 8.1 mg/dl on day 90. The reduction was statistically moderately significant, when it was compared between day0 and day 45 (p<0.01) and day 45 and day90 (p<0.05), but highly significant (p<0.001) when comparison was done between day 0 and day 90. The reduction was found to be 26.1% for this group as depicted in Table-1.

The mean serum total triglycerides level of group I patients was reduced from 141.6 ± 7.1 mg/dl on day 0 to 138.3 ± 5.9 mg/dl on day 45 and 136.1 ± 5.7 mg/dl on day 90, however, the reduction when evaluated was not significant statistically. The average percentage change between day 0 and day 90 was 3%. (group II patients) for 90 days, the serum triglycerides gradually reduced from 167.3 ± 7.1 mg/dl on day 0 to 150.5 ± 5.7 mg/dl on day 45 and 141.3 ± 6.0 mg/dl day 90. This reduction, when compared were not significant statistically as results of day 0 with day 45 and day 45 with day 90 were compared, but were significant (p<0.05) when comparison was done between day 0 and day 90. The average percentage change being 14.3% between day 0 with day 90 as depicted in Table-1. Mean serum HDL-cholesterol level in 15 primary hyperlipidaemic patients kept only on diet restriction and exercise (Group-I) only increased gradually from 36.7 ± 2.5 mg/dl on day 0 to 41.4 ± 1.9 mg/dl on day 45 and then 45.1 ± 1.6 mg/dl on day 90. This increase in HDL-c when evaluated statistically was found to be non-significant when results of day 0 with day 45 with day 45 and day 90 were compared, but were moderately significant (p<0.01) when HDL levels between day 0 and day 90 were compared. The average percentile increased was 19.5% between day0 and day 90. In 20 patients with primary hyperlipidaemia receiving α-tocopherol (Group-II) for 90 days, the mean HDL increased from 36.0 ± 2.1 mg/dl on day 0 to 41.5 ± 1.5 mg/dl on day 45 and then 46.5 ± 5.5 mg/dl on day 90. This increase was statistically significant (p<0.05), when compared with day 0 and day 45 with day 90 it was highly significant (p<0.001) and day 45 when comparison was made between HDL-c levels of day 0 and day90. The average increase was 32.8% after 90 days as shown in Table-1.

Mean serum LDL-c level in 15 primary hyperlipidaemic patients kept only on diet restriction and exercise (Group-I) reduced from 146.9 ± 4.7 mg/dl on day 0 to 137.9 ± 4.0 mg/dl on day 45 and 127.5 ± 3.9 mg/dl on day 90. This reduction was not statistically significant when compared between day 0 and day 45 or day 45 and day 90, However there was moderately significant (p<0.01) decrease when compared between day 0 and day 90. The decrease was 31.1% after 90 days. In 20 patients treated with α-tocopherol (Group-II) for 90 days, the mean serum LDL-c level decreased from 177.3 ± 6.8 mg/dl on day0, to 138.6 ± 7.9 mg/dl on day 45 and 109.1 ± 7.8 mg/dl on day 90. This reduction in serum LDL-c was significant (p<0.05) between day 45 to day 90, but statistically highly significant (p<0.001) between day 0 to day 45 and day 0 to day90. A 39.0% decrease as noted after 90 days as

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<th>Day 0 Mean ± standard error</th>
<th>Day 45 Mean ± standard error</th>
<th>Day 90 Mean ± standard error</th>
<th>P value day-0 vs. day-45</th>
<th>Percentage Change from days 0 to day 90</th>
<th>P Value</th>
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<tr>
<td>Serum cholesterol (mg / dl)</td>
<td>Group I (n = 15)</td>
<td>211.9±3.7</td>
<td>206.9±3.1</td>
<td>199.9±3.0</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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<td>Group II (n = 20)</td>
<td>247.3±6.4</td>
<td>210.5±8.0</td>
<td>183.8±8.1</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>26.1%</td>
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<tr>
<td>Triglycerides (mg / dl)</td>
<td>Group I</td>
<td>141.6±7.1</td>
<td>138.3±5.9</td>
<td>136.1±5.7</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>167.3±7.1</td>
<td>150.5±5.7</td>
<td>141.3±6.0</td>
<td>&lt;0.05</td>
<td>14.3%</td>
<td></td>
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<tr>
<td>HDL (mg / dl)</td>
<td>Group I</td>
<td>36.7±2.5</td>
<td>41.4±1.9</td>
<td>45.1±1.6</td>
<td>&lt;0.01</td>
<td>19.5%</td>
<td>&lt;0.05</td>
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<tr>
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<td>Group II</td>
<td>36.0±2.1</td>
<td>41.5±1.5</td>
<td>46.5±5.5</td>
<td>&lt;0.05</td>
<td>32.8%</td>
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<tr>
<td>LDL (mg / dl)</td>
<td>Group I</td>
<td>146.9±4.7</td>
<td>137.9±4.0</td>
<td>127.1±3.9</td>
<td>&lt;0.01</td>
<td>13.1%</td>
<td>&lt;0.01</td>
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<td>Group II</td>
<td>177.3±6.8</td>
<td>138.6±7.9</td>
<td>109.1±7.8</td>
<td>&lt;0.001</td>
<td>39.0%</td>
<td></td>
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<tr>
<td>VLDL (mg / dl)</td>
<td>Group I</td>
<td>28.3±1.4</td>
<td>27.7±1.2</td>
<td>27.2±1.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>33.5±1.4</td>
<td>30.1±1.2</td>
<td>28.0±1.2</td>
<td>&lt;0.05</td>
<td>15.3%</td>
<td>&lt;0.05</td>
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Figure in parentheses indicates number of patients. All observations were measured in mg/dl. NS = non- significant.
shown in Table-1.

Mean serum VLDL-c level of (Group-I patients) only decreased from 28.3 ± 1.4 mg/dl on day 0 to 27.7 ± 1.2 mg/dl on day 45 and 27.2 ± 1.2 mg/dl on day 90; however this reduction when evaluated was found statistically non-significant. A decrease of 3.3% was noted after 90 days. In Group-II patients, the mean serum VLDL-c level decreased from 33.5 ± 1.4 mg/dl on day 0, 30.1 ± 1.2 mg/dl on day 45 and 28.0 ± 1.2 mg/dl on day 90. The reduction was significant (p<0.05) when level of day 0 was compared with day 45 and moderately significant (p<0.01) when mean serum VLDL-c levels were compared to between day 0 and day 90, whereas no significant reduction was found between levels of day 90 and day 45. The average decrease was 15.3% as compared day 0 with day 90 as shown in Table-1.

The percentage reduction of cholesterol, LDL & VLDL was statistically significant between the two groups (p<0.5). The Percentage increase of HDL was also significant (p<0.05) between the two groups (Table - I)

DISCUSSION

Diet has a strong impact on the level of cholesterol and triglycerides. There is a less incidence of coronary heart disease and thrombosis in people who take (or consume) large quantities of long chain polyunsaturated fatty acids. These acids are uncommon in normal diets, which typically contain mostly saturated and monounsaturated fatty acids. Since more than 20 years ago, polyunsaturated fat has been found to have a hypocholesterolemic effect when substituted for saturated fat in the diet.16

Patients on diet and exercise regime (Group-I), have reduction of serum triglycerides, VLDL serum cholesterol and LDL. It is evident by a report of NCEP expert panel, that exercise may lower the LDL –cholesterol level.17 HDL-cholesterol increase was demonstrated by Wood et al.18 In that study long distance runners have much higher HDL-cholesterol concentration than sedentary subjects. The rise in HDL concentration induced by physical training may be a consequence of enhanced catabolism of triglycerides rich lipoproteins.19

The present results did not correlate with the results of Levy et al.20 He kept 12 young normal volunteers (aged 18 to 22 years) on both the average American diet and on type II therapeutic diet, which contained cholesterol less than 200 mg/day and a poly unsaturated to saturated fat ratio of 2.5. There was an average drop of 25% in total cholesterol, most of which was in LDL fraction. In the present study the serum cholesterol in 15 patients reduced to 5.6%, which is less than that reported by Levy et al.20 The greater reduction in serum cholesterol is probably because Levy included normal and younger patients where as in the present study the inclusion criteria for patients was primary hyperlipidaemia. The second reason is that Levy used type II therapeutic diet while in this trial type I therapeutic diet was used.

Group II having 20 patients supplemented with vitamin E 400-mg/ day, showed highly significant fall in cholesterol levels. This fall in total cholesterol level is probably due to the fact that vitamin E is transported in lipoproteins mainly LDL. Vitamin E also enhances the clearance of cholesterol through liver and hence affects the total cholesterol level. The contributing factors influencing cholesterol level are diet restriction and exercise. The probable mechanism for LDL cholesterol reduction is again incorporation of vitamin E with LDL –c during its transport. Increased amount of vitamin E in LDL from other lipoproteins may lead to enhanced clearance of LDL.13 Diet and exercise are other contributing factors in lowering the LDL levels. The increase in HDL-c is probably due to decrease in triglycerides levels. Hypertriglyceridermia is one of the factors decreasing the HDL-c.17 In the present study triglyceride is also decreased, which may have a positive effect on HDL-c. Other contributing factors are diet restriction and exercise. The present results are compatible with the result of Herman et al.21 He found that HDL level is increased with the supplementation of vitamin E. According to him the increase in HDL fraction occurred due to redistribution of cholesterol Herman et al. also stated decrease in the total triglyceride levels after ingestion of large doses of vitamin E (600 IU/ day for 3 days).21

The mechanism for decreased triglyceride level as stated by Traber et al. relates with absorption of vitamin E from the intestine in chylomicrons while entering in circulation.22 This incorporation of vitamin E with chylomicrons might result in increased hydrolysis of triglycerides by lipoprotein lipases leading to a less amount of triglycerides in chylomicron remnants, which is delivered to liver.22 The other possibility regarding vitamin E action is that it may interfere in the synthesis of endogenous triglyceride in liver and the other contributing factors are diet restriction and exercise.22

Herman et al. in their clinical observation also found that there is decrease in VLDL after vitamin E supplementation.21 The present findings relate with the result of herman et al. as VLDL levels were decreased,
although Herman et al. did not mention the mechanism. However in another study the possible mechanism as stated by Traber et al is that VLDLs are the only lipoprotein involved in vitamin E secretion from liver, which is also distributed to other lipoproteins. Diet restriction and exercise are also influencing factors.

This study also relates with the study of Prasad and Kalra, who studied the effects of vitamin E on serum cholesterol in rabbits. They observed an increase in the HDL cholesterol and HDL: LDL ratio besides a decrease in the LDL cholesterol and triglycerides.

In another double blind clinical trials 35 diabetics were supplemented with vitamin E capsule, 100 IU/ day orally or placebo for 3 months. Their result showed that vitamin E supplementation significantly lowers lipoproteins and lipid levels in diabetic patients. The study also favours the present study. The present results do not relate with finding of Kesaniemi and Grundy. According to them vitamin E does not decrease plasma total cholesterol, VLDL and LDL-c or triglycerides concentration neither increase HDL-c level. They started the trial with vitamin E 400 mg/day and ended with 800 mg/day, which is a double dose used than the presently used dose, but they did not put patients on diet restriction and exercise, which may be an additional beneficial factor in the present study.

CONCLUSION

Diet restriction and exercise have beneficial significant effect on lipid profile; α-tocopherol have a pronounced beneficial effect on lipid profile.

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ORIGINAL ARTICLE

PRACTICE OF INFORMED CONSENT FOR THE TREATMENT OF TUBERCULOSIS

Sultana Habibullah, Salahuddin Afsar1, Tehzeeb Anwar2

ABSTRACT

Objective: To find out the practice of informed consent obtained and opinion for seeking it, from patients enrolled under direct observation treatment short course for the treatment of tuberculosis in three public sector chest clinics of Karachi and recommendations accordingly.

Study design: A cross-sectional hospital based survey.

Methodology: This survey was conducted on 138 patients selected by systematic random sampling method from Lyari, Nazimabad and Malir chest clinics of Karachi. Independent variables of this study were age, gender, educational level, socio-economic status, place of residence and habits of the patients enrolled in direct observation treatment short course. Dependent variables of this study were information about the diagnosis of the disease, drug’s dose, duration, intake method, its side effects and voluntary consent/approval for enrolling in the treatment regime prescribed by the health care provider. Inclusion criteria of this study were confirmed diagnosed case of tuberculosis according to criteria set by the said clinic, in the initial intensive phase of the treatment. Exclusion criteria were patients of tuberculosis given treatment on trial basis or patients in the continuation phase of treatment.

Results: It was found that 100% patients had no knowledge of informed consent. Patients were informed only verbally about their diagnosis, drugs required to treat their illness, its dose, duration, intake method and side effects by the health staff. Thirty percent patients were unable to recall which part of their body was affected by the disease; 90% remembered the duration of therapy without understanding the difference of initial intensive or continuation phase of the treatment, 57% were taking drugs in the presence of a responsible person; 48% recalled the reason for direct observation of drug intake and 72% were found to be in favor of seeking consent before enrolling themselves in direct observation treatment short course.

Conclusion: In this study it was found that the practice of obtaining informed consent was below the standard level of international and ethical acceptability in the studied public sector chest clinics of Karachi.

Keywords: Informed consent, Direct Observation Treatment Short Course, ethics.

INTRODUCTION

Informed consent is a process by which a patient authorizes health care provider for medical care after discussing its pros and cons.1 In the past it was not necessary to obtain permission for medical care, at present in order to respect patient’s autonomy it has become essential requirement to obtain permission prior to treatment.2 Informed consent comprises of two components-information and consent.

Information refers to the disclosure of the diagnosis, treatment options, its benefits and risks which has to be explained to the patient, consent refers to voluntarily decision of the patient to proceed with the medical care.3 Tuberculosis is one of the diseases included in top 10 global mortality causes and Pakistan ranks 6th among 22 high burden countries.4,5 Despite the availability of National Tuberculosis Control Programme, major problem in controlling this disease is non-adherence to treatment regime resulting in drug resistant strains.6 In order to tackle this problem of non-adherence, WHO launched Direct Observation Treatment Short Course (DOTS) for the treatment of Tuberculosis in 1994. It has five core
components, one of which is direct observation of drug intake of patient by health staff/family member or any other responsible person.\textsuperscript{7} DOTS implementation has caused ethical dilemma throughout the world as individual autonomy and privacy is curtailed when asked to take drug in the presence of another individual. It has also raised question of un-acceptable intrusion in the privacy and liberty of individual.\textsuperscript{8}

Informed consent is ethically, morally and legally mandatory. Law has given right to the patient to draw voluntarily decision for his/her own health care. This study will help to create awareness among individuals about their legal rights and autonomy for drawing independent decision for their own health care besides the responsibilities of health care providers to disclose pertinent medical information to the patient and respect for their decision of autonomy. In order to argue the practice of informed consent in DOTS. This study was conducted with the objectives to find out the practice of informed consent obtained, opinion for seeking it from patients enrolled under DOTS in three public sector chest clinics of Karachi.

**PATIENTS AND METHODS**

This was a cross-sectional hospital based survey conducted in three public sector chest clinics i.e. Lyari, Nazimabad and Malir, of Karachi, from November 2007 to May 2008. Keeping the anticipated population proportion of 10% and 95% confidence level with absolute precision of 5 percentage points. A total of 138 samples were collected.\textsuperscript{9} Systematic random sampling procedure was adopted for the selection of samples and every 3\textsuperscript{rd} patient (as decided by the ethical review committee of DUHS) attending the said clinic were selected for the study. Inclusion criteria for this study were diagnosed cases of tuberculosis according to criteria set by the said clinic and in the initial intensive phase of treatment. Exclusion criteria were tuberculous patients given treatment on trial basis or patients in the continuation phase of the treatment. Independent variables of this study were age, gender, educational level, socio-economic status, place of residence and habits of patients enrolled under direct observation treatment short course.

Dependent variables were elements of informed consent i.e. information about the diagnosis of the disease, treatment required, drugs, its dose, duration of therapy, method of intake, its side effects and voluntary consent i.e. approval/option from the patient for enrolling them in the treatment method prescribed by the health staff. A questionnaire was designed for the collection of data. Principal investigator interviewed the respondents which took 10-15 minutes per performa.

The study was approved by Ethical Review Committee of Dow University of Health Sciences, Karachi no. 02-PMRC/ERB-30 DUHS/ October 2007. Verbal consents were taken from the respondents. Data was analyzed on SPSS version 10; chi-square was used as a test of significance at 0.05 alpha level to find out the association of the variables studied.

**RESULTS**

A total of 138 patients fulfilling the inclusion and exclusion criteria were selected from Lyari, Nazimabad and Malir chest clinics of Karachi. Twenty-one incomplete performa (due to language problem) were discarded and remaining 117 complete performa were analyzed.

There were 58% female and 42% males; 64% were less than 30 years of age; 51% were illiterate; 45% were housewives and 69% were not addicted to anything. In this study 88% patients were diagnosed for the first time and 12% were re-treatment cases due to default, relapse or recurrence. All 100% had not heard about informed consent, but all patients recalled that they were informed by health staff, about their diagnosis, drugs required, dose, its side effects and methods of intake verbally. Thirty percent were not able to recall the part of their body affected by the disease, 90% remembered the duration of treatment without understanding the difference of initial intensive or continuation phase of the treatment, 57% patients were taking drugs in the presence of a responsible person, 48% recalled the reason as to why the drugs should be taken in the presence of a responsible person and 50% patients knew the side effects of anti-tuberculous drugs (Table1). Nearly all patients were unaware, that there was another modus operandi i.e. conventional/domiciliary method for the treatment of tuberculosis. When patients were inquired about their consent for enrolling them in DOTS, it was found that none had been asked for it. On the other hand it was also found that all patients diagnosed positive for tuberculosis in these clinics had to take the anti-tuberculous drugs as prescribed by the health staff. Seventy two percent patients were found to be in favor of obtaining consent before they were enrolled in DOTS. Age was the only variable found to be statistically significant for direct observation of drug intake (p = 0.006)
and duration of the therapy (p = 0.04).

**DISCUSSION**

Successful relationship between physician and patient depends on trust and to maintain trust, patient’s autonomy should be respected by obtaining consent for treatment which is essential for good clinical practice. The purpose of informed consent is to encourage patient’s awareness of risks and complications associated with the treatment and to obtain consent to encounter those risks.\(^{10}\) In this study 100% patients had no knowledge of informed consent. It was obtained neither verbally nor in writing. Some information about the diagnosis, drugs, its dose, intake methods and side effects were given verbally. This finding was consistent with the study conducted to determine the practice of informed consent in 16 public and 10 private radiological centers consulted by patients for advanced radiological procedure where some information was provided by the radiologist which was below the standard to international and ethical acceptability.\(^{11}\) According to law, health care provider should disclose all pertinent information including risks and benefits of alternative treatment/procedure, required by the patient. It is also essential for the patient to decide for his/her own health care and health care provider should respect his/her decision and autonomy, but the patients in the afore-mentioned study were satisfied with the given information to some extent.\(^{11}\) Similarly a study conducted on 200 post operative patients in a public sector hospital to determine the practice of informed consent found that in 8% of the cases surgeons were themselves involved in obtaining consent, 45% were told about the nature and purpose of surgery, 45% knew the possible complications of surgery and 20% were allowed to ask questions.\(^{12}\) This was due to the large number of the patients on operation list and less time available to the health care providers in public sector hospitals. Even then most of the patients were satisfied with the information provided.\(^{12}\) In the present study, 51% patients were illiterate and they had no knowledge of their rights. This was due to cultural factors also, health care providers were allowed to do what is good for the patient. This was one of the reasons as to why practice of informed consent was a neglected procedure. Similarly review showed that informed consent was taken only as a causal formality both by the doctors and by the patients, due to local cultural factor and social customs, this practice needs to be rectified.\(^{13}\) In the present study, it was also noted that patients were satisfied, despite incomplete information being provided to them. This was due to lack of knowledge and lack of importance of their autonomy. The practice of informed consent in our country have many practical problems including inefficient health care system, low literacy rate, poor concept of individual rights and higher social status of the health care provider, all of which needs consideration.\(^{14}\)

When bioethics were started in late 1950s, in western countries, concept of autonomy was largely developed for non-infectious diseases which cannot be applied to infectious disease like tuberculosis where patients act both as a victim and a vector.\(^{15}\) One central reason of WHO to treatment for implementing DOTS was non-adherence of patients due to 8-9 months treatment besides other reasons like poverty, illiteracy and lack of health care. Another question raised was that TB patients once informed of the condition and its infectiousness, will still be persistantly non-adherent to the treatment or not? This dilemma can be solved by discussion among various school of thoughts for consensus. Those having Utilitarian approach would advocate patient’s attitude of non-adherence to treatment as unethical due to potentially harmful effect on the society. Therefore the State should enforce treatment disregarding the consent of the patient. On the other side of the spectrum are pure Libertarians who intend to protect the privacy and autonomy of the individual and thus disregard DOTS.\(^{16}\) In case of tuberculosis where patient acts both as a victim and a vector, due to its mode of transmission, implementing DOTS was violation of individual rights on one hand but on the other hand not implementing DOTS was violation of the rights of others. Therefore, in infectious disease like tuberculosis individual rights could be justifiably over-ridden for example by not obtaining consent for DOTS in order to protect the interest of larger community to protect others from multi-drug resistant strains. Therefore in tuberculosis, Utilitarian approach can be followed after calculating risk benefit ratio. It is the duty of the State to protect others by promoting good practices for the larger community.\(^{17}\)

Childress and Faden had also proposed an ethical framework which consists of five considerations which can be used for considering ethical dimension of public health.\(^{18}\)

These considerations include effectiveness, proportionality,
necessity, least infringement and public justification.\textsuperscript{18} The logic of WHO behind DOTS was supported by data reflecting decrease relapse and resistance rate after its implementation as seen in results.\textsuperscript{19} However, studies conducted in WHO regions on DOTS strategy, including Pakistan, had not found its superiority over self administered method.\textsuperscript{20}

This was a cross-sectional hospital-based study and had many limitations. Firstly, the study was conducted in only three public sector chest clinics and the practicability of informed consent obtained from patients enrolled in DOTS at private clinics was not reflected in this study. Cross-sectional studies are useful for formulation of hypothesis which has to be confirmed in analytical studies. Alpha test was applied with respect to internal validity of the study which revealed 80% reliability meaning that this study is internally valid. Internal validity is tested by alpha test which is a reliability test. It is applied to find out if independent and dependent variables are connected or not for drawing causal inference.

**RECOMMENDATIONS**

The information of the disease and treatment procedures should be provided to all patients enrolled under DOTS/domiciliary/conventional in chest clinics for the treatment of tuberculosis and it should also be documented to protect health care staff from repercussion of nontreatment of patients including their own family members. Options should be sought from patients for DOTS presenting with TB for the first time and compulsory DOTS should only be implemented in patients who are defaulted because principle of autonomy in this disease due to its transmission method and non-adherence to treatment regime demands Utilitarian approach by the State in order to diminish the threat of multi-drug resistant strains in the interest of the community. Based on the option of patients to agree for DOTS or for conventional/domicillary therapy, effectiveness of DOTS strategy could be studied in our settings.

**CONCLUSION**

In the studied public sector chest clinics of Karachi, it was found that in spite of available guidelines, the practice of informed consent was below the standard level of international and ethical acceptability.

**ACKNOWLEDGEMENT**

Authors are grateful to the Director, Ojha Institute of Chest Disease and incharge Chest Clinics, Karachi for their co-operation in the collection of data for this research study.

**Table 1: Practice of informed consent for treatment of Tuberculosis**

<table>
<thead>
<tr>
<th>Independent and dependent variables</th>
<th>N = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent Variables</strong></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49(41.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>68(58.1%)</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
</tr>
<tr>
<td>10 – 29 years</td>
<td>75(64.1%)</td>
</tr>
<tr>
<td>30 - 60 + years</td>
<td>42(35.9%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>60(51.3%)</td>
</tr>
<tr>
<td>Primary</td>
<td>17(14.5%)</td>
</tr>
<tr>
<td>Secondary &amp; Higher</td>
<td>40(34.2%)</td>
</tr>
<tr>
<td><strong>Dependent Variables</strong></td>
<td></td>
</tr>
<tr>
<td>Know the part of body involved by disease</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>82(70.1%)</td>
</tr>
<tr>
<td>No</td>
<td>35(29.9%)</td>
</tr>
<tr>
<td>Know the duration of therapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>105(89.7%)</td>
</tr>
<tr>
<td>No</td>
<td>12(10.2%)</td>
</tr>
<tr>
<td>Know the reason of direct observation of drug in take</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56(47.9%)</td>
</tr>
<tr>
<td>No</td>
<td>61(52.1%)</td>
</tr>
<tr>
<td>Know the side effect of drug</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58(49.6%)</td>
</tr>
<tr>
<td>No</td>
<td>59(50.4%)</td>
</tr>
<tr>
<td>Treatment with direct observation (DOTS)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67(57.26%)</td>
</tr>
<tr>
<td>No</td>
<td>50(42.74%)</td>
</tr>
</tbody>
</table>

**REFERENCES**


LIPID PROFILE AND SERUM INSULIN LEVELS IN GESTATIONAL DIABETES

Rubina Aziz¹, Tabassum Mahboob²

ABSTRACT

Objectives: To evaluate the glucose intolerance, insulin, and lipid profile in women who developed gestational Diabetes, compared to healthy pregnancy.

Design: Observational study

Patients and Methods: One hundred pregnant women, 50 healthy as control group and 50 already diagnosed gestational diabetic women as study group were selected. Plasma fasting (FBS) and post prandial glucose (RBS), serum insulin and serum lipid profile (total lipids, cholesterol, triglycerides, HDL-cholesterol and LDL- cholesterol) of both were monitored. Mean values were compared using t-test.

Results: Mean FBS [124.76±4.22 vs. 90.06±1.20 mg/dl], mean RBS [221.38±6.68 vs. 120.32±1.97 mg/dl], insulin [32.10±0.83 vs. 17.88±0.54 μIU/ml], mean cholesterol [216.60±5.87 vs. 166.38±3.19 mg/dl], mean triglycerides [189.36±6.76 vs. 106.28±2.85 mg/dl], LDL-cholesterol [131.08±4.73 vs. 102.48±2.18 mg/dl] and total lipids [825.24±16.92 vs. 653.96±15.40 mg/dl] were higher in GDM groups as compared to normal controls (p<0.01). Mean HDL-cholesterol [41.24±0.65 vs. 48.34±0.66 mg/dl] showed significantly lower concentration in GDM group as compared to controls (p<0.01).

Conclusion: Mean insulin and lipid levels, except HDL-cholesterol, were significantly higher in gestational diabetes compared to controls.

Keywords: Gestational diabetes, hyperlipidemia, insulin resistance, hypertriglyceridemia, high density lipoproteins, low density lipoproteins.

INTRODUCTION

Gestational Diabetes is defined as glucose intolerance that is first diagnosed during pregnancy.¹ The incidence of Gestational Diabetes Mellitus (GDM) has doubled over the last 6–8 years. GDM carries long-term implications for the subsequent development of type 2 diabetes in the mother and increased risk of obesity and glucose intolerance in the offspring.² Normal pregnancy has been characterized as a "diabetogenic state" because of the progressive increase in post prandial glucose and insulin response in late gestation.³,⁴ Gestational diabetes is a complication of pregnancy associated with an increase in maternal and perinatal morbidity.⁴ Women with gestational Diabetes mellitus are at an increased risk of the development of diabetes (usually type 2) after pregnancy.⁵ The underlying pathophysiology of gestational diabetes is a function of decreased maternal insulin sensitivity or increased insulin resistance. Insulin resistance is defined as the inability of a defined concentration of insulin to affect a predictable biological response of nutrient metabolism at the level of the target tissue. Significant alterations in glucose metabolism

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Received: January 21, 2008; accepted: November 27, 2008


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occur in women who develop gestational diabetes relative to pregnant woman with normal glucose tolerance. Decreased insulin response to a glucose challenge was also demonstrated in women with gestational diabetes in late gestation. Pregnancy and diabetes have an additive effect on the development of an atherogenic lipid profile. Importantly, this is exaggerated earlier in pregnancy in gestational diabetes. The hallmarks of insulin resistance syndrome are glucose intolerance; hyperinsulinemia, a characteristic dyslipidemia, obesity, (in particular with central fat distribution) and hypertension.

In the view of above findings the present study was designed to evaluate the status of blood glucose and insulin levels and lipid profile in women who had developed gestational Diabetes compared to those who did not.

**PATIENTS AND METHODS**

This study was carried out on a total of 100 pregnant women (50 normal pregnant women and 50 gestational diabetic women) of same age in third trimester of pregnancy, selected from Obstetrics and Gynaecology wards and outpatients departments of Holy Family Hospital, Civil Hospital, Jinnah Post Graduate Medical Center and Godhra Muslim Medical Center, Karachi from December 2004 to February 2005.

Inclusion criteria for Group I (control group) were normal pregnant women without family history of Diabetes or other endocrine disorders, or history of taking any hypoglycemic or hyperglycemic medicines.

Group II (gestational diabetic) included diabetic women, where the diagnosis was made using the criteria after performing a fasting 3-h, 100-g oral glucose tolerance test (OGTT) with a screening test (50-g oral glucose challenge) showing a 1-h glucose value <140 mg/dl (7.8 mmol/l).

All pregnancies with hypertension, metabolic disorder or fetal abnormalities were excluded from the study.

Fasting plasma glucose, serum insulin and lipid profile (total cholesterol, triglycerides, HDL- cholesterol, LDL- cholesterol and total lipids) samples were obtained in fasting state. Post prandial glucose samples were taken 2 hours after of breakfast. Plasma glucose (mg/dl) were determined after enzymatic oxidation in the presence of glucose oxidase. The hydrogen peroxide formed reacts, under catalysis of peroxidase, with phenol and 4- aminophenazone to form a red-violet quinoneimine dye as indicator. Serum insulin (μIU/ml) were measured by an enzyme immununometric assay on the Immulite analyzer. Serum total cholesterol (mg/dl) was determined after enzymatic hydrolysis and oxidation. Indicator quinoneimine was formed from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase11 by standard kit methods.

Serum triglycerides (mg/dl) were determined after enzymatic hydrolysis with lipases. The indicator was a quinoneimine formed from hydrogen peroxide, (4-aminophenazone and 4-chlorophenol under the catalytic influence of peroxidase) by standard kit methods. Chylomicrons, very low density lipoproteins and high density lipoproteins were precipitated by addition of phosphotungstic acid and magnesium ions to the sample. The cholesterol content of the supernatant was determined enzymatically) by standard kit methods. LDL was precipitated by addition polyvinyl sulphate to the sample and the concentration was calculated from the difference between the serum total cholesterol and the cholesterol in the supernatant after centrifugation, by standard kit methods. Total lipids in mg/dl were estimated by standard kit method. Body Mass Index (BMI) was calculated by dividing body weight (kg) by the square of height (meters). Verbally informed consent was obtained from all women.

The Data was analyzed using SPSS (Ver.15) soft wear. The descriptive statistics was shown as mean ± SEM. The independt two-samples “t” test was employed to compare the two groups. The P—Value less then 0.01 was assumed as asignificant difference.

**RESULTS**

Clinical and laboratory parameters are given in Tables- 1 and 2 respectively.

Mean age [23.66±0.35 vs. 23.62±0.41 years], mean gravid status [2.00±0.15 vs. 2.22±0.18], mean gestational
ages [31.42±0.14 vs. 31.98±0.21 weekly] and mean BMI [27.92±0.47 vs. 27.62±0.25] of the gestational diabetic group and control group were not significantly different as shown in table 1.

The mean plasma fasting glucose [124.76±4.22 vs. 90.06±1.20 mg/dl] and mean postprandial glucose [221.38±6.68 vs. 120.32±1.97 mg/dl] concentration in GDM group were significantly higher than normal pregnant women (p<0.01). Mean serum insulin [32.10±0.83 vs. 17.88±0.54 μU/ml] concentration in GDM group was significantly higher as compared to normal controls as shown in table 2 (p<0.01).

Mean serum cholesterol [216.60±5.87 vs. 166.38±3.19 mg/dl], mean serum triglycerides [189.36±6.76 vs. 106.28±2.85 mg/dl], mean LDL-cholesterol [131.08±4.73 vs. 102.48±2.18 mg/dl] and mean total lipid [825.24±16.92 vs. 653.96±15.40 mg/dl] concentrations were also higher in GDM groups as compared to normal pregnant controls. While mean HDL-cholesterol showed significantly lower concentration in GDM patients as compared to normal [41.24±0.65 vs. 48.34±0.66 mg/dl] as shown in table 2.

Table 1: Clinical characteristics of the control and gestational diabetic groups (GDM).

<table>
<thead>
<tr>
<th>S #</th>
<th>Parameters</th>
<th>Control (n=50)</th>
<th>GDM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age (years)</td>
<td>23.62±0.41</td>
<td>23.66±0.35</td>
</tr>
<tr>
<td>2</td>
<td>Gravida</td>
<td>2.22±0.18</td>
<td>2.00±0.15</td>
</tr>
<tr>
<td>3</td>
<td>Gestational age (weeks)</td>
<td>31.98±0.21</td>
<td>31.42±0.14</td>
</tr>
<tr>
<td>4</td>
<td>BMI</td>
<td>27.62±0.25</td>
<td>27.92±0.47</td>
</tr>
</tbody>
</table>

Table 2: Plasma glucose, serum insulin and lipid profile of normal and gestational diabetic groups.

<table>
<thead>
<tr>
<th>S #</th>
<th>Investigations</th>
<th>Normal controls (n=50)</th>
<th>GDM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FBS (mg/dl)</td>
<td>90.06±1.20</td>
<td>124.76±4.22*</td>
</tr>
<tr>
<td>2</td>
<td>RBS (mg/dl)</td>
<td>120.32±1.97</td>
<td>221.38±6.68*</td>
</tr>
<tr>
<td>3</td>
<td>Serum insulin (μU/ml)</td>
<td>17.88±0.54</td>
<td>32.10±0.83*</td>
</tr>
<tr>
<td>4</td>
<td>Serum cholesterol (mg/dl)</td>
<td>166.38±3.19</td>
<td>216.60±5.87*</td>
</tr>
<tr>
<td>5</td>
<td>Serum triglycerides (mg/dl)</td>
<td>106.28±2.85</td>
<td>189.36±6.76*</td>
</tr>
<tr>
<td>6</td>
<td>HDL-cholesterol (mg/dl)</td>
<td>48.34±0.66</td>
<td>41.24±0.65*</td>
</tr>
<tr>
<td>7</td>
<td>LDL-cholesterol (mg/dl)</td>
<td>102.48±2.18</td>
<td>131.08±4.73*</td>
</tr>
<tr>
<td>8</td>
<td>Total lipids (mg/dl)</td>
<td>653.96±15.40</td>
<td>825.24±16.92*</td>
</tr>
</tbody>
</table>

* P<0.01 as compared to control denoting significance.

DISCUSSION

This study showed that fasting and postprandial glucose, serum insulin, serum cholesterol, serum triglycerides, LDL-cholesterol and serum total lipid concentrations were higher in women who developed gestational Diabetes as compared to the normal pregnant women. Normal pregnancy has been characterized as a "diabetogenic state" because of the progressive increase in postprandial glucose and insulin response in late gestation. There is higher glucose production and lower glucose clearance after an overnight fast as compared to normal pregnant women as shown in this study and also supported by Xiang et al. These two factors (high glucose production and low clearance) contribute to elevation of fasting glucose levels in Gestational Diabetes Mellitus. Gestational diabetes does not occur due to defective secretion of insulin as supported by Seely and Solomon.

In the present study higher insulin levels (table 2) were found compatible with other studies by Catalano et al, Setji et al, Butte, and Toescu et al. The pathophysiology of gestational diabetes is a functional decrease of maternal insulin sensitivity or increased insulin resistance. Insulin resistance is defined as the inability of a defined concentration of insulin to affect a predictable biological response of nutrient metabolism at the level of the target tissue. Various hormones like cortisol, prolactin , progesterone and human placental lactogen rise with the advancement of pregnancy, so the insulin resistance occurs and becomes worse and maximum in IIIrd trimester of pregnancy. Since insulin resistance is related to defect in pancreatic beta cells functions mothers at this time with beta cell functional deficiency become glucose intolerant.

We also found that levels of serum total cholesterol and LDL-cholesterol were also higher, as noted in some other studies. While in some studies cholesterol concentrations did not differ significantly between gestational diabetic and control mothers. Lipid metabolism changes during pregnancy and lipolysis is increased as a result of insulin resistance. VLDL remains in the plasma for longer period because of a decrease in the activity of lipoprotein lipase, and leads to accumulation of LDL. The LDL particles in plasma vary in size due to variable amount of cholesterol, Contained in them. Pregnancy and Diabetes have additive effect on the development of atherogenic lipid profile. Importantly,
Lipid profile and serum insulin levels in gestational diabetes

this is exaggerated earlier in pregnancy in gestational diabetes. Therefore higher concentrations of total and LDL-cholesterol is found in gestational diabetic patients.

In this study, it was also found that with increasing insulin resistance serum triglycerides also increased while HDL-cholesterol decreased as shown in table 2. This is also supported by some others studies. Insulin-regulated carbohydrate, lipid and protein metabolisms are affected to a variable degree. Lipid metabolism changes during pregnancy, the anabolic phase of early pregnancy encourages lipogenesis and fat storage in preparation for the rapid fetal growth in late pregnancy. Lipolysis is increased as a result of insulin resistance, leading to increased triglycerol concentration. The ability of insulin to suppress free fatty acids with advancing gestation were found in Gestational Diabetes Mellitus, hence insulin resistance is responsible for the hypertriglyceridemia in Gestational Diabetes Mellitus.

CONCLUSION

In the view of the above findings, it is concluded that there is a positive relationship between insulin resistance and hyperlipidemia in pregnancies complicated by Gestational Diabetes. Mainly the insulin resistance is responsible for the accumulation of cholesterol and triglycerides in serum, which in turn elevates LDL-cholesterol and decreases HDL cholesterol.

REFERENCES


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**Errata**

Due to inadvertent composing error, there was a discrepancy in title of an article in issue 2 of volume 2 as stated in the index and the main contents. The title should be read as “Relationship of central corneal thickness with measured intraocular pressure” by Mashhooduzafar and Ziauddin A. Shaikh.
ORIGINIAL ARTICLE

HELICAL CT SCAN IN EVALUATION OF METASTATIC NECK ADENOPATHY

Amber Paras, Bushra Rehan

ABSTRACT

Objective: To determine the diagnostic accuracy of helical computed tomography (CT) in detection of metastatic neck lymphadenopathy with histopathological correlation.

Design: Comparative cross sectional study.

Patients and Methods: This study was conducted in the Departments of Diagnostic Radiology and Pathology, Karachi from August 2005 to June 2006. A group of 51 patients was included in this study. Helical CT scan was carried out after an IV bolus injection of approximately 100 ml. of contrast medium. CT scans were evaluated for metastatic lymphadenopathy i.e. abnormality of nodal size and architecture and irregular nodal enhancement. The radiological findings on the CT scans were compared with the pathological findings.

Results: The study included 51 patients with age ranging from 22 to 77 years. Correct assessment of malignancy was made on CT scan in 48 patients. CT scan was false positive in one and false negative in two patients.

Conclusion: Contrast enhanced Helical CT proved to be accurate for preoperative evaluation and subsequent management of cervical metastatic neck adenopathy.

Keywords: Helical computed tomography (CT). Cervical lymphadenopathy. Malignant

INTRODUCTION

Regional metastasis is one of the most important factors in the prognosis and treatment of patients with head and neck cancers. In addition, because lymphatic metastasis is a frequent event that impacts prognosis, a decision to treat the lymph nodes in the neck has to be made in almost all patients, even if metastases are not apparent, clinically. It is therefore important to assess, as reliably as possible, whether a patient has regional lymph node metastases or not.1

CT scanning is now used routinely for the preoperative evaluation of the neck because, presumably, it helps decreasing the incidence of occult cervical lymphadenopathy.2

Introduced in 1998, multiple spiral CT scanning promises further improvement of temporal and spatial resolution (in the longitudinal axis). This technique permits rapid scanning of large volumes of soft tissue during quiet breathing. The volumetric helical data permits optical multiplanar data and 3-dimensional reconstruction. Improvement of the assessment of tumor spread and lymph node metastases in arbitrary oblique planes is another advantage of spiral technique.2

This study was done to prospectively evaluate the CT scans of patients with suspected metastatic neck lymphadenopathy over a ten month period and compare there findings with those seen on histopathology, which was taken as a gold standard.

References:


PATIENTS AND METHODS

This is a cross sectional comparative study of 51 patients presented in outpatient clinics or admitted with suspected head and neck masses or cervical lymphadenopathy. All patients were referred to the department of radiology for CT scan from August 2005 to June 2006.

Out of the 51 patients 34 were males and 17 were females. The age ranged from 22 to 77 years and mean age was 49±1 years.

CT scanning of the neck for evaluation of subjective symptoms, palpable masses, or known conditions began with a general neck survey examination prior to more detailed and focused protocols.

The patients were imaged supine while breathing quietly. Scanning was started from the base of the skull to the clavicles with contiguous 4- or 5-mm-thick slices. A digital lateral scout radiograph is done in the beginning as it assists in planning. Intravenous contrast was administered with a power injector through a venous catheter. Total volume and injection rates of contrast were tailored to the patient size, venous access, and general medical conditions.

Scanning was performed with a collimation of 5 mm, a pitch 1, 120 KVP, and 200 mA. CT examination was carried out after an IV bolus injection of approximately 100 ml. (1.5 - 2 ml/kg of body weight) of Iopamidol at a rate of 3.0 ml/sec.

An initial delay of 30 to 35 seconds, from the start of the injection to the beginning of scanning, allowed adequate intravascular contrast enhancement. An examination requiring two ranges usually requires infusion of more intravenous contrast.

CT scans were evaluated by radiologists experienced in reporting head and neck studies and each scan was reviewed by two radiologists. The image interpretation was done on the basis of primary diagnostic criteria and supportive features for metastatic neck lymphadenopathy. These criteria are shown in table 1. CT scans were interpreted as positive for metastatic nodes if two or more of diagnostic criteria were present. Pathologic analysis was the reference standard by which imaging was judged. The specimen collected for histopathology was either obtained with excisional biopsy or en bloc dissection with adequate surgical margins and maximum nodal yield.

The total number of nodes, number of benign nodes, number of malignant nodes, number of necrotic malignant nodes, and maximum dimension of the nodes were recorded for each patient. For the purpose of correlating imaging and pathologic findings, nodes were divided into the following regions on each side of the neck: submental, submandibular, parotid, upper internal jugular (above the level of the hyoid), middle internal jugular (between the hyoid and cricoïds), lower internal jugular (below the cricoïds), posterior triangle, and supraclavicular fossa. This allowed the surgical specimen to be correctly oriented to ensure accurate identification of each individual node for correlation of pathologic and radiologic findings. CT results were compared with findings obtained at histopathologic examination. The final diagnosis of metastatic neck lymphadenopathy was confirmed at histopathologic examination.

The true-positive, true-negative, false-positive, and false-negative results were recorded. The causes of false-negative or false-positive result were recorded at the time of correlation of pathologic and radiologic findings. Positive cases, including true positive and false negative and negative cases, including true negative and false positive cases were calculated. Then sensitivity, specificity, positive and negative predictive values (PPV and NPV respectively) and accuracy were calculated.

RESULTS

Correct assessment of malignancy was made in 48 out of 51 patients’ scan (94%). Incorrect assessment was made in 3 scans (6%). Out of 48 scans correctly evaluated 39 were true positive for malignancy and 9 were true negative. Out of the 3 CT scans proven to be incorrectly evaluated, malignancy was falsely interpreted as positive in one patient who had enlarged non necrotic nodes and negative in two patients, who had lymph nodes within upper limits of normal size without appreciable necrosis or rim enhancement.

Size of the lymph node was an important primary diagnostic criterion. Measurements of nodal size were made by means of a comparison with a centimeter scale printed on each image. The nodal size cutoff point was taken 10mm. In 40 patients with positive CT findings for metastatic neck adenopathy, enlarge nodes were found in 33 patients (82.5%). In rest of the 7 patients (17.5%) other two criteria suggestive of metastasis with supportive features were present. In 11 patients with negative CT findings for metastasis six nodes out of 11, had size within normal limits.

Detection of nodal necrosis is the most reliable sign for...
diagnosing metastasis. In 40 patients with positive CT for metastatic neck adenopathy 31 patients (77.5%) had areas of central necrosis >3mm.

The third diagnostic criterion was irregular post contrast enhancement. In 40 patients with a positive CT for metastasis 27 patients (67.5%) had abnormal rim enhancement of nodes on post contrast studies. Apart from these diagnostic criteria, few supportive features for diagnosing metastatic neck adenopathy were also identified and they included presence of primary tumor in head and neck region, abnormal shape of node and lymph node adipose metaplasia.

Out of 40 positive CT scans 28 patients (70%) had concomitant primary neck mass as supportive feature. Out of twenty eight, 27 patients (96.4%) had squamous cell carcinoma of oro and naso pharynx and 1 patient (3.5%) had lymphoma. Out of remaining 12 patients, seven patients had primary tumor in abdomen found on further evaluation.

Out of 40 positive CT scans 27 patients (67.5%) had round shaped lymph nodes instead of normal bean shape. Area of adipose metaplasia larger than 1 mm (minimal diameter) was found in 17 patients (42.5%) out of 40 positive CT scans for metastatic adenopathy.

Metastatic neck lymph adenopathy was correctly excluded prospectively in 9 out of 51 patients (specificity, 90%). The overall accuracy was 94% for diagnosing metastatic neck adenopathy. The positive and negative predictive values were 97% and 81% respectively

**DISCUSSIONS**

The important role of the Computed Tomography in oncologic neck imaging is, first, to provide accurate pretreatment staging of the tumor for planning medical, surgical, and radiation interventions and, second, to monitor response to therapy and provide surveillance after curative treatment.

Cervical nodal metastases have a major influence on the prognosis of patients with head and neck tumors. These metastases influence not only the risk of local recurrence, but also the risk of distant metastases.1,3

Adults with suspected neck mass were included in our study, who were referred by physicians or surgeons. The aim of this study was detection of metastases with the help of CT in malignant nodes and not to compare the different imaging modalities for the detection of malignant nodes.

Pathologic-radiologic correlation of each node provided the mean to compare CT and histopathology. The CT interpretation used by us was based on the diagnostic criteria described in many studies.

There is a large range of overlap in sizes between benign and malignant lymph nodes. Both the minimum and maximum axial diameter was taken to predict tumor positive nodes in our study. 42 patients out of 51 evaluated for nodal metastasis had enlarged lymph nodes.

33 cases out of 42 were positive for metastasis. In our study sensitivity, specificity and accuracy of CT for accurate measurement of lymph node was 100%. We also found that by increasing the minimal axial diameter by 1mm for lymph nodes in the subdiagnostic region, optimal value for sensitivity, specificity and accuracy can be obtained.

In a study done by Micheal et al. they took the minimum axial diameter criteria for diagnosing metastatic lymphadenopathy. The most useful minimal axial diameter in their study was between 10 and 12 mm.4 Necrosis was chosen because it is frequently found in nodal metastases from carcinomas of the head and neck and because the identification of necrosis with imaging is a reliable sign of a metastatic node.5-7

In our study, CT accurately diagnosed necrosis in 33 cases while it was unable to diagnose in 2 cases, in one false negative case the patient was 47 years old male patient, known case of CA larynx, the size of the lymph node was within upper limit of normal and there was no obvious necrosis.

Another patient who was a 53 years old lady, also had lymph nodes within upper limit of normal in sub mental and sub mandibular regions on histopathology, and it turned out to be malignant with small necrotic area of about 3mm.

The sensitivity, specificity, and accuracy of CT for detection of necrosis were calculated from the total group of benign and malignant nodes.

In our study the sensitivity, specificity, and accuracy for detecting nodal necrosis is about 93%, 100%, and 82% respectively.

In the king et al.5 study, necrosis in metastatic nodes was used as the main criteria and they also compared different imaging techniques like CT, MRI and Ultrasound. In their studies the results of each modality were compared for sensitivity, specificity and accuracy. In their study CT
analysis for detection of necrosis in 89 malignant nodes showed accuracy, sensitivity and specificity of 92%, 91% and 93% respectively.

In another study by Micheal et al. the sensitivity of the criterion of tumor necrosis, cystic tumor growth or tumor keratinization in area larger than 3mm was 32% per node with a specificity of 100%. Contrast-enhanced CT is considered to be the best modality for identification of necrosis. A sensitivity of 74% and a specificity of 94% have been reported for areas of necrosis larger than 3 mm.4

In our study irregular contrast enhancement in the nodes, caused by tumor necrosis, cystic tumor growth or (avascular) keratinization was used as a predictor of malignancy.

27 patients out of 40, with positive CT for metastasis 27 patients had abnormal rim enhancement.

In the Micheal et al. study, irregular contrast enhancement was the most specific criterion with a specificity of 100% In our study 6 patients out of 9, who were true negative for metastasis had enlarged, necrotic nodes with thick rim of enhancement, unlike metastasis where there is irregular enhancement. Out of 6 nodes 4 had calcification. Histopathology revealed chronic granulomatous disease –tuberculosis.

The presence of a conglomerate nodal mass on CT scan with central lucency and thick rim of enhancement and minimally effaced facial planes has been reported to be suggestive of tuberculous adenitis, especially if the patient has a strongly reactive tuberculous skin test.9-11 The enhanced walls of these multichambered masses are thicker than those usually defined as rim enhancement of necrotic nodes secondary to metastatic carcinomatous disease.12 Calcification of lymph nodes is also considered to be highly suggestive of tuberculous adenitis.13

Out of 40 patients with positive CT scan 28 (70%) had concomitant primary neck mass. Out of 28 patients, 27 patients (96.4%) had squamous cell carcinoma of oro and naso pharynx while only one patient (3.5%) had lymphoma.

In the remaining 12 patients, 7 had primary tumor in abdomen, on further evaluation.

If the primary site itself is not visible the pattern of adenopathy may suggest primary location. Knowledge of the lymphatic drainage of the head and neck proves valuable in such instances.14,15 (Table 2)

Out of 40 patients with positive CT scan 27 (67.5%) had rounded shape of lymph nodes instead of normal bean shape.

Non metastatic nodes were characteristically shown on CT images as discrete and kidney-shaped, with soft-tissue structures in the hilum composed of fat tissue concaving into the central portion of the node.16

Area of adipose metaplasia larger than 1mm was found in 17 patients (42.5%) out of 40 with positive CT scans for metastatic adenopathy.

### Table 1: Diagnostic criteria for metastatic neck adenopathy

<table>
<thead>
<tr>
<th>Primary Criteria</th>
<th>Supporting Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Abnormal size of the node</td>
<td>1) Presence of primary tumor in head and neck region</td>
</tr>
<tr>
<td>2) Abnormality of internal architecture, including necrosis.</td>
<td>2) Abnormal shape</td>
</tr>
<tr>
<td>3) Irregular enhancement after contrast.</td>
<td>3) Lymph node adipose metaplasia</td>
</tr>
</tbody>
</table>

### Table 2: Probable source of nodal metastasis

<table>
<thead>
<tr>
<th>Level</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Oral cavity, submandibular gland.</td>
</tr>
<tr>
<td>Level 2</td>
<td>Nasal pharynx, oral pharynx, parotid, supraglottic larynx.</td>
</tr>
<tr>
<td>Level 3</td>
<td>Oral pharynx, hypopharynx, supraglottic larynx.</td>
</tr>
<tr>
<td>Level 4</td>
<td>Subglottic larynx, hypopharynx, esophagus, thyroid.</td>
</tr>
<tr>
<td>Level 5</td>
<td>Nasal pharynx, oral pharynx.</td>
</tr>
<tr>
<td>Level 6 &amp; 7</td>
<td>Thyroid, larynx, lung.</td>
</tr>
</tbody>
</table>

**Note:** Bilateral nodes are common with cancers of soft palet, tongue, epiglottis, and nasal pharynx.

### CONCLUSION

The study shows that contrast enhance helical CT can be used to evaluate metastatic neck adenopathy using the following radiological criteria:

1. Nodes with minimal axial diameter of more than 10 mm should be considered metastatic.
2. All nodes that show irregular enhancement on CT and are surrounded by a rim of enhanced tumor or lymph node tissue should be considered metastatic.
3. Presence of central necrosis greater than 3 mm should also be considered metastatic can be detected by contrast enhanced helical CT.

Use of this rapid, man-operator dependent and highly accurate examination may decrease delays in appropriate medical or surgical therapy as well as unnecessary delayed observation.
REFERENCES


CASE REPORT

ACUTE MYOCARDIAL INFARCTION WITH LEFT BUNDLE BRANCH BLOCK (LBBB): SIGNIFICANCE OF SGARBOSSA CRITERIA

Ayaz Hussain Shaikh, Bashir Hanif, Faiza Malik, Khursheed Hasan

ABSTRACT
A middle aged female presented in emergency department with chest discomfort. Her old electrocardiogram (EKG) showed left bundle branch block (LBBB) signs. EKG performed in the emergency room revealed left bundle branch block with 4-6 mm discordant ST segment elevation in leads V1-V3 and 1mm concordant ST segment elevation in lead V4. Diagnosis of acute anterior wall STEMI was made based on Sgarbossa criteria. She underwent angiography which showed total occlusion of proximal left anterior descending artery which was stented. She had uneventful post-stenting course in hospital and was discharged. The case highlights the significance of Sgarbossa criteria which can be applied to diagnose acute myocardial infarction in the presence of LBBB so that prompt thrombolytic or primary angioplasty can be performed.

Keywords: Acute myocardial infarction, left bundle branch block, Electrocardiogram, Sgarbossa Criteria.

INTRODUCTION
Left bundle branch block (LBBB) is the result of conduction block in left bundle of conduction system. Presence of LBBB is frequently associated with underlying organic heart disease including hypertension, coronary artery disease and cardiomyopathy. LBBB is associated with poor prognosis and long-term survival in patients with CAD. The Framingham study found that one half of patients with new LBBB died within 10 years.1 Presence of LBBB obscures the typical EKG findings of acute myocardial infarction (AMI) which is an obstacle in the management of patients due to difficulty in making decision regarding reperfusion therapy. Various electrocardiographic criteria had been proposed to diagnose acute myocardial infarction in the presence of LBBB, out of which Sgarbossa criteria is the most sensitive and specific.2 This criteria in not commonly used in clinical practice due to lack of awareness among the emergency physicians. The purpose of reporting this case is to emphasize the importance of applying Sgarbossa criteria to diagnose acute myocardial infarction in the presence of LBBB.

CASE REPORT
A female, 55 years of age, diabetic and hypertensive with family history of coronary artery disease presented in the emergency department with two hours history of retrosternal chest discomfort with radiation to jaws and left shoulder. She had history of vaginal hysterectomy for uterine fibroids two weeks back for which she had cardiac workup including echocardiogram and electrocardiogram that had shown left bundle branch block (LBBB) pattern ( Figure 1). On arrival in emergency department, she was haemodynamically stable, maintaining oxygen saturation at room air. She had no added heart sounds and her lungs were clear. Her electrocardiogram showed left bundle branch block with 4-6 mm discordant ST segment elevation in leads V1-V3 and 1mm concordant ST segment elevation in lead V4 ( Figure 2). Diagnosis of acute anterior wall STEMI was made. She received chewable aspirin, sublingual nitrates, loaded with clopidogrl, intravenous
Acute myocardial infarction with left bundle branch block (LBBB): significance of Sgarbossa criteria

heparin, beta blockers and was started on tirofiban infusion after double bolus with the intention of primary angioplasty. She responded well to initial treatment and her chest discomfort reduced by about 50%.

She underwent primary angioplasty within 120 minutes of her presentation to emergency department. The pre–procedure angiogram showed 100% occlusion in proximal left anterior descending artery. Successful angioplasty and stenting of proximal left anterior descending artery was performed and TIMI III flow was achieved. Her post stenting electrocardiogram showed narrow complex morphology with deep symmetrical T wave inversion in precordial leads with reciprocal changes in inferior leads (Figure 3). She had subsequent uneventful course and was discharged.

DISCUSSION

The evolution of reperfusion therapy in the treatment of acute myocardial infarction (AMI) has highlighted the extraordinary importance of rapid and accurate diagnosis of infarcts due to thrombosis of a major epicardial vessel. The presence of AMI can be established by a wide variety of diagnostic tests, but the narrow temporal window for significant myocardial salvage with reperfusion dictates that the clinical presentation and the 12-lead ECG remain the principal tools available to make the decision about reperfusion therapy.

Classical electrocardiographic changes in transmural infarction include ST segment elevation >1 mm in contiguous leads however development of new left bundle branch block (LBBB) or well described changes in patient with pre-existing LBBB can also establish the diagnosis of transmural myocardial infarction and stratify patients with acute coronary syndrome who can benefit from immediate reperfusion strategies. With LBBB, the course of ventricular activation is altered which secondarily affects ventricular repolarization. The QRS, ST-segment and T wave of the EKG are always affected by LBBB and the early signs of transmural infarction will be obscured by the changes due to the conduction abnormality.

Multiple studies have evaluated the ability to diagnose AMI when LBBB is present. The work of Sgarbossa et al. is instructive in this regard. They developed diagnostic criteria for transmural infarction when LBBB was present using data from the GUSTO-1 Trial (the derivation or training sample) and from a control population with LBBB and stable ischemic heart disease (the validation sample). Three ECG criteria based on ST segment displacement were found to have independent diagnostic value.

<table>
<thead>
<tr>
<th>Table 1: Scores for independent electrocardiographic criteria</th>
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<tr>
<td>CRITERION</td>
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<tr>
<td>ST-segment elevation&gt;1 mm and concordant</td>
</tr>
<tr>
<td>ST-segment depression&gt;1 mm in lead V1, V2, or V3</td>
</tr>
<tr>
<td>or ST-segment elevation&gt;5 mm and discordant with QRS complex</td>
</tr>
</tbody>
</table>

Electrocardiographic score of 3 is used to diagnose acute myocardial infarction and 2 is suspicious for AMI (Table-1). The criteria is highly specific, a total score of 3 or more provide specificity of 96% for diagnosis of acute myocardial infarction in presence of left bundle branch block. A meta analysis of studies on Sgarbossa criteria concluded that interobserver agreement was good-excellent, patients with Sgarbossa score of 3 have a moderate-high positive likelihood ratio (PLR) and likely to have acute myocardial infarction. Sgarbossa score 2 is less specific with less PLR and a score less than 2 does not rule out AMI. In this case Sgarbossa score was 7 providing high specificity for diagnosis of acute myocardial infarction which was confirmed by raised cardiac markers and finding of angiogram. This emphasizes the practical utility of these criteria which can be used to guide management in cases with AMI in the presence of LBBB and high Sgarbossa score.

![Figure 1: Baseline electrocardiogram of the patient.](image)
REFERENCES


CASE REPORT

CONGENITAL SINGLE CORONARY ARTERY: A RARE ANOMALY

Rashid Ahmed, Binish Rasheed, Shahzad Babar Kureshi

ABSTRACT

Congenital coronary artery anomalies (CAAs) affect approximately 1% of general population undergoing coronary angiography. The incidence of single coronary artery is very rare specially in the absence of any structural heart disease and accounts for 0.024% – 0.044% of cases. This case report describes a single coronary artery arising from right aortic cusp which was trifurcating into right coronary artery (RCA), circumflex artery (CX) and left anterior descending artery (LAD). The left anterior descending (LAD) followed a malignant course between main pulmonary artery and aorta making it vulnerable to ischaemia. The advantage of multi detector computed tomographic angiography (MDCTA) lies primarily in its high diagnostic and anatomic accuracy because of its three dimensional (3D) capability and flexible post processing.

Keywords: Coronary artery anomalies (CAAs), Single coronary artery, Multi detector computed tomographic angiography (MDCTA)

INTRODUCTION

Coronary artery anomalies affect approximately 1% of general population undergoing coronary angiography.1 The incidence of single coronary artery is extremely rare and it accounts for 0.024% – 0.044%.2 Majority of coronary artery anomalies are associated with structural congenital heart diseases including mitral prolapse, Tetralogy of Fallot, Rubella syndrome, Hurler’s syndrome etc.3 Transposition of great vessels is particularly associated with single coronary artery.

The conduction is traditionally diagnosed on catheter-based angiography. With recent advances in computed tomography, computed tomography based angiography using multi-detector technology (MDCTA) can provide multidimensional imaging allowing a non-invasions diagnosis.

This case report describes the isolated occurrence of single coronary artery in an adult male.

CASE REPORT

A 47 years old male was referred for CT angiography with recurrent chest pain for last 4 years. Coronary risk factors elicited on history and available laboratory reports included positive family history for angina, hypertension, borderline Diabetes mellitus, and hypercholesterolemia.

On physical examination his blood pressure was 120/80 mmHg. Heart rate was 60 beats/min. He had no previous cardiac evaluation. Rest of the physical examination was normal.

MDCTA was performed with standard protocol which revealed single coronary artery arising from right aortic cusp with trifurcation into right coronary artery (RCA),
left anterior descending artery (LAD), and circumflex artery (CX). The LAD followed a malignant course proximally between aorta and pulmonary artery and distally intramuscular course with only non-significant proximal disease (Figures 1 and 2). The CX, posterolateral ventricular (PLV) and posterior descending (PDA) arteries showed normal course. No other structural cardiac disease was found. The case was referred to cardiologist for symptomatic management and follow up.

![Image](https://example.com/image1)

**Figure 1:** Volume rendered image showing single coronary artery arising from right sinus of Valsalva and trifurcating RCA, LAD and CX.

![Image](https://example.com/image2)

**Figure 2:** MIP image showing malignant proximal course of LAD between aorta and pulmonary artery (PA).

**DISCUSSION**

Majority of CAA s are insignificant hemodynamically and only 20% cause symptoms. The symptoms range from angina, syncope, arrhythmias, myocardial infarct, and sudden death. About 5 – 35% of sudden death in young people are due to CAA s.

Broadly coronary artery anomalies are classified as anomalies of origin, course and termination. Single coronary artery comes under anomalies of origin.

This case stands in R-III B subgroup single coronary artery according to Lipton’s classification modified by Yamanka and Hobbs. This classification is based on the site of origin and anatomical distribution of branches and is grouped as I, II and III. It is designated with “R” or “L” depending on whether the ostium is located in right or left sinus of Valsalva; further described with letter “A”, “B” and “P” for ‘Anterior’, ‘Between’ and ‘Posterior’ pattern with respect to aorta and pulmonary artery.

The prognosis of single coronary artery varies from normal life expectancy to sudden death. The chances of sudden death increases with proximal stenosis of single coronary artery in the absence of collateral or if a major coronary branch follows the malignant interarterial course between aorta and pulmonary artery. As LAD in this case followed this malignant course, it is more prone to ischaemia even in the absence of atherosclerosis. The cause of ischaemia might be compression between grade vessel, kinking of anomalous vessel, myocardial squeezing and vasospasm.

The diagnostic modality used for diagnosis was multi-detector computed tomographic angiography (MDCTA). The advantage of MDCTA among other modalities like magnetic resonance angiography (MRA), transesophageal echo (TEE) and conventional angiography lies primarily in its high diagnostic and anatomic accuracy. The topography of anomalous vessel is clearly displayed in 3D images as opposed to two dimensional conventional angiography. This technique offers excellent spatial resolution with flexible post processing like multiple intensity projection, volume rendering and multiplaner reconstruction.

So MDCTA is an ideal non-invasive method to detect and delineate course of anomalous vessels and thus facilitates cardiac catheterization, later on if such be required.
REFERENCES


SHORT COMMUNICATION

CESAREAN DELIVERY RATES AND INDICATIONS AT A TEACHING HOSPITAL

Shakira Perveen, Subhana Tayyab

ABSTRACT
A descriptive study was conducted to assess the cesarean delivery rates. Indications and fetomaternal outcome at the Department of Gynecology and Obstetrics, Unit 1V, Sindh Govt. Lyari General Hospital, Karachi, from June 2005 to May 2008. Demographic and obstetrical data of the subjects under going cesarean section was collected. During the study period, 506 cesarean sections were performed at the rate of 22.92%, 22.78% and 22.83% in respective years. Unbooked cases were 47.43 %. Primiparous women were 33.5 %. Majority (80.83 %) were between 21-30 years of age. Elective cesarean sections were 16.2% and emergency section were 83.79%. Main indications of cesarean sections in primiparous women were dystocia (35%), malpresentation (17.6%) and fetal distress (16.4%). In multiparous women, main indications were previous cesarean section (53%), malpresentation (12.7 %) and dystocia (12.5 %). Projected maternal mortality ratio was 197.6/100,000 live births and perinatal mortality rate was 69/1000 live births.

Keywords: Cesarean section, Cesarean section rate, primipara, Maternal mortality ratio, Perinatal mortality rate (PNMFR).

INTRODUCTION
A cesarean section rate (CSR) is a summary measure of the rate of CS administered to prevent or treat pregnancy complications in specific, high risk subpopulation (medically justified CS) plus the rate of CS administered to a low risk subpopulation (medically unjustified CS). Over the past 25 years, there has been sustained increase in CSR around the world, with massive public interest and debate on both, the cause and appropriateness of this increase. The CSR has increased in USA from 20.7 % in 1996 to 29.1% in 2004; and in England and Wales from 16% in 1995 to 21.5 % in 2000; the trend is similar in less developed countries.

The trend of increasing CSR may indicate a trend towards a more costly medical delivery system. An alarming high morbidity and mortality associated with operative delivery in developing countries such as Pakistan makes it a matter of concern. It is doubtful that the improvement in perinatal outcome is linked to high cesarean deliveries.

Countries with the lowest perinatal mortality rates in the world have CSR less than 10%. Many factors have contributed to this rise. A deeper knowledge of the causes, risk factors and indications for the first CS is required in order to have direct influence on its frequency and consequently in decreasing or modifying repeat CS prevalence.

The objective of this study was to assess current cesarean section rates, indications and fetomaternal outcome at a teaching hospital.

This descriptive study was carried out in the department...
of Gynecology and Obstetrics, Unit IV, Sindh Govt Lyari General Hospital DUHS from June 2005 to May 2008. All deliveries that took place in the department were retrospectively analyzed through manual medical chart review to record cesarean section rates, indications and fetomaternal outcome. Detailed demographical and obstetrical data, factors influencing CSR like age, parity, booking status were collected on specifically designed performa. Indications of cesarean sections in nulliparous were compared with parous women. Data was analyzed using SPSS 13.0 descriptive statistical package. Comparisons between proportions were carried out using Chi-square test and P-value of <0.05 was considered significant. Indications were classified as emergency for acute maternal or fetal complications and elective when decision of cesarean section was made before onset of labor. Women were labeled unbooked when did not receive any form of antenatal care in our health facility or were referred from other health facilities. Maternal mortality ratio was calculated as the number of maternal deaths per 100,000 live births. Perinatal mortality rate was calculated by number of perinatal deaths per 1000 births. A partogram was maintained during every labor by the registrar. The registrar, senior registrar or consultant, conducted the CS, depending upon the risk factors.

During three-year study period, 2214 cases were delivered. Vaginal deliveries were 1708 (77.1%) and cesarean deliveries were 506, (22.85%). Out of the 506 cases of CS, 202 (22.92%) were conducted in the first year, 172 (22.78%) in the second year and 132 (22.83 %) in the third year of study. The overall CSR remained stable. Emergency CS were 424 (83.8%) and elective CS were 82 (16.2%). Primiparous women were 170 (33.5%) and multiparous were 336 (66.40%). Out of the 240 unbooked cases, 53.6% were primiparous and 46.4% were multiparous.

Majority of primiparous (90.5%) and multiparous (75.9%) both booked and unbooked women, were between 21-30 years of age (Table I). Frequency of emergency CS in multiparous versus primiparous women was 1.7:1. Main indications of CS in primiparous women were dystocia 35%, malpresentation 17.6% and fetal distress 16.4%.

In multiparous women main indications of CS were previous CS in 53 %, malpresentation in 12.7% and dystocia in 12.5%. (Having previous one or more cesarean, the most common indication in multiparous women (178 cases, 53%, p <0.001) and dystocia in nulliparous women 60 cases 35% p <0.001). The projected maternal mortality ratio was 197.6/100,000 live births.

Complications of cesarean hysterectomies were observed in 2 cases (0.4%), acute renal failure in 1 case (0.20%), intraperitoneal hemorrhage in 1 case (0.2%), bladder injury requiring repair in 1 case (0.20%), wound infection in 25 (4.9%), superficial wound dehiscence in 14 (2.7%), urinary tract infection in 22 (4.3%), breast engorgement in 8 (1.5%), and pyrexia in 11 (2.1%) cases. Blood transfusion was required in 21(4.1%) emergency and 8 (1.5%) elective CS cases. Perinatal deaths were 35 giving a perinatal mortality rate of 69.1/1000 births. Stillbirths were 17 (48.57%) and neonatal deaths were 18 (51.4%).

Numerous factors can influence clinician’s decision to perform CS, such as clinician’s training, the use and appropriate interpretation of fetal heart rate monitoring, local culture, the availability of hospital support services, health care delivery system and legal factors in some cases.7

World Health Organization (WHO) has recommended for the past 20 years that CSR should not be higher than 15%. The demographic changes since then, particularly the increasing maternal age, suggest that a target rate of 20% might be more realistic nowadays.8 The rates we report here are higher (22.85%, 22.78%, and 22.83%) and remained stable in each year of study. CSR of this study are comparable with other studies in Pakistan (21.3%) at Quetta.5 Another Gynaecology and Obstetrics department unit of the same hospital found CSR of 22.3%.9 Maternal and all perinatal deaths were seen in emergency cases except one where there were previous two CS and the baby was anencephalic. Perinatal deaths were due to birth asphyxia, prematurity and congenital defects.

The results of this study indicate that primiparity and previous CS are important contributing factors. It is thus suggested that the rate of CS may safely be reduced by reviewing and auditing indications for CS in primiparous women, proper fetal monitoring, and a trial for vaginal birth, even after a previous cesarean section,
as recommended by others, should be given.\textsuperscript{10}

REFERENCES


TECHNIQUE

CATECHOLAMINE ASSAY BY RADIOENZYMATIC METHOD – A PROTOCOL

Nasim Karim¹, Joshua R. Berlin²

ABSTRACT

Catecholamines are a group of compounds identified by the catechol nucleus. The significant catecholamines found naturally in the body are epinephrine, nor-epinephrine and dopamine. They are found in various tissues of the body like brain, adrenals, GIT, blood, urine and cerebrospinal fluid in picogram quantities. Knowledge of catecholamines is important in the diagnosis and management of pheochromocytoma, CNS tumours like neuroblastoma, Diabetes mellitus, hypertension, coronary disease, angina pectoris, myocardial infarction etc. Analytical techniques for determination of catecholamines have been developed which are generally based upon the use of isolated enzyme catechol-O-methyltransferase (COMT) to transfer a radioactive methyl group from S-adenosyl-L-methionine (SAM) to an endogenous catecholamine acceptor molecule to form a radioactive O-methyl catecholamine derivative. This article gives a basic outline of the catecholamine assay along with a simplified protocol that can be easily performed in the laboratory. Keywords: catecholamine; radioenzymatic assay, Catechol-o-methyltransferase (COMT).

INTRODUCTION

Catecholamines are best known as neurotransmitters and hormones which are produced and secreted by the central and autonomic nervous system.¹ Secretion from the adrenal medulla is part of the fight or flight reaction. Thus the perception or even anticipation of danger, fear, excitement, trauma, pain, hypovolemia, hypotension, anoxia, hypothermia, hypoglycemia and intense exercise causes rapid release of epinephrine and norepinephrine. Epinephrine secretion specifically increases in response to mild hypoglycemia, moderate hypoxia and fasting even through sympathetic nervous system activity may remain constant or may decrease.²

Concentration of nor-adrenaline (NA) and adrenaline (A) in plasma are widely used as an index of sympathoneuronal and/or sympatho-adrenomedullary activity.³⁻⁶ Highly sensitive methods are needed in order to determine the very low catecholamine concentrations in small plasma samples. Analytical techniques have been developed with which circulating nor-epinephrine and epinephrine can be measured at the picomole level of sensitivity.⁷⁻⁹ The difficulties met when estimating the minute amounts of catecholamines present in the blood of man and various animal species are reflected by the divergent data found in the literature.¹⁰ Wide variations and factors concerned with techniques crucially affect the reliable measurement of the plasma catecholamine concentrations.¹¹

An early method for measuring catecholamine levels in mammalian systems was spectrofluorometric assay of Von Euler and Floding in 1955 but this assay system was found to be relatively insensitive with poor accuracy.¹² Axelrod and Tomchick (1958) reported catechol – O–methyl transferase enzyme and later referred it to as COMT, an enzyme which transfers a methyl group from a donor molecule to a catechol nucleus thereby forming
a 3–methyl moiety.\textsuperscript{13} Later investigators used radiotracers and other techniques including chromatography but the basis were the same that is the use of COMT – enzyme and tritiated methyl donor, S – adenosyl–methionine to determine the catecholamine levels in the plasma and in the tissue supernatants.

The radioenzymatic assay of catecholamines therefore have an enzymatic aspect covered by COMT- enzyme and radioisotopic aspect being fulfilled by tritium labeled methyl donor S –adenosyl – L – methionine.

THE RADIOENZYMATIC CATECHOLAMINE ASSAY

It brings together an aliquot of the supernatant of the deproteinized tissue homogenate, blood serum or plasma or biological fluid, with the enzyme catehol – O methyltransferase (COMT), the tritium labeled methyl donor S – adenosyl – L – methionine, a cation of oxidation number +2 which allows the methyl transfer to proceed, a compound which stabilizes the enzyme substrate system, and an agent which preferentially removes calcium ions from interference with the enzymatic reaction. It incubates together the components of “1” for a time, temperature and pH sufficient to O– methyleate substantially all of the epinephrine and norepinephrine. It extracts the O – methylated epinephrine and norepinephrine with an organic solvent in which the O – methylated epinephrine and norepinephrine are preferentially soluble. It repartitions the O – methylated epinephrine and norepinephrine into an aqueous solution of sufficient strength to protonate the amine. It oxidizes O – methylated epinephrine and norepinephrine to vanillin. It extracts vanillin from the aqueous solution with an organic solvent in which the vanillin is preferentially soluble, and counts the radiation emitted from the vanillin.

PRE–REQUISITES AND BRIEF DESCRIPTION OF ASSAY

Various mammals in which catecholamines can be assayed using radioenzymatic assay include human, horse, cattle, dog, cat, rat, mouse, rabbit etc. Biological fluids (urine, CSF, lymphatic fluid), blood; any tissue with sympathetic innervation like vascular tissue, liver, adrenal, kidney or brain, can be used in this assay. Depending upon the picogram concentration, a general sample aliquot of the system to be assayed is from 10 to about 50 Pl. Urine and tissue samples are diluted first and then used because of their high catecholamine content. The enzyme COMT is found in a variety of mammals like rat, cow, pig, mouse, cat, rabbit, human etc. Widely dispersed throughout the systems for example, liver, kidney, spleen, brain, intestines etc. The preferred species for isolation of this enzyme is rat and the preferred organ for its isolation is liver. S – adenosyl – L – methionine methyl is the labeled methyl donor employed in the enzymatic O – methylation. It is made by radiochemical methods and is commercially available from New England Nuclear Corporation. The tritium label is at the methyl position. Methyl donor should be present in the incubation mixture having specific activity between 5 – 15 Ci/mmol. For COMT enzymatic system to be active at least one of a number of cations of oxidation number and +2 must be present in the incubate. They are magnesium, cobalt and manganese but magnesium is preferred. It is used as magnesium chloride with a concentration range of 10 – 100 mM. Preferably about 25 – 35 mM should be present in the incubation mixture. Enzyme – substrate system should be stabilized by a compound which should maintain the integrity of the system by preventing oxidation of the catecholamines and assists in the continued activity of the enzyme during the incubation. Such compounds are glutathione (preferably), dithiothreitol, ascorbic acid, sodium metabisulphate etc. Its concentration range in the incubate ranges from 1 to about 10 mM preferably 2 – 4 mM. The incubate should have an agent which preferentially removes calcium ions from interference with the enzymatic conversion such agents are EGTA, sodium-oxalate etc. EGTA is preferred. Concentrations from 5 to about 25 mM of EGTA in the incubation mixture can be used. The enzymatic incubation is carried out in standard laboratory equipment for a time and at a pH and temperature which allows the enzymatic conversion to go to completion. The pH should be kept between 7-10, preferred pH range being 8 – 9. Buffer solutions suitable for the incubation are tris- phosphate etc. The temperature of the incubation should be 35°C to 40°C preferably 37°C. Incubation is allowed to proceed for a period of 15 minutes to 2 hours preferably 60 minutes. The incubation is stopped by lowering or elevating the temperature or the pH can be raised or lowered. It is preferred to stop incubation by lowering of temperature and introduction of higher pH. The stopping solution should contain carrier quantities of metanephrine, normetanephrine and methoxytyramine.
A concentration from 2 – 4 mM can be employed. The O – methylated catecholamines are removed from the incubate by solvent extraction. Any organic solvent which is immiscible with water can be used like butanol, isoamylalcohol, hexanol, toluene etc. Better preferred are certain mixtures of organic solvents specifically a 35 – 75 % volume to volume mixture of toluene:isoamyl alcohol. The organic extract of O – methylated catecholamines is repartitioned into an aqueous acid of sufficient strength to protonate the amine function of the catecholamines. Formic, acetic, hydrochloric and sulphuric acids can be used for this purpose. Because aqueous phase is denser than the organic phase, separation of the two phases is facilitated by freezing the aqueous phase. Freezing shortens the assay time and allows for a cleaner, more precise separation of the organic phase from the aqueous phase. The aqueous acid extract is preferentially dried down under reduced pressure and taken up in basic solution. The metanephrine and normetanephrines are oxidized to vanillin. The oxidation of the beta-hydroxyl-O–methylated catecholamines is accompanied by contacting them with an oxidizing agent as sodium metaperiodate at a pH 7 – 12, at a temperature 0– 50°C for a period of 2 – 30 minutes. The time of the reaction is preferably 2–10 minutes. The metanephrines and normetanephrines should be quantitatively oxidized to vanillin. Oxidation is completed or stopped generally by a glycerol solution. The pH of the system should be at or below 7. The vanillin is extracted into an organic solvent immiscible with the aqueous fraction. This organic solvent should be relatively non-polar so as to effect a good separation between vanillin and relatively polar side products. Examples are benzene, toluene, diethyl ether etc. Aqueous phase is freeze up and organic phase is removed into a scintillator vial. The scintillator is solubilized within an organic solvent, the combination of scintillator and solvent is referred to as liquid scintillation medium. The organic solvent containing vanillin is added to the liquid scintillation medium and counted. The specificity of the assay is further improved by contracting the vanillin containing organic solvent with an aqueous acid, thereby removing additional water soluble impurities. It is preferred to have the aqueous acid phase in contact with the liquid scintillation medium. In this way the number of separate transfers and phase separation is minimized. When vanillin is added to the liquid scintillation medium, the vanillin remains in the organic layer and is counted by the scintillator. However any tritium labeled contaminant extracted into the aqueous acid phase is not counted since the scintillator is in the organic phase and the tritium emission beta ray is stopped by the aqueous phase and interface. Various radioemission counting techniques can be employed but liquid scintillation counting technique is preferred.

The sensitivity of the assay is determined as the level of catecholamines which has double the counts of the blanks. The standard curve for the assay is obtained by assaying known quantities of epinephrine, norepinephrine and dopamine alongside the unknown and blank. The counts obtained with the known concentration of epinephrine, norepinephrine or dopamine is plotted against the concentration. The unknown concentration of catecholamine is then determined by the number of counts emitted with reference to the standard curve.14

**PROTOCOL OF CATECHOLAMINE RADIOENZYMATIC ASSAY BEING DONE IN LABORATORY**

Take 50 μl of plasma, add 50 μl of methylation mixture. Incubate in water bath at 37°C for 60 minutes with gentle shaking. After 60 minutes add 50 μl of carrier solution. Extract into 2 ml of Toluene – isoamylalcohol liquid by vigorous shaking with vortex for 30 seconds. Centrifuge at 4000 rpm at 5°C for 5 minutes. Freeze the aqueous phase at –70°C using dry ice and acetone till the lower part freezes. Decant (pour out) the organic phase into tube having 100 μl of 0.1 N Acetic acid. Vigorously shake at the vortex for 30 seconds. Centrifuge again at 4000 rpm at 5°C for 5 minutes. Freeze and discard the upper organic layer using the dry ice and acetone. Dry the acetic acid layer under reduced pressure for 90 minutes at medium speed. Dissolve the catecholamines in 1 ml of 1 N NH₄OH. Vigorously shake at the vortex for 30 seconds. Add 50 μl of sodium periodate (NaIO₄ 4% w/v). Shake at the vortex for 10 seconds. 5 minutes later add 50 μl of glycerol 10% v/v solution. Shake at the vortex for 10 seconds. Add 0.3 ml (300 μl) of pure glacial acetic acid. Shake at the vortex for 10 seconds. Add 10 ml of toluene – scintillation fluid 10:0.5. Vigorously shake at the vortex for 30 seconds. Centrifuge again at 4000 rpm at 5°C for 5 minutes. Freeze the aqueous phase with dry ice and acetone. Pour out the organic layer into scintillation vial having 2 ml of 0.1 N acetic acid. Count the radioactivity with the liquid scintillation counter using program number 10 for a period
of 1 minute for each vial. Subtract the blank CPM (counts per minute) from the standards and samples and plot the Log graph.15,16

**CALCULATIONS**

**Total catecholamines**

The data summarized below provided an example for the calculation of total NA and A in the total catecholamines

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Description</th>
<th>Radioactivity (cpm) Total NA + A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Blank</td>
<td>106</td>
</tr>
<tr>
<td>2.</td>
<td>Blank</td>
<td>86</td>
</tr>
<tr>
<td>3.</td>
<td>50 µl plasma # 1</td>
<td>880</td>
</tr>
<tr>
<td>4.</td>
<td>50 µl plasma # 1</td>
<td>907</td>
</tr>
<tr>
<td>5.</td>
<td>50 µl plasma # 1 + Std</td>
<td>7464</td>
</tr>
<tr>
<td>6.</td>
<td>50 µl plasma # 1 + Std</td>
<td>7688</td>
</tr>
</tbody>
</table>

All standards are 200 picograms (sum of concentration of NA and A).

<table>
<thead>
<tr>
<th>Description</th>
<th>Average radioactivity (cpm) Total NA + A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>96</td>
</tr>
<tr>
<td>Plasma # 1</td>
<td>894</td>
</tr>
<tr>
<td>Plasma # 1 + Std</td>
<td>7566</td>
</tr>
</tbody>
</table>

Catecholamine concentration (pg/ml) =

\[
\frac{\text{cpm (sample)-cpm blank}}{\text{cpm (sample + std) – cpm sample}} \times \frac{\text{pg standard}}{\text{ml sample vol}^{**}}
\]

Plasma sample #1 (total catecholamines NA + A)

\[
\frac{894-96}{7566-894} \times \frac{200}{0.05} = 478 \text{ picograms/ml}
\]

In this calculation standard is the sum of NA and A which is 200 pg.17 assay.

**SOLUTIONS REQUIRED IN LABORATORY FOR CATECHOLAMINE ASSAY:**

1. **Plasma Additive Solution Preparation**
   For each ml of blood 20 µl of plasma additive solution is required. Plasma additive is 950 mg EGTA, adjusted to pH 6.5 with 1 N NaOH (approx. 0.2 gms of NaOH pellets). Final volume is 30 ml. To each 10 ml of this solution, 600 mg reduced glutathione is added on the day of working and is stored in refrigerator at 2-4°C.

2. **Methylation Mixture preparation**
   100 ml 0.3 M Tris buffer at pH 8.2 adjusted with concentrated HCl is required. For each 200 ml of 0.3 M Tris buffer use 7.268 g Tris base. To make 100 ml of 0.3 M Tris buffer, are 99 ml of 0.3 M Tris buffer. 1.10 g of EGTA, 4.6 mg Benzyloxyamine (1 ml from stock solution of 23 mg/5 ml equal to 4.6 mg/ml), and 1.77 g MgCl₂. Recheck and adjust the pH to 8.2 if different and store in refrigerator at 2-4°C.

3. **[3H] S–ADENOSYL–METHIONINE (SAM); specific activity: 5 – 15 Ci/mmol 500 µCi/ml**
   For each sample, 5 µl is required which is equal to 2 – 2.5 µCi. Store in refrigerator at 2-4°C.

4. **Catechol–O–Methyl Transferase Enzyme (COMT)**
   Dissolve in COMT reconstitution solution. Aliquots are made and stored at -20°C.
   For a 50 µl plasma sample, 10 µl of COMT solution is required which contains 6 U of commercially prepared COMT per sample in our Laboratory. The quantity of COMT in units needs to be evaluated through experiments in each laboratory but the volume used is fixed to 10 µl per 50 microliters of sample.

**COMT – reconstitution solution**

Dissolve 0.154 g Dithiothreitol (DTT) into 10 ml Deionized H2O. Make reconstitution solution with 0.0121 g Tris Base, 0.0372 g EDTA and 0.01 g Bovine Serum Albumin (BSA), pH 7.5 (with NaOH) in a final volume of 9.9 ml. For final 10 ml reconstitution solution for COMT, add 100 µl of DTT to this salt solution. From this 10 ml solution, take out ½ ml and inject into the iivial having COMT powder. Shake and mix well. Make aliquots 50 µl each and store at -20°C. Solution preparation and aliquoting should be done on ice.

5. **CARRIER SOLUTION**

Ten ml of 0.8 M Borate buffer pH 10.0 is adjusted with 1 N NaOH. Make 100 ml of 0.8 M Borate Buffer at pH 10.0. 4.94 gm Boric acid and 3.2 gm NaOH pellets dissolved into 100 ml Deionized H₂O having a pH of 11. To each 10 ml of borate buffer on the day of working add
0.234 g EDTA, 0.002 g Normetanephrine, and 0.002 g methoxytyramine. The final pH is 10.0. Keep on ice.

**Procedure:**

Weigh out the boric acid required for 100 ml of D-HFO. Add it to D-H2O less than 100 ml. Stir it with the metal stirrer. Heat the solution (without metal stirrer) for 40–50 seconds in microwave. Again stir it with metal stirrer till it is completely dissolved and solution is clear. Add D-H2O to make it 100 ml in total. Now add NaOH pellets and dissolve it completely by stirring. Check the pH. It should be 11 because when ETDA will be added it will fall down to 10. Store this solution in refrigerator at 4°C.

When required for use take out 10 ml and heat it in the microwave for 30 seconds. Add EDTA to it. Check the pH to be 10. Add the required amount of normetanephrine and methoxytyramine to this solution. Dissolve them and take out the solution in a test tube. Keep this test tube immediately in the ice bucket. Take out the required amount of borate buffer solution needed for the assay in a separate test tube. Cap it and place in the ice bucket. Discard the rest of the solution.

**Precautions:**

Plain boric acid solution can be made and kept in the refrigerator for 1 week or till it does not dissolve on heating any more. Heating is necessary in making the borate buffer so as to keep the boric acid in solution in dissolved form otherwise precipitation will occur. EDTA, normetanephrine and methoxytyramine should be added only on the day of use. Before adding EDTA 10 ml of borate solution should always be heated to help dissolving the EDTA otherwise precipitation will occur. Once normetanephrine and methoxytyramine is added the solution should be kept in the ice bucket till use. Fresh solution should be made when required for use.

**6. Toluene – Isoamylalcohol (3:2 v/v)**

To each 60 ml of toluene add 40 ml of isoamylalcohol in a glass bottle with plastic cap. Keep bottle in the hood covered in aluminum foil.

**7. Acetic Acid 0.1 N**

750 μl of glacial acetic acid added in 99.25 ml of deionized H2O to make 100 ml of 0.1 N acetic acid. Keep in the hood, in a glass bottle with plastic cap.

**8. Heparin Solution (10 U/ml)**

Stock 1: 0.01 g heparin powder and 2 ml deionized H2O. Working solution is made of 120 μl of stock 1 + 9.88 ml deionized H2O. Store in refrigerator at 2 – 4°C. Add 0.16 ml of heparin to the syringe prior to each ml of blood drawn.

**9. 10% v/v Glycerol Solution**

It is made with 1 ml of glycerine (99 %) + 10 ml of deionized H2O. Store in refrigerator at 2-4°C in a plastic tube with cap.

**10. 4% Sodiumperiodate NaIO₄ Solution**

0.4 mg NaIO₄ is added to 10 ml of deionized H₂O and stored in refrigerator at 2-4°C in a plastic tube with cap.

**11. Toluene – Scintillation Fluid Solution (10:0.5)**

100 ml of toluene and 5 ml of scintillation fluid are kept in a glass bottle with plastic cap in the hood covered with aluminum foil to protect from light degradation.

**12. 1 N Ammonium Hydroxide is commercially available as such.**

All solutions should be made weekly. If any solution becomes turbid before this period it should be discarded and prepared again.

**PLASMA SAMPLE PREPARATION**

The rat is anaesthetized with sodium pentobarbital (Nembutal) given through intraperitoneal injection in a dose of 50 mg / kg body weight. Blood is then taken from the external jugular vein using polyethylene (PE- 50) catheter in a heparinized syringe and also through direct cardiac puncture using 3 ml heparinized syringe with 20 gauge needle. Heparin is used in a concentration of 10 U/ml and for each ml of blood 0.16 ml of heparin is used. To each ml of heparinized blood 20 ml of plasma additive solution is added to a glass test tube & is mixed by a gentle tilting of the glass test tube 3-4 times. Plasma was
immediately separated by centrifugation in a refrigerated centrifuge at 4000 rpm for 15 minutes at 4°C. Aliquots of plasma sample are made and stored at -70°C until analysis is done. Glass tubes used should be pre-chilled and sample should be constantly kept in ice.18

ACKNOWLEDGEMENT

This work was done by the author as a part of her post doctoral fellowship under the supervision of Dr. Berlin.

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GOOD COMMUNICATION AND HEALTH OUTCOME

Firdous Jahan, Riaz Qureishi

Health care is integrated with four elements: physical care (surgical or medical), cognitive care to provide clear information for patients to help themselves and to adhere to advice, behavior care whereby patients can modify their habits and lives, and psychological care either of primary psychological factor or those secondary to physical illness. It is mandatory for a modern health care professional to provide care that is evidence based, patient centered and shared in a collaborative partnership.¹

Family physicians take care of the physical, mental and emotional health of both, their patients and their families. They know family’s health history and how it can affect patients and are trained to care for their patients through all stages of life. Family doctors are trained in all areas of medicine. They can diagnose and treat the full range of problems people usually bring to their doctors and know when to treat himself, and, if necessary, when to bring in another specialist for the appropriate care of his patient.

The best health outcome depends upon accurate diagnosis and appropriate treatment. A patient centered communication provides a more complete clinical picture which leads to improvement in health outcomes such as symptom resolution, reduced psychological distress, improvement of health and functional status, relief from pain and anxiety control. Broad dimensions of care of most concern to patients are: respect for patients’ values, preferences, expressed needs, coordination of care and integration of services within the clinical setting. Communication between patients and health care providers, dissemination of accurate, timely, and appropriate information, and education about the long-term implications of disease and illness are essential ingredients of care. Other important factors which need consideration are enhancing physical comfort, emotional support and alleviation of fears and anxiety, involvement of family and friends, transition and continuity from one locus of care to another.²

Patients want to be able to trust the competence and efficiency of their care givers. They want to be able to negotiate the health care system effectively and to be treated with dignity and respect. They want relief from pain and discomfort and worry about functional disabilities. Also they want to understand how their sickness or treatment will affect their lives, and fear that their doctors may not be telling them everything known about their case. They worry about caring for themselves away from the clinical setting. They also worry about the effect their illness will have upon them, their family, friends, and finances.

Effective clinician-patient communication is directly linked to improved patient satisfaction, adherence to suggested treatment, and subsequently, health outcomes. However, patients, particularly those from minority backgrounds, are often dissatisfied with their ability to communicate with their physician.³ Many times patients had trouble understanding their doctor, whether they felt their doctor did not listen, and if they had medical questions during the consultation that they felt they couldn’t ask. Factors which improve patients’ adherence to medical advice are clinician’s understanding the patients need and eliciting all health concerns including patient being comfortable enough asking questions with sufficient time.

Differences in styles of communication between patient and clinician, which can lead to discomfort and miscommunication, include both verbal and non-verbal communication, eye contact, touch, and personal space. Direct eye contact may be avoided in some cultures, while in others it is a sign of respect and paying attention. Providers of health care should be aware of their own tendencies and should be sensitive to the preferences of their patients. Another key aspect of communication is level of assertiveness,
which may range from deference to aggressiveness. It should not be assumed that a quiet patient agrees with the plan outlined by the health care provider. A deferent patient may simply be hesitant to voice a conflicting view; making it crucial to ask for the patient's input and encourage verbalization of any disagreement. Good relationship with patient depends on better orientation to the process of consultation, facilitative comments, active listening, humor and time management.\(^4\)

Communication issues become more complex when preferences around relating "bad news" to a patient need to be considered. Care providers may incorrectly assume that patients should be informed of results and diagnoses, just as they themselves would wish such news delivered. Personal and/or cultural preferences for a direct or indirect approach vary and should be elicited from patients, ideally before ordering an important test. Sense for the patient's general communication style and adapting a style of communicating to fit best with him/ hers is essential.\(^5\)

Trust is a crucial element in the therapeutic alliance between patient and health care provider. It correlates directly with adherence to physician recommendations and patient satisfaction. Mistrust of the health care system also affects patient's use of services, and results in inconsistent care, doctor shopping, self-medicating, and an increased demand for referrals and diagnostic tests by patients. Effective communication can explore the patient's perspective and provides focused reassurance. Many patients respond well to being given options and some control over their health care decisions. A good health care provider communicates clearly, listens attentively and carefully, avoids medical jargon, and checks regularly for feedback from the patient.\(^6\)

Many patients wish to make decisions about their own medical care, based on information and guidance provided by their health care providers. Families may even wish to exclude the patient from decisions, to avoid what they perceive as undue stress for the patient. A common issue occurs when a family asks the health care team to withhold a terminal diagnosis from a patient. In this situation, the family as a unit is trying to do what they feel is best for the individual patient. However, this conflicts with ethical belief of care provider which places great value on patient autonomy and the "right to know." A negotiation might lead to an accord agreement in these situations, if the patient himself/herself agrees to allow her family to make medical decisions on her behalf.\(^7\)

Many of the myriads of traditions and customs that help to shape a person's cultural environment have a significant relation to health and illness, including issues relating to dietary practices, folk remedies, and certain religious customs. It is important to have an awareness of their importance, as well as openness and skills to explore them further with individual patients. Many of these health-based traditions and customs are directly related to the patient's world-view, religious, or spiritual beliefs. Illness and death are among the most powerful and mysterious phenomena in our existence. People often seek meaning in these experiences through spirituality. Some patients have spiritual or religious beliefs that prevent them from having certain tests or treatments, such as blood transfusions. Patients seeking care for a medical issue come with certain beliefs about the cause of their symptoms, concerns about their illness, and expectations about potential treatment. Limited education, low health literacy, lack of information, or mistrust of medicines may lead people to develop their own ideas about the causes, consequences, and appropriate treatment of their illness. Sometimes beliefs are simply misunderstandings about medical information. A good family physician should communicate his or her patient effectively to eliminate these thought process and misunderstanding among patients and their relatives. Poor communication between doctors and patients are due to, lack of knowledge, and skills, authoritarian attitude, failure of empathy and sometime personal failures like short temperedness or ignorance. Patients difficulty in communicating with doctors are feeling of inferiority, anxiety and its consequences, misconceptions, conflicting information, forgetfulness, language barrier and disinclination to disclose their concerns.

Learning communication skills in times of change and uncertainty depends on an emotional openness to self and others. Medical educators should use knowledge of patients’ perceptions of care to focus teaching on areas that will help trainees to meet patients’ expectations. Teaching communication skills should be included at all levels of medical education and, even more importantly, should be a mandatory element of the medical school curriculum and programs of continuing medical education.\(^8\) This can be achieved only with the support of all grades of doctors in all specialties. As more organizations become aware of the importance of physician communication skills, competency
in these skills becomes a standard that physicians must attain. In addition to the best technical and medical treatment possible, patients also want a supportive environment and a medical team that cares about them.\textsuperscript{9}

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WHAT ARE SYSTEMATIC REVIEWS AND PROTOCOLS?

What is evidence-based health care?

Evidence-based health care is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services. Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests, and the predictive power of prognostic factors.1

Evidence-based clinical practice is an approach to decision-making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits that patient best.2

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.3

What is a systematic review?

To help identify which forms of health care work, which do not, and which are even harmful, results from similar randomized controlled trials need to be brought together. Trials need to be assessed and those that are of good quality and unbiased can be combined to produce both a more statistically reliable result and one that can be more easily applied in other settings. This combination of trials needs to be done in as reliable a way as possible. It needs to be systematic. A systematic review uses a predefined, explicit methodology. The methods used include steps to minimize bias in all parts of the process: identifying relevant studies, selecting them for inclusion, and collecting and combining their data. Studies should be sought regardless of their results.

A systematic review does not need to contain a statistical synthesis of the results from the included studies. This might be impossible if the designs of the studies are too different for an averaging of their results to be meaningful or if the outcomes measured are not sufficiently similar. If the results of the individual studies are combined to produce an overall statistic, this is usually called a meta-analysis. A meta-analysis can also be done without a systematic review, simply by combining the results from more than one trial. However, although such a meta-analysis will have greater mathematical precision than an analysis of any one of the component trials, it will be subject to biases that arise from the study selection process, and may produce a mathematically precise, but clinically misleading, result.

What is a systematic review of diagnostic test accuracy?

Diagnostic tests aim to reduce uncertainty about an individual’s condition and aid in the diagnosis and detection of disease. A plethora of tests are available for almost every condition imaginable. Many tests exist to detect the same condition and new tests are being developed all the time. A perfect test would identify all patients with the target condition, without making mistakes, but perfect tests are rare and the users of a test wish to know how well the test discriminates between individuals who have the target condition and those who have not, also known as the diagnostic test accuracy.

The accuracy of diagnostic tests is studied by comparing the result of the test under evaluation with the results of a test known to be very good (the reference standard) in the same patients/participants. Clinicians, policymakers and patients routinely face a range of questions regarding diagnostic tests. They want to know if testing improves outcome, would like to know what test to use, to purchase or to recommend in practice guidelines, and how to interpret the results of testing. Systematic reviews can help practitioners and decision makers in answering these questions, by summarising the available evidence and helping to explain differences among studies on the same question. As with elsewhere in science, systematic reviews and meta-analyses can be used to obtain more precise estimates, when small studies addressing the same test and study participant types in the same setting are summarised. This combination of studies needs to be done in as reliable a way as possible. For this reason, it needs to be systematic. Systematic reviews of test accuracy use a predefined and explicit methodology.

Accuracy measures the ability of the test to distinguish between persons with and without the target condition. Good accuracy is desirable but is not the only information required to assess the effectiveness of a diagnostic test. To show that one test does more good than harm in terms of patient outcomes, one may require randomized controlled trials of test and treatment strategies.

Systematic reviews of diagnostic test accuracy are powerful tools for producing reliable and precise measures of the accuracy of a test for specific patient/participant group and setting. Systematic reviews and meta-analyses of test accuracy may be the preferred source of such evidence, but building reviews and summarizing study results can be methodologically challenging. The information obtained from these reviews is useful for assessing the accuracy of a test or tests but evidence from randomized controlled trials of combined ‘test and treatment’ strategies, and reviews of such studies, are needed to assess the effects of tests on patient outcomes.

What is The Cochrane Collaboration?

The Cochrane Collaboration is an international not-for-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. The Cochrane Collaboration was founded in 1993 and named after the British epidemiologist, Archie Cochrane.

References


Reference : The Cochrane Library website:http://www3.interscience.wiley.com/cgi-bin/mrw/home/106568753/WhatAreSystematicReviews.html;
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The material submitted for publication may be in the form of an Original research, a Review Article, evidence-based reports, Special article, Commentary, Short communication, a Case Report, Recent Advances, New techniques, view points on Clinical/Medical Education, Adverse Drug Reports or a Letter to the Editor. Original articles should normally report original research of relevance to clinical medicine, and may appear either as papers or as short communications. The paper should be of about 2000 words, with no more than six tables or illustrations; short communications should be of about 600 words, with one table or illustration and no more than five references. Clinical case reports and brief or negative research findings may appear in this section.

Review article should consist of structured overview of some relatively narrow topics providing background and recent development with reference to the original literature. An author can write a review article only if he/she has written a minimum of three original research articles and some case reports on the same topic.

Letters should normally not exceed 400 words, have no more than 05 references, and be signed by all the authors; preference is given to those that take up points made in contributions published in the journal. **Editorials are by invitation.**

Authors should keep one copy of their manuscript for reference, and send three copies (laser copies or inkjet, photocopies are not accepted) to the Managing Editor, Journal of the Dow University of Health Sciences. The author should also submit an electronic copy of the manuscript typed in MS Word. Any illustrations or photographs should also be sent in duplicate. People from outside Pakistan can also e-mail their manuscript.

Each manuscript should include a title page (containing e-mail address, fax and phone numbers of the corresponding author), abstract, text, acknowledgements (if any), references, tables, and legends. Each component should begin on a new page, in the following sequence: title page; abstract and at least three key words; text; acknowledgements; references; tables (each table, complete with title and footnotes, should be merged in the manuscript); and legends for illustrations.

The manuscript should be typed in double spacing as a single column on 8 1/2”X 11” (21.5cm X 28.0 cm) white bond paper with one inch (2.5cms) margin on both sides. It should not exceed 3000 words, excluding tables and references. There should be no less than 20 or more than 40 references in an Original Article and no less than 40 or more than 60 in a Review Article. If prepared on a word processor / computer, the diskette, properly protected, or CDs should be sent with the manuscript.

TABLES AND ILLUSTRATIONS

Tables and illustrations should be merged within the text of the paper, and legends to illustrations should be typed on the same sheet. Tables should be simple, and should supplement rather than duplicate information in the text; tables repeating the information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 1/2” X 11” (21.5 X 28.0 cms) paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scatter grams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be merged in the manuscript. For scanned photographs highest resolution should be used.

S.I. UNITS

System International (S.I) Unit measurement should be used. All drugs must be mentioned in their generic form. The commercial name may, however, be mentioned within brackets, if necessary.

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Figures and photographs should only be sent when data cannot be expressed in any other form. They must be unmounted, glossy prints in sharp focus, 5” X 7” (12.7X17.3 cms) in size. They may be in black and white or color. Negatives, transparencies, and X-ray films should not be submitted. The number of the figures, the name of the author(s) should be printed on the back of each figure/photograph.
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REFERENCE NUMBERING AND FORMAT

References should be numbered in the order in which they are cited in the text. At the end of the article, the full list of references should give the names and initials of all the authors (unless there are more than six when only the first Three should be given followed by et al). The author(s) names are followed by the title of the article; title of the journal abbreviated according to the style of the Index Medicus (see "List of Journals Indexed," printed yearly in the January issue of Index Medicus); year volume and page number; e.g.: Hall RR. The healing of tissues by CO2 laser. Br J Surg: 1971;58:222-5. Reference to books should give the names of editors, place of publication, publisher, and year. The author must verify the references against the original documents before submitting the article.

PEER REVIEW

Every paper will be read by the staff editors of the editorial board. The papers selected will then be sent to one or more external reviewers. If statistical analysis is included, further examination by a statistician will be carried out.

ABSTRACT

Abstracts of original article should be in structured format with following sub-headings:
i. Objective, ii. Design, iii. Patients & Methods, iv. Result, v. Conclusion. Four elements should be addressed: why did you start? what did you do? what did you find? and what does it mean? Why did you start is the objective. What did you do constitutes the methodology and should include design, setting, patients or other participants, interventions, and outcome measures. What did you find is the results, and what does it mean would constitute your conclusions. Please label each section clearly with the appropriate sub-headings. Structured abstract for an original article should not be more than 250 words.

Review article, case report and other requires a short, unstructured abstract. Commentaries and short communications do not require abstract.

INTRODUCTION

This should include the purpose of the article. The rationale for the study or observation should be summarized; only strictly pertinent references should be cited; the subject should not be extensively reviewed. Data or conclusions from the work being reported should not be presented.

METHODS

Study design and sampling methods should be mentioned. Obsolete terms such as retrospective studies should not be used. The selection of the observational or experimental subjects (patients or experimental animals, including controls) should be described clearly.

The methods and the apparatus used should be identified (with the manufacturer's name and address in parentheses) and procedures described in sufficient detail to allow other workers to reproduce the results. References to established methods should be given, including statistical methods; references and brief descriptions for methods that have been published but are not well-known should be provided; new or substantially modified methods should be described, giving reasons for using them, and evaluating their limitations. All drugs and chemicals used should be identified precisely, including generic name (s), dose (s), and route (s) of administration.

RESULTS

These should be presented in a logical sequence in the text, tables, and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized.

DISCUSSION

The author's comment on the results, supported with contemporary references, including arguments and analysis of identical work done by other workers. A summary is not required. Brief acknowledgement may be made at the end.

CONCLUSION

Conclusion should be provided under separate heading and highlight new aspects arising from the study. It should be in accordance with the objectives.

REPRINTS

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