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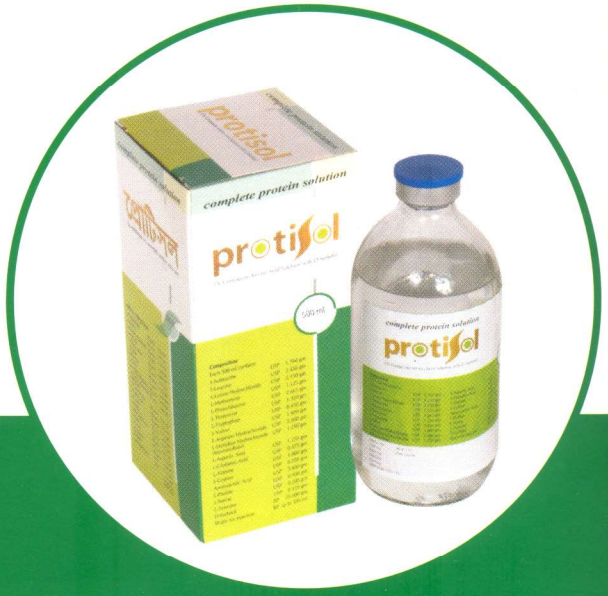

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The ORION medical journal

Editor's Choice

The ORION, 7 years of Trust & Service

The ORION is celebrating seven years of trust & services with 24th issue accentuating the local research studies and endorsing national diseases epidemic with native treatment protocol. This is the unique scientific publication that has been relentlessly serving the doctor's community of Bangladesh since September, 1998. Each esteemed readers of The ORION, has always been a guiding light in this journey over the years.

This enormous achievement is possible because of arduous efforts of the valued authors, fabulous contribution of the respective members of 'The Advisory' & 'The Review Board'. The ORION also accredits the members of 'The Editorial Board' and all its well-wishers for enduing such immense asseveration.

The Editorial of this issue focuses Rhabdomyolysis, resulting from skeletal muscle injury is one of the important cause of acute renal failure *(P-354)*. Thereafter a review article gives updated information about manifestation, medical and surgical treatment of heart failure - a burning issue of current health care sector in our country *(P-355)*.

A review article on "Contrast-induced nephropathy interest of cardiologist" nicely discusses the aspects of contrast induced nephropathy and its relation with the percutaneous coronary interventions *(P-359)*. Another review article on "Role of biochemical markers in clinical cardiology" documents the role of different markers in early detection of myocardial damage *(P-363)*.

A modern concept of treatment of Polycystic ovarian syndrome along with its principle underlying disorder is informatively established in the article "Metformin : a newer intervening agent for PCO" *(P-368)*. Another article on "Lumber sympathectomy : A review" highlights the indication, procedure and complication of this surgical procedure *(P-370)*.

A very interesting article "The role of gynecologist in management of male associated infertility" nicely sketches the initial evaluation of male partner, normal parameter and management of the male with abnormal semen *(P-372)*.

A descriptive type of cross sectional study *(P-373)* reveals the influencing risk factors for increasing trends of kala-azar in a rural community of Bangladesh. Another study highlights in case of acute diarrhea that blindness can be prevented by medication on eye and with the correction of dehydration *(P-376)*.

The case report of this issue *(P-378)* confers on very interesting and relatively uncommon disease of a middle aged man called Adult Onset Still's Disease (AOSD).

The opinion and suggestion of the valued readers are always appreciated to make The ORION medical journal ameliorated steadily.

May the Almighty bless all in the spirit of good health. The ORION wishes all a very colorful Bangla Shuvo Noboborsho-1413 with happy life in every moment.

DR. MOHAMMAD ZAKIRUL KARIM
Chief Editor
The ORION medical journal

Acute renal failure due to rhabdomyolysis

Ahmed S[1]

The ORION 2006 ; 24: 354

Rhabdomyolysis may be defined as clinical and laboratory syndrome resulting from skeletal muscle injury with release of potentially toxic intra-cellular component into systemic circulation. During the blitz of London, Bywaters described the major clinical sequelae of rhabdomyolysis, including the first causative association with acute renal failure.[1] Rhabdomyolysis has been implicated the cause of acute renal failure in approximately 5 to 7% of cases.[2,3] Rhabdomyolysis literally means "striped muscle dissolution". However, a more useful definition is "skeletal muscle injury, reversible or irreversible, that alters the integrity of the cell membrane sufficiently to allow the escape of cell contents into the extracellular fluid".

These cell contents include enzymes such as creatine kinase, glutamic oxaloacetic transaminase, lactate dehydrogenase, aldolase; the heme pigment, myoglobin; electrolytes such as potassium and phosphate; and purines. Creatinine kinase is the most sensivitive enzyme marker of muscle injury[4] and is readily determined in most hospital laboratories. The increase plasma concentration of these released substances such as creatine kinase (CK) permits the clinician to diagnose this syndrome. Muscle accounts for approximately 40% of total body mass and falls victim to wide variety of toxic, ischemia, traumatic, infections, inflammatory and metabolic insult.[5] The rhabdomyolysis syndrome has been recognized for centuries. Renal complications of rhabdomyolysis become firmly entrenched in medical literature after the classic description of the "Crush Syndrome" as result of bombing raids of London during World War II.[1]

Mechanism of myohaemoglobinuric renal injury includes renal vasoconstriction, intraluminal cast formation and direct heme protein induced cytotoxicity.[6] Laboratory measures for diagnosis of rhabdomyolysis solely on the basis of serum creatine kinase (CK) elevation which is usually greater than 1000 U/L, is approximately five times greater than upper limit of normal level. Elevation of serum myoglobin concentration and /or the presence of myoglobinuria also indicate skeletal or cardiac muscle injury. However, detection of these phenomena is neither a practical nor sensitive way to diagnose rhabdomyolysis for a variety of reasons. Serum levels may fall to normal by the time a patient is hospitalized owing to the rapid clearance of myoglobin from plasma within 1 to 6 hours by both renal excretion and metabolism to bilirubin.[7] In addition, myoglobinuria correlates poorly with myoglobinemia.[8]

Other causes of elevated CK level such as due to myocardial infarction or cerebral infarct or immediate post operative period should be excluded. Renal failure is defined loss of renal function as evidenced by a serum creatinine level greater than 200 µmol/L. Several factors namely previous renal disease, hypertension, diabetes mellitus, drugs or toxic exposure, sepsis, burns, ischemic injury, dehydration and hypotension can lead to acute renal failure independent of rhabdomyolysis.[9] Increased serum potassium, phosphorous and uric acid levels and decreased serum bicarbonate are noted in cases of acute renal failure due to rhabdomyolysis. A total of twenty four cases of acute renal failure due to rhabdomyolysis were studied in Dhaka Medical College in last 3 years in terms of clinical presentation, biochemical parameters including prognosis after treatment. Common presentation was anorexia, nausea & vomiting (91%), followed by oliguria (83%) and generalized body ache (50%) cases. Main causes were physical assault 50%, near-drowning and vigorous exercise 12% each and other causes were road traffic accident, convulsion (epilepsy), self induced trauma, septicemia, post partum eclampsia. Mean serum CPK was 2341 IU/L; mean blood urea and serum creatinine were 161 mg/dl and 10 mg/dl respectively. Among 24, 6 patients (25%) were treated conservatively and 18 (75%) received dialysis treatment in the form of intermittent peritoneal dialysis or acute hemodialysis. Twenty (83%) patients were cured completely and 2 patients (8.3%) were discharged with risk bond (DORB) and 2 patients (8.3%) expired.[10]

The incidence of acute renal failure due to rhabdomyolysis in our centre is 6.25% which is consistent with other studies. The important causes of rhabdomyolysis in Western countries like alcohol & drugs, polymyositis are lacking in our study. Two cases of ARF due to rhabdomyolysis were also reported in two different journals and treated successfully.[11,12] It is concluded that acute renal failure due to rhabdomyolysis is a serious condition and prognosis is good if correct treatment is offered including dialysis support in time. Secondly, appropriate attention & measures should be taken to prevent development this serious condition.

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Management of heart failure: An update

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The ORION 2006 ; 24 : 355-358

Introduction

Heart Failure is a common problem worldwide including in our country particularly in the elderly age group. In our country there is no definite data regarding incidence of heart failure, though the magnitude of the problem is supposed to be definitely significant. In the Western world the annual incidence is 2-4% between 35 and 64 years and 10% in patients over 65 years of age. In USA, 5 million people have heart failure. In recent decades management has improved as well as the prognosis, though in many ways cost of management in hospitals is very high. In USA and Europe there are updated guidelines from "National Advisory Body" on regular basis published at regular intervals regarding management of heart failure. In our country that is yet to come. Doctors should themselves acquire the updated knowledge regarding the management of HF.

Definition

Heart failure is a condition when the heart cannot maintain an adequate cardiac output to meet the demand of the body or can do so at the expense of an elevated filling pressure.

Causes of HF

Almost all forms of heart diseases can cause HF. Extra cardiac factors also contribute due to an increased work load.

Cardiac Causes

• IHD & MI • Hypertension • Cardiomyopathy - DCM - HCM + HOCM - Restrictive cardiomyopathy • Myopcarditis • Valvular H. Diseases- - All forms • Cardiac arrhythmia- - Atrial Fibrilation and Atrial Flutter	- Atrial Tachycardia - VT - Complete Heart Block • Pericardial disease- - Pericarditis, Pericardial effusion with or without temponade • Endocarditis & Endomyocardial fibrosis • Others -VSD, ASD, Pulmonary hypertension-Primary and Secondary

Non cardiac causes

• Anaemia • Thyrotoxicosis • Beri-beri	• Padget's Disease • A-V malformation • Volume overload

Precipitating Factors

Infection, anaemia, physical and emotional stress, excess fluid and salt intake, some drugs and other physical illness can further precipitate HF.

Forms of HF

Acute vs. Chronic Heart Failure :

Acute HF develops suddenly which may be due to severe IHD, acute MI, Hypertension, Heart block, Tachyarrhythmia, Myocarditis, Endocarditis, Pulmonary embolism, volume overload, valvular heart disease. When there is gradual impairment of cardiac function almost due to any cause, a chronic H.F. supervene. A number of compensatory mechanisms take place. Minor additional factor may precipitate overt or Acute H.F.

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Left vs. Right HF and Biventricular HF :

LV, LA, Mitral and Aortic valves comprises the left side of the heart. In LVF, LV output goes down and left atrial, Pulmonary venous pressure goes up causing accumulation of fluid before left side of heart causing Pulmonary congestion and edema. Acute M.I., IHD, Hypertension, Mitral & Aortic Valvular Diseases, cardiomyopathy are the common causes and they presents with dyspnoea, orthopnea, cough, frothy sputum which may be blood-tinged, or frank pulmonary edema. A gradual onset causes a reflux increase in pulmonary arterial pressure which can protect pulmonary edema.

In right sided heart failure, right ventricular output goes down causing accumulation of fluid before right side of heart causing edema,Increased JVP, Congestive hepatomegally, Ascities, Pleural effusion etc. Lung disease, pulmonary embolism, pulmonary and tricuspid valvular disease, and pulmonary hypertension are the common causes of isolated right heart failure. However, right sided HF are commonly due secondary to left sided heart failure, so in fact, biventricular failure supervene. A combined pulmonary congestion and accumulation of fluid in periphery are the manifestations of biventricular heart failure.

Systolic vs. Diastolic Failure :

In systolic failure the ventricle is unable to pump out blood due to poor contractility and is usually dilated, commonly due to CAD, DCM, and Pulmonary embolism. It is classical or familiar form of HF. In diastolic failure there is diminished LV filling due to poor ventricular relaxation and compliance due to stiffness. It is equally important like systolic failure. LVH (Hypertensive), HCM, HOCM, IHD, Amyloidosis, constrictive pericarditis, endomyocardial fibrosis are the common causes of diastolic dysfunction. In fact in many instances it is systolic and diastolic disturbances combined, playing the role.

Forward vs. Backward Failure :

Hypothetically in forward failure there is decreased cardiac output causing a decreased renal blood flow, activating RAA system resulting in fluid accumulation. In backward failure theory, the ventricle fails to discharge the blood from it and increases the back pressure causing accumulation of fluid in interstitial places. In fact both mechanism plays along with more complex pathophysiological factors.

High vs. Low Output Failure :

In Hyperthyroidism, Anaemia, Pregnancy, A-V malformation, Beriberi, Padget's disease, there are high cardiac output causing increased workload on heart causing heart failure. In others the cardiac output is low.

Pathophysiological Consideration

Cardiac output is the function of preload, afterload and myocardial contractility. In majority of patient with HF, the primary abnormality is impairment of ventricular function and in others there is increase outflow resistance,i.e. in hypertension aortic and pulmonary valvular diseases, which ultimately causes ventricular dilatation and myocardial functional impairment. In the beginning, sympathetic activation provides ionotropic support and maintains cardiac output. In myocardial failure there is decreased stroke volume

causing increased blood accumulation in ventricle after systole and increases venous pressure (increases the preload) which helps to maintain normal cardiac output. But afterwards both the mechanism causes increase HR and increased filling pressure which has deleterious effect. Diminished renal perfusion activates RAA axis and there is increased ADH secretion, causing fluid retention, accumulation in interstitial space and ultimately increases peripheral resistance contributing to deleterious effect on heart and HF and a vicious cycle starts.

However, stretched atrial myocytes secretes ANP (Atrial natriuretic peptide) and stretches left ventricular myocytes secretes BNP (ß-type natriuretic peptide), both has beneficial effects as they cause natriuresis, vasodilatation, smooth muscle relaxation causing decreased afterload making a counter-balance.

Endothelium dependent vasodilation is impaired (decreased endothelium secretion) and NO activity (vasodilator) is blunted causes deleterious effect on heart also. Also, changes occur in cardiac contractile gene expression involving sarcolemmal Ca-channel contributing to poor myocardial contractility.

Currently more focus is being paid to ANP & BNP (or NT-Pro BNP- a byproduct of BNP) as impending biochemical marker of HF, and also trials are going on for therapeutic benefit of these in HF and benefit of endothelin antagoinist.

Clinical Manifestation

Symptoms - Depends on underlying causes & type of HF.

1. Dyspnoea : Initially on effort and then occurs with less effort or even at rest. Orthopnoea and PND may also be present. Patient may also present with cough and cardiac asthma or frank acute pulmonary edema. Cheney-stokes type of breathing may occur particularly HF with HTN or CAD.
2. Swelling of body : Common manifestation often with leg swelling and abdominal distention with low Urinary output.
3. Fatigue & weakness : Common symptom
4. Abdominal symptoms : Anorexia, nausea, abdominal pain and fullness are frequently complained.
5. Cerebralsymptoms : Headache, insomnia, anxiety, confusion, lack of concentration, and memory disturbance may be present.

Physical signs

• Evidence of - Dyspnoea - Orthopnoea • Cold extremity • Weight loss-cardiac cachexia • Edema	• Cyanosis • Pulse - Tachycardia - Pulsus alternance - Irregular pulse • BP-low • JVP - raised

- *CVS :* Cardiomegally, evidence of valvular heart disease, 3rd and 4th heart sounds, and summation gallop may be present.
- *Chest :* Creps and dullness over base, evidence of frank pulmonary edema or pleural effusion may be present.
- *Abdomen :* Ascities, hepatomegally, spleenomegally, jaundice, may be present.

Assessment of severity of HF

NYHA guidelines regarding classification of severity of HF can be used to assess severity.

Investigation

- ECG : for evidence of ischaemia, MI, hypertension, arrhythmia.
- X-Ray chest : cardiac size, pulmonary congestion, edem pleural effusion.
- Haematological and biochemical : CBC, electrolyte, ure creatinine, sugar, LFT, cardiac enzymes in acu execerbation to exclude acute MI.
- ANP, BNP, NT : Pro BNP done to screen LV dysfunction a treatment monitoring. Thyroid function test in appropria test can be done.
- Urine : routine examination
- Echocardiography : 2D & Doppler echo. done to establis systolic & diastolic dysfunction of LV and RV and severity HF. Echo may reveal aetiology of HF - valvular disease, IH cardiomyopathy, intra-cardiac thrombosis.
- Cardiac Catherization : It is indicated in acute decompensated LHF, severe acute HF, not responding t treatment, HF with unknown aetiology, Patient with angi pectoris, patient with MR and AV disease.
- Others : Cardiopulmonary exercise testing, 24 hours holt monitoring, resting and stress radionuclide angiography a done in special circumstances.

Management

A full clinical assessment about severity, type of HF, i aetiology, precipitating factors, and concomitant illness shoul be done and accordingly management is planned. Aim o treatment is prevention, maintenance, improved quality of li and survival.

General Management

Physical activity - In acute HF or acute on chronic HF rest i bed, if needed propped up position advocated. DVT is avoide by leg exercise where appropriate, elastic support stockin and S/C heparin. Prolonged bed-rest is avoided and a condition improves, low level endurance exercise i encouraged avoiding strenuous activity.

Dietary Modification - Large meal avoided, weight reducin diet advocated where appropriate. In DM, renal failure, an lipid disorder, modification of diet is advocated accordingly Generally, salt and water intake is restricted. Smoking shoul be stopped.

Immunization : Influenza and Pneumococcal vaccine should b given.

Drug Counseling : Patient should avoid-

• NSAID and Coxib	• Tricyclic anti-depressant
• Class 1 antiarrhythmic drug	• Lithium salt
• Calcium channel blocker	• Cortico steroids.

Counseling regarding diuretic self-dose modification according to weight gain and fluid retention should be done.

Pharmacological Therapy

- *Oxygen :* High concentration oxygen inhalation is given through variable performance mask if patient is breathless particularly in acute HF or HF with acute execerbation.
- *Diuretic :* Diuretics give symptomatic relief of generalized edema and pulmonary edema. It reduces the preload also. Different types of diuretics are available. Dose, route and type of diuretics are chosen according to severity of HF keeping in mind the side-effects.

Loop diuretics	Thiazides	K+ sparing
Frusemide	Bendrofluazide	Sprironolactone
Bumetamide	Chlorthalidone	Amiloride
Torasemide	Metolazone	Triamterene
	Indapamide	

I/V loop diuretics are potent and give quick relief of breathlessness of pulmonary edema. It causes hypokalaemia. Thiazides are mild diuretics. Potassium sparing diuretics are also mild. All diuretics can be used in HF alone or in combination with others. Spironolactone among them, the only one diuretic gives 30% mortality benefit (RALES study) in moderate to severe HF but causes hyperkalaemia. Loop diuretics (e.g.Frusemide) can be combined with spironolactone to get synergistic effect with balancing side-effects of potassium disturbance which can be beneficial in severe HF.

a. ACEI : Benefits of ACEI are well established in HF with significant mortality benefit (CONSENSUS & SOLVD Study) as well as in M.I. with asymptomatic HF (SAVE study). It is recommended as 1st line therapy in HF.

They can cause 1st doze hypotension, dry cough, and allergic angioedema. They are started with low doze and increased thereafter step-wise.

ACEI	Initial dose	Maintenance dose
Captopril	6.25mg BD	25-50mg TID
Enalapril	2.5mg OD	10mg BD
Lisinopril	2.5mg OD	5-20mg OD
Ramipril	1.25-2.5mg OD	2.5-5mg BD

b. ARB : Are also used in HF, particularly if patient cannot tolerate ACEI with mortality benefit though not superior to ACEI. ARB can be combined with ACEI in managing HF. Losartan Potassium, Valsartan, Irbesartan, Candesartan, are the examples of ARB. They are also started with low doses and are increased step-wise.

- *Beta-Adrenoceptor Antagonist :* Beta-blockers are useful in chronic stable heart-failure. MERIT, CIBIS2 study has shown improved symptomatic class, exercise tolerance, LV function & mortality benefit using Metoprolol, Bisoprolol respectively. US Carvedilol study using Carvedilol- a non-selective vasodilator beta-blocker with additional anti-oxidant properties has also demonstrated a significant improvement in mortality. All these drugs can be given with ACEI, Diuretics but should be started with low dose titrating slowly over a month. Transient worsening of HF may occur but afterwards it improves the symptoms of HF. However, it should be used cautiously to manage such cases.

BB agent	1st Dose	Increment (mg/day)	Target dose	Titration period
Bisoprolol	1.25	2.5, 3.75, 5, 10	10	Week-Month
Meloprolol	12.5/25	25, 50, 100, 200	200	Week-Month
Carvedilol	3.125	6.25, 12.5, 25, 50	50	Week-Month

- *Cardiac Glycosides :* Digoxin gives symptomatic benefit when used in HF particularly if associated with Atrial Fibrillation. However it does not give any mortality benefit. The dose is 0.125-0.25 mg daily. In the elderly and in Renal Failure the does is further reduced. It can cause digitalis toxicity particularly with high dose, dehydration, and hypokalaemia. Serum digoxin level should be monitored to maintain optimum dose. Drug holiday is maintained to avoid tachyphylaxis.

- *Nitrate :* It is used if patient is having angina and symptoms of dyspnoea. Its overall benefit in management of HF by evidence is lacking.

- *Ionotrophic Agents :* Intravenous continuous infusion of Dopamine (2-10 µg/kg/min) and Dobutamine (2.5-10 µg/kg/min) are used in acute LVF, after cardiac surgery, AMI with Shock, Pulmonary Edema, and in patient with refractory HF as a bridge to transplantation. Their use is carefully monitored. Similarly Milrinone, Amrinone can be used simultaneously like Dopamine/ Dobutamine for short period only for symptomatic benefit as probably it eventually increases the overall mortality.

- *Vasodilators :* Sodium nitropruside and hydralazine can be rarely used if vasoconstriction persist despite ACEI therapy in HF.

- *Antiarrhythmic Agents :* Beta-blockers used in HF are in fact beneficial for different types of Arrhythmia including Ventricular Tachyarrhythmia. Amiodarone is the only drug other than beta-blockers without negative ionotrophic effect which can be used in both supra-ventricular as well as ventricular arrhythmia. DC Shock to restore sinus rhythm and digitalis are the options for managing AF.

- *Anticoagulants :* Patient with HF are at increased risk of pulmonary and systemic embolism including stroke and is treated with I/V heparin followed by oral warferrin. Presence of clot in the LV is also treated in the same line. Patients with AF are also treated with warferrin. Hospitalized bed-ridden patients without such complications should receive S/C prophylactic heparin therapy. Alternatively, low-molecular weight heparin can be used instead of heparin.

Surgery

Revascularization - The role of revascularization is unclear because of increased mortality. In selective patients particularly with hibernating, stunned myocardium, revascularization can be beneficial.

Pacemaker - Bi-ventricular pacing can be considered in patient with decreased ejection fraction and ventricular dyssynchrony, SA node disease, and in Heart Block patient.

ICD- Implantable cardioverter defibrillators are considered with bi-ventricular pacing in those who remain symptomatic with severe HF.

Heart Replacement Therapy - Heart transplantation is the treatment of choice in young patients with intractable HF. Availability is limited. One year survival is over 90% and five years survival is over 75%. Ventricular assist device and artificial heart can be used in bridging to transplantation in acute severe myocarditis and in patients with permanent haemodynamic support. These are done in specialized centers with advanced facilities.

Conclusion

Judicial approach to the management of HF will eventually reduce the overall mortality and improvement of symptoms of HF. In our country, because of financial constraints and lack of cardiac transplant availability all support for HF cannot be provided for the mass population.

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Contrast-induced nephropathy interest of cardiologist

Patwary MSR[1]

The ORION 2006 ; 24 : 359-362

Abstract

Contrast-induced nephropathy is defined as appearance or exacerbation of impairment in renal function occurring within three days following intravascular administration of contrast media and in the absence of alternative etiology. There are several risk factors that predispose to contrast-induced nephropathy-pre-existing renal dysfunction, diabetes mellitus, congestive heart failure, multiple myeloma, dehydration, nephritic syndrome, vascular disease, high dose of contrast media, intra-arterial injection of contrast media, high osmolar contrast media, repeated doses of contrast media at short dose intervals, concurrent use of nephrotoxic drugs (e.g. NSAIDS, aminoglycosides), and elderly patients. Pre-existing renal dysfunction, especially when secondary to diabetic nephropathy, is the most important risk factor. Extra cellular volume expansion and use of low osmolar contrast media are the two most effective measures to prevent contrast-induced nephropathy. Overall data on N-acetyl cysteine are also favorable. Iso-osmolar contrast media are less nephrotoxic than low osmolar contrast media and may become the media of choice for patients undergoing percutaneous coronary interventions in high-risk patients. Long-term outcome after percutaneous coronary interventions is significantly worse in patients who develop contrast-induced nephropathy. Some prophylactic approaches to be effective against contrast-induced nephropathy in patients who had risk factors for developing contrast-induced nephropathy. Some of these important aspects of contrast-induced nephropathy are discussed in this article.

Introduction

Contrast-induced nephropathy (CIN) is the common cause of in-hospital acute renal failure due to a marked increase in the number of diagnostic and interventional radiological imaging procedures. Nephrotoxicity induced by contrast media varies in severity from a mild, non-oliguric, transient increase in serum creatinine to severe oliguric renal failure requiring renal replacement therapy (dialysis). The incidence of CIN in patients with normal renal function is <1% with intravenous and 2-7% with intra-arterial administration of contrast media.[1-4] The incidence is higher (16%) in nonazotemic diabetic patients.[4] The incidence may be as high as 33% in patients with preexistent azotemia.[3] Incidence of 3-16% has been reported in patients undergoing percutaneous coronary interventions.[5-7] Patients undergoing percutaneous coronary interventions (PCI) often have associated risk factors for developing contrast-induced nephropathy, such as diabetes mellitus, congestive heart failure and pre-existing renal impairment. The most important risk factor is presence of renal dysfunction before angiography. Important pharmacologic and other interventions that have been studied for prevention of CIN include volume expansion, mannitol, loop diuretics, dopamine, dopamine-1 receptor agonist (fenoldopam), calcium antagonists, theophylline, N-acetyl cysteine, atrial natriuretic peptide, endothelin receptor antagonist, hemodialysis after contrast administration, and periprocedural hemofiltration. Both in-hospital and long term mortality are increased in patient who undergone percutaneous coronary interventions develop CIN. Mortality is higher in patients who require dialysis.

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Definition of Contrast-Induced Nephropathy

Contrast-induced nephropathy is defined as appearance or exacerbation of impairment in renal function occurring within three days following intravascular administration of contrast media and in the absence of alternative etiology. Most studies have taken an increase in serum creatinine of more than 25% of baseline or an absolute increase of 0.5 mg/dl above baseline as the required criteria.[8]

Pharmacology of Contrast Media

All modern contrast agents are based on iodine, which by virtue of its high atomic number and chemical versatility has proved to be an excellent agent for intravascular opacification.[9] More than 99% of injected contrast media is excreted through kidneys. Elimination half-life following intravascular administration in patients with normal renal function is about 2 hours. About 98% of contrast media is excreted within 24 hours.[8]

There are three types of contrast media available

First-generation contrast media or high osmolar contrast media

These include agents such as diatrizoate that are ionic and have high osmolarity (>1500 mosm/kg). This property is responsible not only for increased incidence of pain and heat sensation on administration but also for high incidence of CIN.

Second-generation contrast media or low osmolar contrast media

These include agents like iohexol and iopromide that are non-ionic and low osmolar (600-1000 mosm/kg) with high viscosity. Administration of these contrast media is associated with less injection-associated pain and lesser acute toxicity. Low osmolar contrast media are currently the most commonly used.

Third generation contrast media or iso-osmolar contrast media

These include agents that are iso-osmolar (290 mosm/kg) and have high viscosity. Their administration is associated with less osmotic diuresis, hence less natriuresis, and less effect on medullary hypoxia, reduced volume depletion and reduced activation of vasoactive mediators. They have less adverse hemodynamic effects and reduced injection-related pain and heat sensation. Examples of these media are iodixanol and iotrolan. Studies indicate that these agents may have lowest incidence of CIN.

Pathogenesis of Contrast-Induced Nephropathy

Temporary or permanent renal dysfunction is a serious potential complication of cardiac angiography or PCI. Pathogenesis of contrast-induced nephropathy is complex and several factors have been implicated. The precise mechanism of contrast induced renal dysfunction has not been established. Vasomotor instability, increased glomerular permeability to protein, direct tubular injury or tubular obstruction may be the involved mechanism.[9]

The contrast media induced osmotic diuresis and active transport increases renal metabolic activity and oxygen consumption leading to adverse renal hemodynamic effects. Contrast media also stimulates a rapid influx of extracellular calcium leading to prolonged constriction of renal vasculature. It alters regional blood flow within the kidney; there is preferential reduction of outer medullary flow. In addition, contrast media generate reactive oxygen species which may also reduce the regional blood flow. It can also have direct renal tubular effects. Contrast media is not reabsorbed by renal tubules. These agents produce an osmotic diuresis since contrast media is concentrated 100 times in urine. Increase in intratubular pressure leads to decrease in glomerular filtration rate.The main mechanism of contrast media is perhaps its high osmolarity which results in reduction of renal blood flow.

Nephrotoxicity induced by contrast media varies in severity from a mild, non-oliguric, transient increase in serum creatinine to severe oliguric renal failure requiring renal replacement therapy (dialysis). Typically the serum creatinine starts rising 24-48 hours after contrast exposure and peaks at 4-7 days. Serum creatinine level estimated at 72 hours will detect 90% of those affected. The values tend to return towards normal within 7-14 days. Spontaneous recovery occurs in the majority and <10% require dialysis. Attempts to reverse CIN are usually unsuccessful and supportive care is the mainstay of therapy. A minority of patients become dialysis-dependent.[8]

Risk Factors for Contrast-Induced Nephropathy

There are several risk factors that predispose to contrast-induced nephropathy - pre - existing renal dysfunction, diabetes mellitus, congestive heart failure, multiple myeloma, dehydration, nephritic syndrome, vascular disease, high dose of contrast media, intra-arterial injection of contrast media, high osmolar contrast media, repeated doses of contrast media at short dose intervals, concurrent use of nephrotoxic drugs (e.g. NSAIDS, aminoglycosides), and elderly patients. The most important risk factor is presence of renal dysfunction before angiography. Rudnick et al[10]. found that patients with renal insufficiency have 21 times greater risk of developing CIN compared with patients without renal insufficiency. Diabetes without renal impairment also mildly increases the risk of CIN. Patients with both diabetes mellitus and renal impairment are at maximal risk.[11] The incidence of CIN is 2% in non-diabetic patients with serum creatinine of < 1.6 mg/dl, while it is 3.8% in diabetic patients with renal impairment.[4] Davidson et al.[12] showed that the risk of CIN rises exponentially as baseline serum creatinine increases, if the baseline level is 106 µmol/L or higher. Berns et. al.[13] found the incidence of CIN to be 3.6% in diabetic patients with serum creatinine of <2.0 mg/dl, while it was 27% and 81% when serum creatinine levels were 2.0-4.0 mg/dl and >4.0 mg/dl, respectively.

Congestive heart failure is another important risk factor. It is commonly associated with baseline renal dysfunction and hydration protocols are difficult to carry out in these patients.

A number of randomized controlled trials as well as meta-analyses have found that low osmolar non-ionic contrast media are associated with lesser incidence of CIN as compared with high osmolar ionic contrast media. Rudnick et al.10 correlated the benefit conferred by low osmolar contrast media to the presence of baseline renal impairment or diabetes mellitus. They found that there is no benefit of using low osmolar contrast media in patients who have no renal impairment or diabetes mellitus at baseline. Use of low osmolar cont media, however, reduced the occurrence of CIN by 30-55% patients with one or both of these risk factors. The incidenc CIN is very low if the amount of contrast media injected 100 ml. Repeated contrast media examinations within sh intervals (<48 hrs) is also a risk factor. Meta-analysis of controlled randomized trials by Barrett and Carlisle[14] involv 5146 patients showed that low osmolar contrast media is nephrotoxic than high osmolar contrast media, particularl patients with pre-existing renal impairment. Iso-osm contrast media have recently become commercially availa and are expected to reduce the incidence of CIN. The curre available data, however, are conflicting. Gadolinium chela intended as intravenous contrast media for magnetic resona imaging, was regarded as nonnephrotoxic and it was thou that it could replace iodinated contrast media for radiograp examinations. However, studies in mice have shown then be more nephrotoxic than iodinated contrast media equivalent X-ray attenuating doses.

Pharmacologic and other Interventions for Prevention o Contrast-Induced Nephropathy

Important pharmacologic and other interventions that h been studied for prevention of CIN include volume expans (using: intravenous normal saline (NaCl 0.90%), intraveno half strength saline (NaCl 0.45%), and, oral hydration therap mannitol, loop diuretics, dopamine, dopamine-1 recept agonist(fenoldopam), calcium antagonists, theophylline, N acetyl cysteine, atrial natriuretic peptide, endothelin recept antagonist, hemodialysis after contrast administration, an periprocedural hemofiltration.

Volume expansion : This is the single most important measu that has been documented to be beneficial in preventin CIN.[15,16] Intravenous hydration with isotonic saline, intraveno hydration with half-isotonic saline and oral hydration wit clear fluids have all been shown to be beneficial. Thre subgroups specially benefit from isotonic saline hydratio women, diabetics and patients in whom contrast dose exceed 250 ml. The current data appears to be strongest wit intravenous hydration using isotonic saline.

Hydration with forced diuresis : Most studies have found tha hydration alone is better than hydration combined with diuretic. Study by Solomon et al.[17] showing that forced diuresi is of no benefit in preventing CIN.

Dopamine : Dopamine Infusion in low dose (2-5 ng/kg/ min results in increased renal blood flow that leads to increase glomerular filtration rate. Therefore it was thought to be b benefit in preventing CIN. However, studies of low dos dopamine have produced conflicting results, with no clea benefit for prevention of CIN.

Dopamine receptor agonists : Fenoldopam, a selective dopamin-1 receptor agonist, increases renal blood flow in bot cortex and medulla. It was shown to be beneficial i preventing CIN in early studies in humans.[18] However; recently reported large randomized controlled tria (CONTRAST trial, Stone et al.[19]) did not find significant benefi with fenoldopam.

N-Acetyl Cysteine : Reactive oxygen species have bee implicated in pathogenesis of CIN. N-acetyl cysteine is a free radical scavenger and precursor of endogenous antioxidan glutathione. It is also a vasodilator. With these properties it wa expected to protect gainst CIN. A number of studies were

undertaken which showed conflicting results.[20-26] Birck et al.[22] recently reported a meta-analysis of randomized controlled trials comparing N-acetyl cysteine and hydration with hydration alone to prevent CIN in patients with CRF showed administration of N-acetyl cysteine and hydration significantly reduced the relative risk of CIN by 5 6% (p=0.02) in patients with CRF. N-acetyl cysteine is usually recommended, as it is inexpensive, has low risk and is likely to be of benefit in preventing CIN in high risk patients. However, as the need for dialysis rates was not reduced by N-acetyl cysteine, a hard clinical benefit needs to be demonstrated, before it can be universally recommended for preventing CIN.

Calcium channel blockers : Despite substantial evidence that calcium channel blockers reduce vasoconstriction and maintain GRF following contrast exposure, no clinical benefit was shown in one prospective trial[27] using single dose nitrendipine.

Theophylline : Adenosine is a vasodilator of most vascular beds. A1 receptor stimulation causes cortical vasoconstriction while A2 receptor stimulation results in medullary vasodilation. Human studies, however, have shown conflicting results[28,29]. Though Kapoor et al.[30] Found benefit with use of theophylline. The use of adenosine antagonists may be beneficial in patients where sufficient hydration may be impossible or in patients with a concomitant decrease in renal blood flow (e.g. congestive heart failure).

Atrial natriuretic peptide : Initial reports suggested that atrial natriuretic peptide (ANP) prevents fall in creatinine clearance after contrast exposure. However, a randomized, double blind, placebo-controlled trial showed that intravenous anaritide did not reduce the incidence of CIN in patients with preexisting chronic renal failure, with or without diabetes mellitus.[30]

Endothelin receptor antagonists : Animal studies have suggested role of endothelin, a potent vasoconstrictor, in CIN. Moreover, endothelin receptor antagonists have been shown to prevent fall in renal blood flow. This prompted a randomized trial[31] in humans to study the role of mixed endothelin A and B receptor antagonist. However, the incidence of CIN was found to be higher in endothelin receptor antagonists group, this negative effect was apparent in both diabetic and nondiabetic patients.

Angiotensin-converting enzyme inhibitors : Renin angiotensin system mediated medullary ischemia play role in genesis of CIN. Animal studies showed that angiotensin II antagonists decrease renal vasoconstriction and CIN. Small human studies have also found favorable results.[32]

Hemodialysis : Hemodialysis and peritoneal dialysis safely remove contrast media. Several hemodialysis sessions or three weeks of continuous ambulatory peritoneal dialysis is needed to remove the contrast media. Currently available data do not support use of prophylactic hemodialysis for prevention of CIN. Further trials are needed to clarify the strategy of performing hemodialysis immediately after the administration of contrast media in all patients with CRF.

Hemofiltration : Study by Marenzi et al.[33] recently reported significant prevention of CIN in patients with CRF undergoing PCI by hemofiltration. The degree of benefit conferred by hemofiltration compared to normal saline alone was remarkable: reduction in the incidence of CIN (5% v. 50%), reduction in requirement of dialysis (3% v. 25%),. reduction in in-hospital mortality (2% v. 14%), and reduction in one-year mortality (10% v.30%). The mechanisms of this benefit are not clear.

Summary of prevention of Contrast-Induced Nephropathy

Based on above observations, following general and specific measures should be taken for prevention of contrast-induced nephropathy.

General measures

These include (i) screening for risk factors (ii) use of alternative imaging techniques that do not require iodinated contrast media in high-risk patients (iii) precautions to prevent volume depletion, hypotension and hypoxia (iv) avoiding use of nephrotoxic drugs for at least 24 hours (v) to use minimum possible volume of contrast media, keeping maximal dose to 100-300 ml (depending on serum creatinine), and (vi) allowing adequate time gap (at least 48 hrs) between procedures requiring contrast media.

Specific measures

These include (i) adequate hydration: the single most effective method (ii) use of low or iso-osmolar contrast media, and (iii) use of N-acetyl cysteine.or hemofiltration in patients with impaired renal function.

Conclusions

Contrast-induced nephropathy is an important concern for cardiologists especially in relation to coronary angiogram and percutaneous coronary interventions. Pre-existing renal dysfunction, especially when secondary to diabetic nephropathy, is the most important risk factor. Extra cellular volume expansion and use of low osmolar contrast media are the two most effective measures to prevent contrast-induced nephropathy. Overall data on N-acetyl cysteine are also favorable. For high-risk patients, undergoing percutaneous coronary interventions iso-osmolar contrast media may become the media of choice. A recent study has shown periprocedural hemofiltration to result in remarkably reduce occurrence of contrast-induced nephropathy as well as improved in-hospital and long term mortality.

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MSD NEWS

Medicine Unit-I, CMCH, Chittagong

OLL arranged a round table meeting (RTM) on `Chronic Hepatitis' that was organized by MU-I, CMCH on 16th Feruary`06 at Classroom, MU-I, CMCH. Total participants were about 55.

Gynae Department, SZRMCH, Bogra

A round table meeting was conducted by OLL on `Role of Onium in Dysmenorrhoea' was held on 15th February`06. It was organized by Gynae department of SZRMCH. Dr. Roksana Banu, Asst. Register, Gynae & Obstetrics, SZRMCH was chaired the occasion.

Surgery Unit-IV, SBMCH, Barisal

A RTM was conducted by OLL was organized by SU-IV, SBMCH on `Vertex' at surgery seminar room on 18th March`06. Dr. Md. Khalid, Medical Associate, MSD, OLL was the speaker of the session.

Neurosurgery Department, RMCH, Rajshahi

Orion Laboratories Limited arranged a RTM on 6th March`06 at Neurosurgery department, RMCH. Dr. Md. Lutfor Rahman, Asso. Prof. and Head of the dept. of Neurosurgery, RMCH was chaired the session.

BMCH, Uttara Campus, Dhaka

A round table meeting on `Alve & Procap' was arranged by OLL on 26th March`06 at Redford Chinese Restaurant, Uttara, Dhaka which was organized by the doctors of Bangladesh Medical College Hospital, Uttara Campus, Dhaka. Dr. Ahsanullah,

Director Conference Room, DMCH, Dhaka

Orion Laboratories Ltd. arranged a round table meeting on "Advance trauma life support and basic surgical skill" organized by casualty ward department of surgery, DMCH' on 11th February 2006. Dr. Feroz Quader, Associate Proff. of surgery was the key speaker of the session. About 90 doctors were present on that occasion.

Gynae Unit-III, SOMCH, Sylhet

A round table meeting on `Management of Spasmodic Pain' was held on 22nd February`06. Onium was highlighted in that program. Dr. Gulshan-E-Jahan Bithi, Asst. Prof. GU-III, SOMCH chaired the session. Dr. Mahfuzul Islam, Internee doctor, SOMCH was keynote speaker of the occasion.

Rohonpur THC, Chapainawabgonj

A meeting on 'Role of Multivitamin & Multimineral in Human Body' was held on 12th April `06 at Rohonpur THC. Dr. Sharifur Rahman, THA was the chairperson on the occasion.

INTERNEE DOCTORS RECEPTION PROGRAMS

Dhaka National Medical College Hospital, Dhaka

A grand gala internee doctors reception program of Dhaka National Medical College Hospital was held at Priangon Community Centre on 23rd February`06. Prof. Ataur Rahman Choudhury, Principal & head of the department of medicine was the chief guest of the program. Dr. M. F. T. Ripon, Deputy director, DNMCH was the speaker on the occasion. All doctors enjoyed the raffle draw session of that program.

Comilla Medical College Hospital, Comilla

Orion laboratories limited successfully sponsored an internee doctors reception program of 9th batch, Comilla Medical College at conference room, CoMCH on 8th March `06. Dr. Mohiuddin Dipu, General Secretary, BMA Comilla, Prof. Abdul Haque, Principle & Head, Surgery dept., Dr. Nilufar Parveen, Consultant, Paediatrics dept. & Dr. Sokoruddin Mridha, Superintend, CoMCH were present on the occasion

Role of biochemical markers in clinical cardiology

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Biochemical markers play a pivotal role in the diagnosis and management of patients with acute coronary syndrome (ACS), as witnessed by the incorporation of cardiac troponins into new international guidelines for patients with ACS and in the re-definition of myocardial infarction. Despite the success of cardiac troponins, there is still a need for the development of early markers that can reliably rule out ACS from the emergency room at presentation and also detect myocardial ischaemia in the absence of irreversible myocyte injury. Under investigation are two classes of indicators : markers of early injury/ischaemia and markers of inflammation and coronary plaque instability and disruption. Finally, with the characterisation of the cardiac natriuretic peptides, laboratory medicine is also assuming a role in the assessment of cardiac function.

Introduction

The significance of the contribution of laboratory medicine to clinical cardiology has grown in importance over the years.[1,2] Until 20 years ago, the clinical laboratory only placed at the cardiologist's disposal a few assays for the retrospective detection of cardiac tissue necrosis, such as enzymatic methods for creatin kinase (CK) and lactate dehydrogenase catalytic activities.[3] However, in the later part of the 20th century, highly sensitive and specific assays for the detection of myocardial damage, such as cardiac troponins, as well as assays for reliable markers of myocardial function, such as cardiac natriuretic peptides, have become available, assigning to the laboratory a pivotal role in the diagnosis and follow-up of patients with cardiac disease. This is witnessed by the recent incorporation of these markers into new international guidelines and in the re-definition of myocardial infarction (MI).[4-5] The aim of this paper is to review the current contribution of the determination of biochemical markers to clinical cardiology and to discuss some important developments in this field.

The detection of myocardial necrosis

The World Health Organisation (WHO) has traditionally defined MI as requiring the presence of at least two of three diagnostic criteria, namely, an appropriate clinical presentation, typical changes in the electrocardiogram (ECG) and raised "cardiac" enzymes, essentially total CK or its MB iso-enzyme (CK-MB) activities.[6] In September 2000, the joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) committee published its consensus recommendations for a new definition of MI.[8] In particular, the ESC/ACC definition of acute MI requires the rise and fall of the biochemical marker of myocardial necrosis together with other criteria, comprising ischaemic symptoms, the development of pathologic Q waves, ischaemic ECG changes or a coronary artery intervention.[5] Thus, according to the WHO definition, an acute MI could be diagnosed without biochemical evidence of myocardial necrosis, while the ESC/ACC criteria stipulate that the biomarkers be elevated and, subsequently, be shown to fall in the appropriate clinical context. Quite simultaneously with the ESC/ACC re-definition of MI, other expert committees published companion documents, where in patients with no ST-segment elevation at ECG, but with ischaemic symptoms, a positive cardiac troponin result identifies patients who have non-ST-segment elevation myocardial infarction (NSTEMI) and who could benefit from aggressive medical therapy.[4,5]

The new consensus documents have therefore based the new definition of MI on biochemical grounds, a choice that was guided by the advent of new markers of myocardial necrosis, such as cardiac troponins.[7] The superior troponin's clinical value comes from its higher sensitivity to smaller myocardial injury and its virtually total specificity for cardiac damage.[8] Despite the ability to detect quantitatively smaller degrees of myocardial necrosis, cardiac troponins need 4-10h after symptom onset to appear in serum, at about the same time as CK-MB elevations become detectable, and peak at 12-48h, remaining then abnormal for several days.[10] This prolonged release pattern indeed makes it difficult to diagnose a re-infarction by the use of serial troponin measurements, suggesting a continuing role for CK-MB for this purpose.[1] There is, however, a relationship between the severity of the infarct and the duration of the elevated serum troponins. The release periods of troponin in patients with NSTEMI are significantly less than those with ST-elevation at ECG, and troponin elevations in traditionally defined unstable angina patients, representing microscopic infarct, might last only several hours at a time.

In applying the results of cardiac troponin testing to the defining of MI, one should keep in mind that these markers actually reflect myocardial necrosis but do not indicate its mechanism. Thus, an elevated value in the absence of clinical evidence of ischaemia should prompt a search for other causes of cardiac damage. Many non-ischaemic pathophysiological conditions can cause myocardial necrosis and therefore elevations in cardiac troponin concentrations.[11-17] The occurrence of myocardial damage in clinical contexts other than MI frequently obliges physicians to determine whether such damage occurs in the clinical setting of acute myocardial ischaemia, thus leading to the diagnosis of MI, or not. Strictly speaking, even in the "troponin era", the diagnosis of MI remains clinical. Measurement of cardiac troponin provides a valuable diagnostic test for MI only when used together with other clinical information. In particular, to satisfy the diagnostic criteria for MI, troponin elevations should be accompanied by objective instrumental evidence that myocardial ischaemia is the likely cause of myocardial damage. This should particularly be the case when only one marker measurement is available and its characteristic release kinetics cannot be demonstrated, or when marker changes remain stable over time, or are not consistent with the onset of symptoms.[18] Ideally, three measurements of cardiac troponin are suggested, with a sampling frequency of hospital admission, 6 and 12 h later, to demonstrate changing values. This biochemical strategy can readily show if the temporal variations in the troponin concentrations in serum are consistent with the onset of symptoms and may very often obviate the need for subsequent extensive confirmation testing. An important issue in the practical use of cardiac troponins is the appropriate definition of decision limits. From a clinical perspective, there is evidence that any amount of detectable

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cardiac troponin release is associated with an increased risk of new adverse cardiac events. Currently available data demonstrate no threshold below which elevations of troponin are harmless and without negative implications for prognosis.[19] In agreement with the outcome studies, the consensus documents define myocardial necrosis as an increase of cardiac troponin values which exceeds the upper reference limit of the healthy population, set at the 99th percentile of the value distribution to limit the number of false-positive designations of myocardial injury.[20] On the basis of current available data, however, it would seem reasonable to expect analytical methods to give an undetectable value or a very low troponin value as "normal". None of the commercially available troponin assays has shown acceptable analytical imprecision at these low concentration values to obtain accurate discrimination between "minor" myocardial injury and analytical noise.[22] In the context of clinical practice, a predetermined higher cardiac troponin concentration that meets the requested goal for desirable imprecision, i.e., a total coefficient of variation (CV) $\leq$ 10%, should therefore be used as the cutoff point for MI until the assays are improved.[23] The use of the actual 10% CV troponin concentration, instead of the lower 99th percentile reference limit, as decision cut-off could slightly decrease the clinical sensitivity of the biochemical criterion used for the MI diagnosis, but should permit physicians to avoid the occasional spurious increase in serum troponin concentrations resulting from analytical noise.

It is well demonstrated that the use of the new, more sensitive diagnostic criteria for MI leads to an average increase in the number of infarcts from 20% to 30% in patients admitted with suspected acute coronary syndrome (ACS).[24] However, the percentage of patients re-categorised from angina to MI is also critically dependent on the performance of the troponin assay used. Although higher precision at lower troponin concentrations does not automatically equate with higher clinical sensitivity, the use of a high-sensitivity troponin assay would allow identification of a substantial and additional proportion of patients with MI compared with a less sensitive troponin assay.[25]

Decision limits other than the 99th percentile and 10% CV values have been clinically defined for some of the cardiac troponin methods and used for risk stratification of patients with ACS.[19] Although the data from these clinical trials are compelling, the use of cardiac troponin for MI diagnosis is different from its use for risk stratification. Differences in the prevalence of ACS in different populations have to be considered and if the purpose of measuring cardiac troponin is only to risk-stratify patients with ACS for adverse events, consideration should be given to lowering the troponin cutoff below the 10% CV value. However, these low troponin cutoffs are not likely to be appropriate for the diagnosis of MI in a cohort of patients with chest pain and a lower prevalence of disease where false-positive results, produced by a cardiac troponin assay as a result of analytical imprecision, could have a much larger negative impact.

In addition to differences in the imprecision of the commercially available troponin assays, another possible source of disagreement between methods is the lack of standardisation of assays measuring cardiac troponin I (cTnI). More than 15 companies presently market assays for cTnI measurements by employing different standard materials and antibodies with different epitope specificities. Consequently, different results from different cTnI systems and assay generations may be obtained and this problem may cloud the interpretations of reported data, creating a substantial problem for the clinical and laboratory communities.[26] Theoretically, standardisation and traceability of cTnI measurements require a complete reference measurement system, including a purified troponin complex as the primary reference material, a matrixed (serum-based) secondary reference material and a reference procedure that can be used to assign a cTnI value to the secondary reference material and to evaluate the analytical performance of the field methods. Once obtained, the most important benefit of standardisation is the availability of common reference and decision limits for different commercial assays. However, until adequate cTnI standardisation is possible, reference limits and clinical thresholds need to be determined separately for each assay and platform.[27]

Due to the existence of an international patent, only cardiac troponin T (cTnT) assays from a single diagnostic manufacturer are commercially available, so that result standardisation for this marker is not a problem. On the other hand, a difficult clinical problem with cTnT is the significance of elevated concentrations commonly found in patients with renal failure but no clinical signs of recent myocardial damage.[28] Data from outcome studies have suggested that cTnT elevations are associated with added cardiovascular risk in uraemic patients although a persistent uncertainty remains concerning the connection between elevated serum cTnT and reduced renal function.[28]

Early detection of myocardial damage

Some practical aspects for optimising the sampling protocols and for combining, case by case, troponin measurements with other biomarkers in the clinical routine setting still need to be clarified.[29] In general, it is important that hospitals tailor their diagnostic strategies for the investigation of patients with suspected ACS to local circumstances and to the way that the test results will be used. One appealing approach relies on the use of a combination of two markers to enable the detection of MI in patients who seek care early and late after symptom onset. These should be a rapidly rising marker and a marker that takes longer to rise but is more specific, such as cardiac troponin.[1,7,30] This two-marker strategy is predicated on the assumption that early diagnosis will change care by providing the ability to discharge patients earlier, thus improving flow within the emergency department setting, and by facilitating identification of patients that may be candidates for aggressive interventions and, more generally, facilitating the triage of patients who are admitted to various parts of the hospital. Myoglobin is the marker that currently most effectively fits the role as an early marker.[10] Its concentrations in blood appear quickly, reaching the maximum between 6 and 12 h after the onset of symptoms. It then falls to normal over the next 24 h, rapidly cleared from the serum by the kidneys. Myoglobin has, however, low specificity for cardiac necrosis, so that the use of this marker requires associate cardiac troponin measurements to confirm myocardial injury and eliminate myoglobin false-positives.[31] Some studies have also shown a potential prognostic value for myoglobin in ACS patients.[32] It is however difficult to determine how these could apply to clinical practice.[33] With regard to the sampling protocol for detection of acute MI using the strategy employing early and late markers, specimen collections at the time of hospital admission and 4,8 and 12 h later has been recommended.[10,40,62] Shorter protocols have also been proposed to rapidly exclude MI in the emergency department.[34] Despite the undoubted success of myoglobin for detecting early myocardial necrosis in suspected patients 4-6 h after hospital admission, there is still a need for

the development of earlier markers that can reliably rule out myocardial damage from the emergency room at patient presentation and, hopefully, detect myocardial ischaemia both with and without the presence of irreversible myocyte injury.[35] Fortunately, both industry and academia are relentlessly producing an intense research effort to find new serum biomarkers that are released very early during myocardial ischaemic injury. Under investigation are two main classes of indicators: markers of early injury/ischaemia and markers of inflammation and coronary plaque instability and disruption.

Markers of cardiac ischaemia

Recent publications have explored the rationale for diagnosing myocardial ischaemia in advance, or in the absence, of the occurrence of irreversible damage.[35] As the explicit goal is to maintain micro-circulatory flow to prevent even minor infarctions, only a marker that precedes necrosis and permits the prevention of its consequences can meet clinical needs.[36] A marker of cardiac ischaemia could also be valuable in distinguishing acute MI from non-ischaemic causes of myocardial necrosis that lead to increases in cardiac troponins. The observed increase in free fatty acids unbound to albumin (FFAu) in the blood with acute myocardial ischaemia has recently been evaluated for the early identification of cardiac injury.[36] Two groups of investigators have preliminarily studied the sensitivity of this marker at patient presentation to the emergency room and have shown that FFAu elevations occur well before other, more traditional, markers of cardiac necrosis.[37] In particular, the sensitivity of FFAu at admission was >90% in both studies. The discovery that albumin, in the serum of patients with myocardial ischaemia, exhibited lower metal-binding capacity for cobalt than the albumin in serum of normal subjects was originally made by Bar-Or et al.[38] Based on these observations, an assay was recently developed in which the cobalt not sequestered at the N-terminus of albumin is detected using a colorimetric indicator.In sera of normal subjects, more cobalt is sequestered by albumin leaving less cobalt to react with the indicator. Conversely, in sera from patients with ischaemia, less cobalt is bound by the ischaemia-modified albumin (IMA), leaving more free cobalt to react with indicator. Significant changes in albumin cobalt binding have been documented to occur minutes after transient ischaemia induced by balloon angioplasty and to return toward baseline within 12 h.[39] However, increases in IMA could also be observed during ischaemia related to the injury of organs other than myocardium. In addition, a deletion defect of the N-terminus of albumin has recently been documented in a non-ischaemic individual that was responsible for reduced cobalt binding and, consequently, for false-positive test results.[40] Thus, the specificity of the measurement of IMA for myocardial ischaemia warrants additional investigation.

Markers of inflammation and plaque instability

Substantial evidence supports a pathogenic role for both local and systemic inflammation in ACS. In consideration of the important role that inflammatory processes play in determining plaque stability, recent work has focused on whether plasma markers of inflammation may help improve risk stratification and identify patient groups who might benefit from particular treatment strategies.[42] Of these markers, C-reactive protein (CRP) has been the most widely studied and much has been written and discussed regarding its relationship to inflammation, coronary artery pathology and coronary disease outcome. The landmark study by Liuzzo et al[43] showed that patients presenting with unstable angina and elevated plasma concentrations of CRP had a higher rate of death, MI and need for re-vascularisation compared with patients without elevated concentrations. In more recent trials, other investigators have confirmed the increased risk in ACS associated with higher CRP concentrations.[46] In each of the above studies, the predictive value of CRP was independent of, and additive to, cardiac troponin. More importantly, CRP was found to have prognostic value even among patients with negative cardiac troponin and no evidence of myocyte necrosis.[44] Methodological issues have however been highlighted and the independence between CRP and troponin release questioned.[87] Furthermore, the optimal cut-off for defining high CRP concentrations among patients with ACS remains to be determined. Finally, there is no evidence that CRP is helpful for identifying ACS patients who will benefit from a particular treatment.[45]

CRP is not the only inflammatory marker of coronary events that has been studied. Other biochemical parameters reflecting inflammatory response such as the classical white blood cell (WBC) count, or other more complicated and expensive markers of platelet, monocyte/macrophage and polymorphonuclear neutrophil activation, have been proposed. Increases in WBC have been associated with adverse clinical outcomes and a higher mortality rate in the setting of ACS.[47] With its simplicity and widespread availability, it could represent a very attractive marker for risk stratification in ACS. However, further research should be performed to determine if WBC could be used for targeting specific therapies.

CD40 ligand is a trimeric, transmembrane protein present in platelets and, together with its receptor CD40, is an important contributor to the inflammatory processes that lead to coronary thrombosis. After platelet stimulation, CD40 is rapidly translocated to their surface and then cleaved, generating a soluble fragment [soluble CD40 ligand (sCD40L)] having prothrombotic activity. Recent papers provided important information about the clinical relevance of sCD40L in ACS patients.[48] Elevation of sCD40L indicated an increased risk of cardiac events during six months of follow-up. Furthermore, in patients who were negative for myocardial necrosis, as assessed by cardiac troponin, sCD40L seemed to identify a further subgroup at increased cardiac risk, suggesting that measurement of sCD40L may have additive benefits if combined with the current biochemical standard for MI. Since these studies were primarily designed to assess various therapeutic strategies in selected groups of ACS patients and not to study the clinical value of sCD40L, their results should, however, be confirmed in specific studies performed on unselected populations. As sCD40L is known to be elevated in individuals with a broad spectrum of inflammatory conditions, a question on marker specificity also arises.

Myelo-peroxidase (MPO) is a mediator enzyme secreted by a variety of inflammatory cells, including activated neutrophils and monocytes/macrophages, such as those found in atherosclerotic plaque. It possesses pro-inflammatory properties and may contribute directly to tissue injury. Two recent experiments evaluated MPO as a predictor of cardiac risk in populations with different prevalences of ACS.[49] In both studies, a single measurement of plasma MPO at hospital admission predicted the risk of major adverse cardiac events in the ensuing 30-day and six-month periods. Even in the absence of myocardial necrosis, i.e., consistently negative cardiac troponin, baseline measurements of MPO significantly enhanced the identification of patients at risk. Also, MPO predicted adverse outcome independently of sCD40L; in ACS patients with undetectable troponin concentrations and

sCD40L concentrations below the established diagnostic threshold value, high MPO concentrations remained predictive for increased cardiac risk. This may imply that neutrophil activation represents an adjunct pathophysiological event in ACS that is distinctly different from platelet activation.

Monocyte chemoattractant protein-1 (MCP-1) is a chemokine responsible for the recruitment of monocytes to sites of inflammation that appears to play a critical role in the promotion of plaque instability.[50] In case-control studies, plasma MCP-1 concentrations were associated with restenosis after coronary angioplasty. However, in a prospective study on a large cohort of ACS patients, the distribution of MCP-1 values in the healthy subjects and the study population overlapped considerably. These seem moreover to be a general problem for all the markers of inflammation mentioned here, indicating that they are probably not useful for diagnosing unstable ACS in individual cases.

A growing understanding of the importance of atherosclerotic plaque rupture in the pathogenesis of coronary events has led to the identification of an expanding array of markers for plaque instability.[51] Experimental studies have demonstrated that phospholipase D enzyme activation and consequent release of choline in blood are related to the major processes of coronary plaque destabilisation.[52] Based on these processes, increased blood concentrations of choline have to be anticipated after plaque disruption and myocardial ischaemia in patients with ACS. In a recent study, choline detected troponin-negative patients with high-risk unstable angina with a sensitivity and specificity of 86%. Additional studies are however needed to fully investigate the clinical significance of this marker.

Pregnancy-associated plasma protein A (PAPP-A) is known as a high molecular weight (200 kDa) glycoprotein synthesised by the syncytio-trophoblast and is typically measured during pregnancy for Down syndrome screening. It was reported to be an insulin-like growth factor (IGF)-dependent IGF binding protein-4 specific metalloproteinase, thus being a potentially pro-atherosclerotic molecule. Bayes-Genis et al. showed the presence of PAPP-A in unstable plaques from patients who died suddenly of cardiac causes and described increased PAPP-A concentrations in the serum of patients with both unstable angina and acute MI. PAPP-A measurement appeared to be valuable for detecting unstable ACS even in patients without elevations of biomarkers of necrosis, such as cardiac troponins, thus potentially identifying high-risk patients whose unstable clinical situation might otherwise remain undiagnosed. Preliminary results provide evidence that circulating PAPP-A during ACS is different from PAPP-A isolated from pregnancy sera Physiologically, PAPP-A circulates in a hetero-tetrameric complex consisting of two PAPP-A subunits covalently bound with two subunits of the pro-form of eosinophil major basic protein (pro-MBP), its endogenous inhibitor. PAPP-A found in unstable plaques is conversely present as a homodimer, thus making it difficult to measure PAPP-A by immunoassays which are designed to detect intact molecules. Also, the kinetics of PAPP-A release and the corresponding optimal sampling protocols in ACS remain to be determined.

Cardiac natriuretic peptides

The last part of this review is devoted to consider the role and the importance that biomarkers are assuming in the clinical assessment of cardiac function. This is an area where biochemical tests have traditionally not played any role. With the recent clinical characterisation of cardiac natriuretic peptides, this promises to be an emerging field of Laboratory Medicine.

Natriuretic hormones are a family of related peptides with similar peptide chains as well as degradation pathways. Cardiac natriuretic peptides include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), while other natriuretic peptides, such as C-type natriuretic peptide and urodilatin, are not produced and secreted by cardiac tissue but by other tissues.[53] ANP and BNP derive from precursors, the pre-pro-hormones, which contain a signal peptide sequence at the N-terminal end. The pro-hormones are further split into inactive N-terminal fragments and the biologically active peptide hormones.

Whereas ANP is secreted mainly from atrial cardiomyocytes, BNP is preferentially produced and secreted in the left ventricle, although this may be a simplification, as the right side of the human heart also synthesises and secretes BNP in response to disease. The precise mechanisms controlling production and secretion of cardiac natriuretic peptides are still unclear, although ventricular stretch and wall tension are likely to be important. In general, the plasma concentrations of these peptides are increased in diseases characterised by an expanded fluid volume, such as renal failure, primary aldosteronism and congestive heart failure (CHF), or by stimulation of peptide production caused by ventricular hypertrophy or strain, thyroid disease, excessive circulating glucocorticoid or hypoxia. In agreement with a recent commentary[54], it is therefore surprising that researchers focused for so long on the single issue of whether cardiac natriuretic peptides identified left ventricular (LV) systolic dysfunction or not and did not recognise that these peptides should be used in a more general way in order to detect all cardiac abnormalities, including LV hypertrophy, LV diastolic dysfunction, atrial fibrillation and significant cardiac valve disease. It is now clear that measurement of cardiac natriuretic peptides in plasma does not unequivocally diagnose the specific underlying cause of a myocardial dysfunction but rather verify the need for further cardiac examination. High concentrations of these markers call for further investigations: echocardiography is therefore required to identify the underlying cardiac pathology, revealing the systolic and diastolic ventricular function and thus determining the appropriate treatment. This was instrumental for the ESC to incorporate cardiac natriuretic peptides in the first step for the evaluation of symptomatic patients suspected of having CHF.

Although the reliable role of cardiac natriuretic peptides in the identification and management of patients with symptomatic and asymptomatic ventricular dysfunction remains to be fully clarified, the clinical usefulness of cardiac natriuretic peptides (especially BNP and Nt-proBNP) in the evaluation of patients with suspected heart failure, in prognostic stratification of patients with CHF, in detecting LV systolic or diastolic dysfunction and in the differential diagnosis of dyspnoea has been confirmed even more recently. BNP and Nt-pro-BNP have also emerged as prognostic indicators of long-term mortality early after an acute coronary event. This association was observed across the spectrum of ACS, including patients with ST-elevation MI (STEMI), NSTEMI and unstable angina, those with and without elevated cardiac troponins, and those with and without clinical evidence of heart failure.[55] However, more work remains to be carried out to determine the optimal decision limits for clinical interpretation, as well as the specific therapeutic strategies of persistent cardiac natriuretic peptide elevation in these patients. Quite recently, plasma natriuretic peptide concentrations were also related to risk of cardiovascular events and death in apparently asymptomatic

persons.[56] Important issues related to the clinical use of cardiac natriuretic peptides are still open. A working list could include: the need of standardisation of cardiac natriuretic peptide immunoassays and of better definition of their analytical performance, with regard to the antibody specificity, calibrator characterisation and influence of pre-analytical factors; more complete understanding of cardiac secretion, molecular heterogeneity and metabolism of cardiac natriuretic peptides and knowledge of their biological variation; and, from the clinical point of view, possible differences between BNP and Nt-proBNP, definition of optimal decision limits and use in combination with other biochemical markers, clinical findings, or haemodynamic parameters. Additional studies are also needed to analyse the clinical relevance of cardiac natriuretic peptides in the patient follow-up, as well as their cost-effectiveness in different clinical settings.

Conclusions

Over the last 50 years, the contribution of Laboratory Medicine to the management of cardiac diseases has become increasingly sophisticated[2]. In the 1950s, Karmen et al. first reported that enzyme release from necrotic cardiac myocytes could be detected in the serum and could aid in the diagnosis of MI. The ensuing years witnessed progressive improvement in the cardiac-tissue specificity of biochemical markers and a corresponding enhancement in the clinical sensitivity and specificity of their use. For the foreseeable future, proteomic research for novel biomarker discovery is likely to give further significant contributions. There is now accumulating evidence that a multi-marker strategy, employing a patho-biologically diverse set of biomarkers, is likely to help significantly in the assessment of patients with cardiac disease.[57] In particular, markers of plaque destabilisation and/or markers of myocardial ischaemia could be added to the existing markers of cardiac necrosis and function in this paradigm if shown to contribute additional independent information.

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Metformin : a newer intervening agent for PCO

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Introduction

Polycystic ovarian syndrome is the most common cause of anovulatory infertility.[1] It affects 5-10% of women in the reproductive age group.[2] The disease is characterized by ovarian dysfunction, androgen excess and multiple cysts in the ovary. Clinically patients may present with oligomenorhoea, amenorrhoea, infertility, hirsuitism, acne & obesity. Women with this syndrome have at least seven times the risk of myocardial infection and ischemic heart disease than other woman, and by the age of 40 years upto 40% will have type -II diabetes or impaired glucose tolerance.[3,4]

Aetiology of PCO

The aetiology of the condition is unknown but more recently, insulin resistance leading to hyperinsulinaemia & excess ovarian androgenesis has been indentified as the the principal underlying disorder. Principal insulin resistance is most evident in overweight patients. Studies have shown that over 30% of lean & 75% of obese women with PCOS are hyperinsulinemic.[5] It is still not clear wheather hyperinsulinemia in all these women is secondary to insulin resistance. Further research in molecular biology revealed that there are two underlying defects in the insulin receptors, leading to insulin resistance and hyperinsulinemia. Type A syndromes is due to a point mutation in the DNA sequence coding for alpha & beta subunit of insulin receptor.[6] Type B syndrome is due to the presence of autoantibodies against the insulin receptor that is often associated with other autoimmune disorders. From a clinical point of view, it is evident that hersutism is a marker of hyperandrogenism and Acanthosis nigricans is a cutaneous marker of insulin resistance. Despite insulin registance in adipose & skeletal muscle, the ovary remain relatively sensitive to insulin. Both insulin & insulin like growth factor I have stimulatory effects on thecal andgrogen production.[7] Thus due to peripheral resistance there is relative excess of insulin that enhance ovarian stimulation. Along with this elevated leutinising hormone (LH) concentration brings about thecal hyperplasia, increased androgen secretion, arrests of follicular development and eventually anovulation along with menstrual disturbances. Insulin acts on liver & decrease the production of sex hormone binding globulin (SHBG) & insulin like growth factor-I binding protein. A reduction in SHBG leads to an increase in free androgen level. This high lavel of free androgen interfere with the normal physiological fuction of the hypothalamo-pituitary ovarian axis, leading to increase LH level, anovulation, amenorrhoea & infertility. On the other hand inhibition of production of insulin like growth factors-I binding protein results in an increased concentration of circulating free insulin like growth factor-I, further stimulating ovarian androgen production.[8]

Insulin resistance also lead to an outhead lipohytic response to insulin. It empairs the suppression of release of free fatty acid from adipose tissue. An increased flow of free fatty acid from central sitesenter the portal conculation, increasing the availability of substance to the lever for triglyceride production. Woman with the syndrome also exhibit increased activity of hepatic lipase, that is responsible for the convention of large lipoprotein particle to smaller, more atheongemic species.

Diagnosis of PCO

Diagnosis of the disease can be done on the basis of common clinical features, confirmed by biochemical evidence of endocrine abnormalities and by exclusion of other possible aetiologies.

Clinical features

- Oligomenorrhea or amenorrhea
- Dysfunctional uterine bleeding
- Anovulatory infertility
- Hirsuitism and or acne
- Central obesity

Clinical criteria sugessting insulin resistance are

- BMI greter than 27 kg/m^2
- Waist to hip ratio > 0.85 or
- The presence of acanthosis nigricans

Laboratary tests

- Increased testosterone activity.
- Elevated L.H concentration with normal F. S. H concentration.
- Presence of insulin resistance is evidenced by elevated fasting insulin concentration and elevated glucose-to-insulin ratio.[9] A significant issue is that the laboratory measurement of insulin is technicaly difficult.

Treatment : Treatment of PCO should address the following zones.

- Normalization of menstrual cycle.
- Treatment of infertility &
- Treatment of acne & hirsuitism.

Conventional Treatment of PCO

(1) The combind oral contraceptive pill (OCP) is commonly used to regulate menses. By increasing levels of sex hormone binding globulin (SHBG) and decreasing androgen secretion, it reduces the circulating free testosterone level. But many patient are overweight & obesity is a relative contraindication of OCP. So, this treatment may be unsuitable for obese patient with PCO.[10]

(2) Hirsuitism is addressed by the use of the antiandrogen cyproterone acetate or spironolactone. Their principal mode of action is inhibition of the binding of dihyrotestosterone to its receptor at the hair follicle. Benificial effects can be seen after 3 months but excessive hair growth returns soon after cessation of treatment, cyprotrene acetate way exacerbate irregularity of menstrual cycle are unsuitable for use in those trying to conceive.

(3) Ovulation inducing drug clomiphene citrate is used for the treatment of infertility. By inhibiting the estrogen mediated negative, feedback loop of hypothalamus, it enhances secrection F.S.H. But it carries an increased risk of multiple pregnancy. Also due to potential risk of ovarian cancer, it

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should not be continued more than 6 month.[11] Those failing to conceive after clomiphene treatment usually respond to exogenous gonadotrophin, but this is expensive, not available, needs special care during therapy and is burdened with the risk of multiple pregnancy.

(4) Alternative to Medical treatment includes laser or electrocutery of the ovary.

Modern Concept of treatment of PCO

As there is good evidence to support the hypothesis that reduced peripheral insulin sensitivity & consequent hyperinsulimia are pivotal in the pathogenesis of the diseases, so the modern concept of treating PCO is to reduce the level of insulin.

It can be achieved by-

(1) Reducing body weight- weight reduction has multiple benifit for obese woman with PCO.[12] The weight reduction decrease insulin resistance, corrects the hormonal imbalance, promotes ovulation & regular menses & improve the metabolic consequences of the disorder, but it seems to be hard to achieve.

(2) Insulin sensitizing agent, recent trials in different parts of the world has of the successfully process the efficacy of the drugs in treating PCO related problems.

Metformin : a biguamide, used in non-insulin dependent diabetis mealitus has been used most successfully. Troglitazone, a thiazolidinedione that improve muscle insulin sensitivity in muscle, has been studied, but has recently been removed from the market because of adverse effect on hepatic function. The key rational metformin for use of in women with PCO who are infertile is the presence of a positive correlation between the degree of insulin resistance & anovulatory infertility.[13] It is thought that metformin by suppressing hepatic gluconeogenesis & improving insulin resistance, reduces ovarian hyperandrogenemia & resistances normal ovarian steroidogenesis & PAI-1 levels, thus enhancing ovulation & improving fertility. It has also been shown to reduce systemic LH & PAI-1 levels, both of which increases the risk of miscarriage. It offers the real advantage over clomifen by avoiding the increased risk of multiple Pg (4-11%) and ovarian cancer (used >12 month).[14] First line use of metformin also avoid the cost associated with 2nd & 3rd line therapies for woman with PCO who are infertile, such as gonadotrophin used ovulation induction, laparoscopic ovarian drilling & in vito fertilization (IVF). It acts by improving insulin sensitivity, lowered serum LH, total free testosterone concentration increased in serum FSH.

Patient selection for metformin

It is offered as a first line drug to all women with anovulatory infertility due to PCOS who have; been trying to conceive for a year or more. Hypoglycaemia is extremely rare with if & patient are advised to look out for signs of hypoglycaemia & stop treatment this is suspected. General advise should be given to reduce weight (If BMI>30) stop smoking & alcohol. Pre & peri conceptional folic acid supplementation is given. Before prescribing metformin, renal & hepatic function should be checked as it may cause lactic acidosis, if there is mild renal impairment.

Dose regiment

The usual dose is 500mg TDS daily. To minimise GIT upset women are advised to take the drug prior to meal & increase gradually from once daily. The optimal period of first line metformin monotherapy for fertility is debatable. It may be continued for 6 months if regular ovulation is documented. However if it has not been effective after 6 months of treatment, clomifene should be added for a further 6 month. Metformin should be stopped once Pg is confirmed. Where Pg has not occurred after 1 year at either metformin alone or metformin - clomifene combination therapy, then alternative treatment, namely laparoscopic ovarian drilling, gonadotrophin or in vitro fertilization, should be considered.

Adverse effects & contraindication of metformin

The main immediate adverse effects are gastrointestinal- anoroxia, nausea, vomiting & diarrhoea. Long term use may interfere with vitamin B12 absorption. It may provoke lactic acidosis specially in Patient with renal impairment. It is also contrainicated in chemical conditions that predispose to lactic acidosis eg - severe dehydration, infection, shock, heart failure, recent MI, hepatic impairment & use of x-ray contrast media.

Conclusion

From many studies it can be concluded that, metformin can be offered to woman with PCOS who are anovulatory, whether obese or non-obese. It is suggested that first line metformin use is reasonable, particularly in the context of the hazands of 1st line clomifene use (ovarian cancer & multiple pg) with ovarian hyperstimulation. It has also been shown to reduce the risk of gestational diabetis in woman with PCOS. For the treatment of irregular menses caused by PCOS in women not attempting conception, it may restore ovulatory menses in the majority of the women. So, we can use metformin in the management of patients with anovulatory infertility in PCO before proceeding to ovulation induction with expensive & relatively risky drug like gonadotrophins as well as before in invasive and expensive treatment of ovarian drilling.

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Lumber sympathectomy : A review

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Introduction

The concept of sympathetic denervation as a mode of therapy for arterial occlusive disease was first elaborated and tested by Leriche and Jaboulay in 1913. Their experience with periarterial sympathectomy was disappointing because of reinnervation and vasospasm recurring within weeks of operation. Lumber synpathectomy (LS) or section of the lumber sympathetic chain and excision of one or more ganglia, was introduced by Royle in 1923 in the treatment of spastic paralysis of the lower extremites[1]. By the 1940s, lumber sympathectomy became the primary surgical treatment of arteriosclerotic occlusive disease and its sequalae in the lower extremity. However, the development of direct arterial reconstructive pocedures in the 1950, diminished the importance of LS as a primary operation. While the superiority of results achieved with arterial grafting and endarterectomy became well established, the use of LS declined considerably. Now except for selective circumstances, sympathectomy is rarely performed for lower extremity atherosclerotic vascular disease. Even with best indications, the effectiveness of LS remains controversial.

Anatomy

In the lower extremity the lumber sympathectic system exerts anatomic control over the vasconstriction, sweating and arrectores pilorum activity. Preganglionic neurons in the lateral grey substances of the spiral cord from the level of T_{10} to L_2 or L_3 send axons along the ventral nerve roots to the lumber sympathectic ganglia via white rami communicates. Preganglionic fibres then synapse within the gaglion or ascend or descend as the interganglionic part of the sympathetic chain to synapse with postganglionic neurons in the another ganglion of the chain. The postganglionic fibres exit through grey rami communicates to accompany the peripheral nerves. Postaganglionic fibres may arise from the 1st to the 4th or even 5th lumbar ganglion to travel with the lumbar and sacral nerves to the lower extremities. The foot and leg below the knee are primarily supplied by postganglionic fibres from the L_3 level and below.[2]

The limbar sypathectic trunk contains 4-5 ganglia. They lie retroperitoneally in front of the vertebral column along the medial borders of the psoas major muscles. Four ganglia are usually found in the lumbar chain, but the number may vary between 2 and 8 and rarely one continuos ganglion is found.[3]

Although the variations in position of the ganglia are common, the 2nd and the 4th lumbar ganglia are the more constant ones. The number of rami of any ganglion and their position between the spinal nerves and lumber sympathetic trunk show considerable variation. Cross communication between the right and left sympathectic trunk are also variable.[4] Knowledge of these variations in the anatomic structure may be helpful in performing correctly a lumber sympathectomy. It is to be mentioned here that, because most vascular problems that may require sympathectomy are confined to the foot, resection of 2nd-4th lumber gaglia is necessary.

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Effects of Sympathectomy

Studies to evaluate the effects of lumber sympathectomy on lower extremity blood flow have been done in animal models as well as humans : Cronenwett et al.[5] in the canine model demostrated increased capillary flow. They assumed this arteriovenous shunting was nonnutritive. Hoffman and Jepson[6] using the clearances of[133] xenon in patients found no increase in muscle blood flow after sympathectomy. In summary post sympayhectomy increase in blood flow appears to be mainly in the skin, and its is nonnutritive. Muscle blood flow in the other hand is unaffected.

Indications

Measurement of the physiologic effects of lumber sympathectomy would suggest that its indications are very limited. At present time all would certainly agree that direct reconstruction will deliver more blood flow to an ischaemic limb then lumber sympathectomy.

1. Intermittent claudication : Strandness and Bell[7], Taylor and Calo[8] did not find favourable response for lumbar sympathectomy in patients with claudication. The experimental and objective haemodynamic studies of patients before and after lumbar sympathectomy do not support a beneficial effect of lumber sympathectomy for claudication. Patient with claudication for whom reconstruction is not indicated should rather be advised to stop smoking, attain an ideal body weight and begin a graded exercise programe. Associated medical problems should be vigorausly treated.

2. Rest pain, nonhealing ulcers, gangrene : Patients with mild rest pain who may or may not have superficial nonhealing ulcer of the toes or foot and patients with digital gangrene are best treated with direct revascularisation procedures even to the tibial level.[2] Taylor and Calo[8] noted that 60% of patients with rest pain and localized lesions improved to only 28% in unoperated nonrandomized controls. Kim et.al.[9] obtained 62% and 47% improvements in patient with ulcers and rest pain respectivey. These enthusiastic results are balanced by report of Froysaker[10] who noted only 2 of 32 limbs with ulceration were improved by LS. Similar reports was also published by Pairoelero et al.[11] When comparing these somewhat favourable clinical results to the experimental work that indicated the increase in skin blood flow was nutritive, we have an apparent paradox. It may well be that patient selection is the key. Walker and Johnston[12] looked at 7 variables prior to and after phenol LS. These Variables were ankle systolic presssure, presence or absence of a somatic neuropathy, extent of ischaemic damage, presence or absence of diabetes mellitus, infection, age and sex. Among these the most important predictive variables were the level of ankle systolic pressure (greater than 30 mm Hg), absence of somatic neuropathy and minimal tissue damage. All authors[6,12] are in agreement on 2 points concerning patients with gangrenous lesions. First, extensive gangrene (deeper than skin and subcutaneous tissue) will not respond to LS alone. Second, all patients with with reconstructable peripheral blood vessel should undergo revascularisation. The debate concerns the value of LS in those patients for whom no reconstruction is possible. Enthusiasts rarely perform LS, sceptics do so often.[2]

3. Causalsia and vasospastic phenomena : All these may occur as isolated manifestations but are more often associated with occlusive arterial disease. The central role of the sympathetic nervous system is perpetuating causalgic pain makes sympathetic devarvation particularly suitable for this entity. Lower extremity vasospasm, cold intolerance and hyperhydrosis respond remarkably well to LS. However, prior to consideration of LS, maximal medical therapy with calcium channel blockers, cold avoidance and ceasation of smoking must be earnestly persued to overcome vasospasm. In the same way analgesics, tricyclic antidepressants, α^2 adrenergic blockers and physiotherapy should tried in a stepwise manner according to symptom of responsiveness of causalgia.

Predictive testing

In a search to better select patients who might have a favorable outcome from LS, numerous testing modalities like ankle brachial index (ABI), distal thigh arm pressure, toe temperature after nerve block, pedal arterial resistance index etc. have been offered. From a clinical standpoint a moist, cool foot with intact sensation would seem more favourable than a dry, insensitive foot. Most patients, however, do not fit these extremes. According to most of the authors, selection of patients for LS should be based on 3 simple assessment criteria, which were derived retrospective, multifactorial analysis designed to differentiate responders from nonresponders. These criteria are-

1. An ABI of greater than 0,3
2. Absent neuropathy on physical examination and
3. Limited forefoot tissue loss.[1,12,13]

The procedure

The anterolateral approach of Flowthow is most popular because the incision is well tolerated, dissection remains retroperitoneal and exposure is adequate. After proper dissection the lumbar sympathetic chain is located medial to the psoas muscle and lies over the transverse process of lumbar spine. The left lumbar ganglia lie adjacent and lateral to the abdominal aorta and on the right, just beneath to edge of the inferior venacava. Tactile identification of the lumber chain by plucking discloses a characteristics "Snap" as a result of tethering of the nodular chain by rami communicates. Other vertical band like structures in this region like genitofemoral nerve, paravertebral lymph nodes or ureter, do not recoil as briskly. Once identified the mid portion of the sympathetic chain is dissected free of surrounding tissues and retracted with a right angled clamp or a nerve hook to draw it up. The surgeon facilitates orientation and gangleon numbering by identifying the sacral promontory and an adjacent lumber vein that usually crosses the sympathetic chain in front of or behind the third lumbar ganglion. The chain and at least two lumbar ganglia are removed and hemostasis done. Other approaches for lumber spine are the posterior one of Royle and anterior of Adson. The posterior approach is not favoured because of significant postoperative paraspinal nerve spasm. The anterior approach is applicable only for LS combined with an abdominial aortic or other intrapertoneal procedure.[1]

In developed countries, the technique of laparoscopic LS has gained popularity in recent times. The time tested instruments, dissestion maneuvers along with videoscopic magnification, that have proved so effective in thoracoscopic dorsal sympathectomy are employed in LS.[14,15]

Complications of lumbar sympathectomy

Major complications result from failure to appreciate normal anatomic relationships with resultant injury to the genitofemoral nerve, ureter, lumber veins, aorta and inferior venacava. Most common complications following LS are postsympathectomy neuralgia, sexual dysfunction and failure to achieve the desired objectives of pain relief or tissue healing.

Postsympathetictomy neuralgia

It usually begins 1-2 weeks after LS and appears in upto 50% of patients. It is localised to the thigh (anterolateral), worse at night and rarely responds to medications. It usually remits spontaneously within 8-12 weeks.

Sexual dysfunction

It consists of retrograde ejaculation, and occurs in 25-50% patients undergoing bilateral LS including the L_1 sympathetic ganglia.

Failure lumber sympathetictomy

Failure to achieve the desired objective of pain relief or tissue healing is blamed on several factors. These include an incomplete sympathectomy as a result of a technically incomplete operation or as a result of cross innervation that makes a complete sympathectomy impossible. Latter recurrence may be caused by regenerating nerves or increased function of previously inconsequential crossed fibres.

Conclusion

LS has been included in the armamentarium of the vascular surgeon since 1924. Since the development of reconstructive arterial procedures, LS is much less commonly performed, because its effect do not support the clinical benefits of the operation. At present the role of LS in the modern managemnet of lower extremity vascular disease is quite minor. Causalgic pain remains its best indicaton. In addition there does remain a small group of patients with non-reconstrucable vascular occlusive disease, who will have a favourable response to LS. However, these benefits are usually short term. Proper patient selection and preoperative noninvasive vascular evaluation will render best results of LS in selected group of patients.

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The role of gynecologist in management of male associated infertility

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Introduction

A parimary diagnosis of a male factor is made in about 30% infertile couple[1]. When a couple failure to conceive for a reasonable period usually comes to a gynecologist for advice. Then the role of gynecologist is to ascertain whether the male or female factor is primarily responsible. In general, compared to female infertility, less is known about male infertility and the treatment out come have been poorer.

Initial evaluation of male partner

Due to social barrier the gynecologist cannot do physical examination of the male partner. So the initial evaluation of the male infertility should include a general health history and a specific assessment of factor contributing to infertility such as congenital abnormalities prior paternity, coital problems, exposure of toxin, previous surgery, previous infections (mumps orchitis), treatment. Drug and medications and general health (diet, exercise, review of systems) and a semen analysis at a minimum.

Coital problems

These include low coital frequency, impotence and ejaculatory disorders. The treatment in this area may range from psychosexual counseling to correcting organic causes of dyspareunia. In some cases, husband lives abroad and meet with wife once a week or 2-3 months yearly. So it is advised concerning the optimal timing of intercourse second daily for the 4-6 days spanning presumed ovluation.[4]

Normal semen parameter

A semen analysis usually excludes significant male factors. Optimum parameters are usually observed after 2-3 days of abstinence.

Semen analysis reference values (WHO 1999)[2]

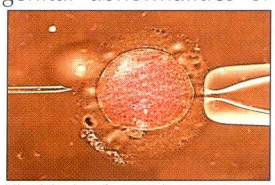
Volume	2.0 ml or more
P^H	7.2 or more
Sperm concentration	20 x 10^6 sperm/ml or more
Total sperm number	40 x 10^6 sperm / ejaculation
Motility	50% or more motile (grades a+b) or 25% or more with progressive motility (grade a) within 60 minutes of ejaculation.
Morphology	Not specified
Vitality	75 % or more live, excluding dye
White blood cells	Fewer than 50% motile sperm with beads bound
MAR test	Fewer than 50 % motile sperm with adherent particles

Management of the male with abnormal semen

If semen analysis reveals abnormal or borderline parameter, the history should be reviewed and the test should be repeat after 1 month because even a normal month, man exhibits significant variation in his semen parameter overtime[3]. If repeat semen analysis shows oligospermia or azospermia then serum. F.S.H (Follicle stimulating hormone), TSH (Thyroid stimulating hormone) is to be done. Then the gynecologist should refer the patient to an urologist or moern specialized centre for further therapy. The urologist should evaluate the man for evidence of varicocoele, testicular atrophy or other urogential abnormalities. Where the male is receiving drug therapy which depresses spermatogenesis, this may be able to be withdrawn or at least modified over a period of 6-12 months.

For infertile men with normal findings on physical examination & normal hormone parameters and whom no clear etiology of infertility exists, a number of therapies with no clear substantiation of benefits have been suggested. Hypothermia has been advocated particularly where scrotal temperature is higher than normal. Excessive exercise is to be avoided. There is no role of chlomiphene citrate or thyroid hormone in euthyroid individual[3]. Intrauterine insemination (I.U.I) has a success rate of 12-16% of oligospermia[1].

In case of azoospermia due to congenital absence of the vas, successful aspiration of the epididymis (MESHA) is to be done in the specialized center for artificial reproductive technique (ART). Azoospermia secondary to vasectomy, microsurgical vasovasostomy is frequently successful. Azoospermia with high level of FSH is due to congenital abnormalities or chromosomal abnormalities. In that case donor insemination or child adopion is to be advocated. So, the ultimate therapy for male factor infertility with abnormal semen parameter is ART which includes IVF (invitro fertilization), GIFT (Gamette intrafallopian transfer), ICSI (Intra cytoplasmic sperm injection) and ZIFT (Zygote intrafallopian transfer).



Microinjection of a sperm in a mature oocyte as part of invitro fertilization procedure

Conclusion

Last, and most importantly the gynecologist must know how to disclose the male infertility factors among the infertile couple because it is very sensitive issue and counsel them about next plan of treatment (adoption or ART). The couple is then referred to the urologist or modern specialized centers for ART. The gynecologist also gives the information about the success of further therapy.

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Influencing risk factors for increasing trends of Kala-azar in a rural community of Bangladesh

Mamoon ABA[1], Chowdhury MZU[2], Hossain M[3], Jahan K[4], Hoque MM[5], Chowdhury SA[6], Majumdar MK[7]

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Abstract

This was a descriptive type of cross sectional study carried out among the people of a selected village (Lahiripara) in Fulbaria upazila under Mymensingh district of Bangladesh. The study area was endemic for kala-azar. The objective of the study was to find out the influencing risk factors for occurrence of high rate of kala-azar infection. It also determined the sero-prevalence of kala-azar in that community. A total of 218 respondents were studied from 46 households. All the members of the households were interviewed and their blood samples were taken to find out the sero-prevalence by using ELISA test. In the study, 12.4% of the respondents were found sero-positive for kala-azar. Among the important risk factors like economic condition, 81.5% sero-positive cases had less than 4000 taka monthly family incomes. In addition, 81.5% of the sero-positive kala-azar cases lived in mud houses, 11.1% in tin houses and 48.1% of them had cracks and crevices in their house floor. Furthermore, 63.0% of the patients did not use mosquito net and 51.9% of them possessed cattle shade, which are also contributing factors for high rate of kala-azar infection. About the knowledge of spreading and prevention of kala-azar, it showed that 45.7% respondents did not know how the disease is transmitted. On the other hand, those who knew, among them 36.9% of respondents answered that the disease could be transmitted by food, 28.3% by close contacts with the patients and 21.7% by using clothes of patients & mosquito borne both. Only 2.1% replied that it was transmitted by bite of sand flies. Regarding prevention of kala-azar, 36.9% replied that it could be prevented by not using clothes of patients, 30.4% by avoiding used utensils of patients and 23.9% by using mosquito net. It showed that most of them had incorrect knowledge about the disease prevention and control which demands urgent B.C.C (Behavioral Change Communication) activities in the kala-azar endemic area from government as well as non-government level.

Keywords

Kala-azar, Risk factors, Sero-prevalence etc.

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Introduction

Visceral Leishmaniasis (VL), commonly known as kala-azar is a chronic febrile disease caused by the protozoan parasite, *Leishmania donovani* and its sub-species.[1] Kala-azar is characterized by chronic fever, hepato-splenomegaly, emaciation and anaemia.[2,3] Fever is of gradual or sudden onset. It is persistent and irregular, often with two daily peaks, with alternating periods of apyrexia and low-grade fever. Post Kala-azar Dermal Leishmaniasis (PKDL) may occur after the apparent cure of systemic disease.[4] It is a rural disease affecting peasants, male and youngs more and if untreated, has a mortality rate of almost 100%.[4,5,6] The disease agent is transmitted from the reservoir host to the susceptible host by a tiny insect usually known as sand fly.[2,3] Visceral leishmaniasis occurs widely throughout the world, viz South America, South Africa, the Mediterranean countries, India, Bangladesh and China. It is now endemic in 88 countries with a total 350 million people at risk.[4] Worldwide there are estimated to be approximately 500,000 cases of visceral leishmaniasis per year and many of them are associated with epidemics particularly in Indian subcontinent and Sudan.[7] The large number of endemic countries illustrates the global importance of the problem.[8] At present the disease is a re-emerging major public health problem in our country and has been reported from 41 out of 64 district. The number of cases is increasing and reports from the district health authorities indicate that >15000 new cases can be expected annually.[9] The current prevalence is estimated as 40,000 cases. The total population at risk is more than 20 million.[10] A recent study showed that the high prevalence of kala-azar positive cases were seen in the district of Mymensingh, followed by that of Tangail, Gazipur, Dhaka, Sirajgonj and Manikganj districts of Bangladesh.[11]

Now a day, the disease shows widespread geographical distribution and is being reported from previously non-endemic areas. Economic and demographic circumstances that contribute to increased prevalence include: new agro-industrial project, large-scale migration of populations, unplanned urbanization, and man made environmental changes.[12] Sand fly is found to take rest in cattle shades in much greater number than in human dwelling. The density of it here is 8-10 times higher than human dwelling. In human dwelling they are usually found inside cracks and crevices of the wall, loose bricks, behind furniture, underside the beds, in empty boxes and on hangings in the living room. Out door resting places are bushes, rodent's burrow, rat holes in trees and bases of banana clumps.[5] The risk of infection can be reduced by sanitation measure, viz elimination of breeding places (e.g., cracks in mud and stone wall, rodent borrows, removal of firewood, bricks or rubbish around houses), location of cattle shades and poultry at a fair distance from human dwellings and improvement of housing and individual protective measures such as avoiding sleeping on the floor, using fine-mesh net around the bed, insect repellents for temporary protection and keeping the environment clean.[4]

Methods and Materials

It was a descriptive type of cross-sectional study conducted in Lahiripara village of Fulbaria upazila under Mymensingh district. As kala-azar is endemic in Fulbaria upazila, the study

area was selected purposively. The sample size was calculated as 198 with error tolerated .01. The sample size was increased to 218 to cover all the members of the calculated 46 households. Multi stage sampling method was followed for the selection of the village of the study. Systematic random sampling method was followed with sampling interval 11 for the selection of households to collect the data. Every 11th house was selected based on GR number. Data was collected by using checklist and semi-structured questionnaire. Blood sample was collected from all of the members of households for laboratory diagnosis. Enzyme-Linked Immunosorbent Assay (ELISA) test was applied for the serological test of kala-azar. Test was done in the Microbiology laboratory of National Institute of Preventive and Social Medicine (NIPSOM) and Bangladesh Institute of Research and Rehabilitation in Diabetes Endocrine and Metabolic Disorders (BIRRDEM). SPSS software was used for the data entry and analysis.

Results

A total of 218 household's members were included in this study. Among them 12.4% persons were found sero-positive to kala-azar and risk factors of high rate of kala-azar infection are described below.

Figure - I : Household's members by serological test (ELISA) results for kala-azar (n=218)

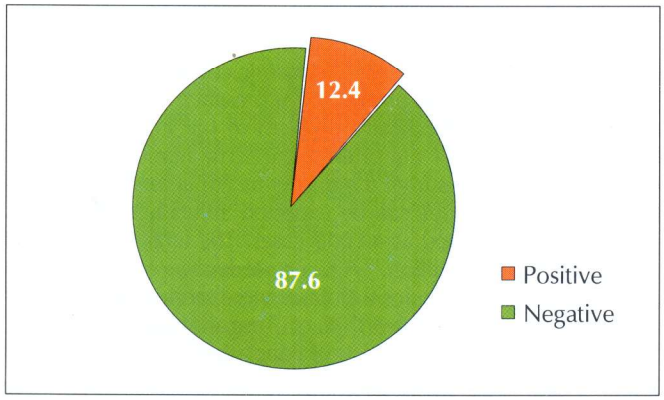

Table - I : Distribution of family income by serological test results (n = 218)

Monthly Family income	Serological test results		Total
	Positive	Negative	
< 2000 taka	14 (51.9%)	75 (39.3%)	88 (40.4%)
2001-4000 taka	8 (29.6%)	78 (40.8%)	88 (40.4%)
> 4000 taka	5 (18.5%)	38 (19.9%)	42 (19.2%)
Total	27	191	218

X^2 = 1.694 df =2 p = 0.429

Table - II : Occupation by serological test results (n = 218)

Occupation	Serological test results		Total
	Positive	Negative	
Student	13 (48.2%)	59 (30.9%)	72 (33.0%)
Farmer	7 (25.9%)	22 (11.5%)	29 (13.3%)
House-wife	2 (7.4%)	67 (35.1%)	69 (31.7%)
Day labour	1 (3.7%)	10 (5.2%)	11 (5.0%)
Businessman	1 (3.7%)	2 (1.0%)	3 (1.4%)
Dependant	2 (7.4%)	26 (13.6%)	28 (12.8%)
Service holder	0%	4 (2.1%)	4 (1.8%)
Others	1 (3.7%)	1 (0.5%)	2 (0.9%)
Total	27	191	218

Table - III : Types of houses by serological test results (n = 218)

Types of houses	Serological test results		Total
	Positive	Negative	
Mud-house	22 (81.5%)	144 (75.4%)	166 (76.1%)
Tin house	3 (11.1%)	25 (13.1%)	28 (12.8%)
Thatched	2 (7.4%)	12 (6.3%)	14 (6.4%)
Tin-shade	0	10 (5.2%)	10 (4.6%)
Building	0	0	0
Total	27	191	218

Table - IV : Presence of cracks and crevices in the floor of houses by serological test results (n = 218)

Cracks and crevices in floor	Serological test results		Total
	Positive	Negative	
Yes	13 (48.1%)	84(44.0%)	97 (44.5%)
No	14 (51.9%)	107(56.0%)	121 (55.5%)
Total	27	191	218

X^2 = 0.166 df =1 p = 0.683

Table - V : Presence of cattle shade by serological test results (n=218)

Presence cattle shade	Serological test results		Total
	Positive	Negative	
Yes	14 (51.9%)	100 (52.4%)	114 (52.3%)
No	13 (48.1%)	91 (47.6%)	104 (47.7%)
Total	27	191	218

X^2 = 0.002 df =1 p = 0.961

Table -VI : Distribution of mosquito net users by serological test results (n = 218)

Using mosquito net	Serological test results		Total
	Positive	Negative	
Yes	10 (37.0%)	77 (40.3%)	87 (36.9%)
No	17 (63.0%)	114 (59.7%)	131 (60.1%)
Total	27	191	218

x^2 = 0.106 df = 1 p = .745

Table -VII : Knowledge of respondents about spreading of kala-azar (n = 46)

Mode of spread (knowledge)	Number of respondents	Percentage
Food borne	17	36.9%
Close contacts with patients	13	28.3%
Using clothes of patients	10	21.7%
Mosquito borne	10	21.7%
Water borne	2	4.3%
Sand fly	1	2.1%
Air borne	0	0%
Don't know	21	45.7%

Table - VIII : Knowledge of respondents regarding prevention of kala-azar (n = 46)

Way of prevention	Number of respondents	Percentage
Avoiding using clothes of patients	17	36.9%
Avoiding used utensils of patients	14	30.4%
Using mosquito net	11	23.9%
Cleaning surrounding bushes	6	13.0%
Avoiding sleep in cow shade	0	0%
Closing cracks & crevices of floor	0	0%
Using repellents	0	0%

Discussion

The purpose of the study was to find out the influencing risk factors contributing high rate of kala-azar infection as well as determination of sero-prevalence in the rural community. The major findings of the present study revealed that out of 218 people, 12.4% of them were found sero-positive to kala-azar. It indicates that the disease exists with a high magnitude in that endemic area of rural community. Moreover, it is seen that the disease is also wide spread in many areas of Bangladesh[11].

Kala-azar was more common among low socio-economic groups and usually strikes the poorest of the poor[4]. Primitive housing and low standards of hygiene increase the risk of transmission in peridomestic areas[6]. In the present study, it was found that higher number (51.9%) of sero-positive cases, the monthly family income was less than 2000 taka which as considered low. Besides, 29.6% of kala-azra patients had monthly income 2001-4000 taka that also may be considered low. So both the groups constituted (81.5%). In a study by Talukder[13] and Hossain[14] revealed that 61.9% and 76% of the kala-azar patients monthly income was less 2000 taka respectively. A study supported by WHO/UNDP/WORLD BANK/TDR revealed that about 90% of cases comes from low socio-economic groups.[15] So the results of this study consistent with findings of those studies. Though, no statistically significant relationship between kala-azar and economic condition was found (p value = 0.429, P > 0.05).

Kala-azar has an important relationship with occupation. The previous study carried out by Talukder[13] revealed that it was more common among farmers (25.9%), followed by students (20.8%). However, in this study kala-azar was more prevalent among student (48.1%), followed by farmers (25.9%). One of the reasons of the differences may be that due to poor socio-economic condition of the study area students might help their parents in farming in addition to their study. It is known that sand flies are found 8-10 times higher in cattle-shade than human dwelling.[5] In human dwelling they are usually found inside cracks and crevices of soil and buildings, earthen bowel for cow feeding, tree holes, bushes.[4,6] In our study most (81.5%) of the kala-azar patients dwelling houses are mud-houses. A study carried out by Hossain[14] revealed that 95.37% of kala-azar patient used to live in kaccha house. Another study showing that increased incidence of the disease among those who live in houses with walls made of mud and cow-dung.[5] The present study also stated that 48.1% of sero-positive kala-azar cases had cracks and crevices in the floor of the houses. Another study by Talukder[13] revealed that 61.9% had cracks & crevices in their house floor. But in a study by Hossain[14], showed that 95.4% had cracks and crevices in their house floor. From the above findings, we may conclude the dwelling in mud houses and presence of cracks and crevices in the floor of the house are the important factors in occurrence of kala-azar. However, no statistical significant relationship was seen.

The cattle shade remains in or near living room, the risk of occurrence of kala-azar increases more as sand fly found more in cattle shade. The Present study shows that 51.9% of sero-positive kala-azar cases had cattle- shade near or within the living room. In a study by Talukder[13] it was revealed that 68% had cattle-shade nears their living room and 5.4% keeping within living room. In a study by Hossain[14], it revealed that 47% kept their cattle within living room. The difference may be due to socio-cultural difference between two study areas. From the above findings presence of cattle-shade in or near the living house is an important risk factor for the disease occurrence. However, there was no statistically significant relationship (p value= 0.961, p > 0.05). The study also describes the relationship between mosquito net users with serological test results. Here it found that among the sero-positive cases, (63.0%) did not used to use mosquito net. But the association was not statistically significant (p value = 0.745, p > 0.05).

The study findings stated the knowledge of the respondents about spread and prevention of kala-azar. Interesting finding was that only (2.1%) of the respondents could answer the transmitting agent of kala-azar and the higher (36.9%) number of them replied that the disease should transmitted by food, followed by close contacts with the patients (28.3%) and 21.7% by using clothes of patients. Regarding prevention of the disease, the higher (36.9%) number of respondents replied that the disease could be prevented by avoiding using clothes of patient, only (23.9%) by using mosquito net. From the above findings it can be said most of them had incorrect knowledge about the disease prevention and control. No study was found regarding knowledge about the disease and its prevention and control among people of the endemic area in our country. However, a study was carried out in Nepal on 1988, showed that the villages had poor knowledge about transmission, with most villagers perceiving that mosquitoes, instead of sand flies were responsible for transmission of infection[16]. So result of this study can be considered as consistent with findings of other studies mentioned. Surprisingly, it is true that there is very limited active on going kala-azar prevention B.C.C (Behavioral Change Communication) activities in that area from government as well as non-government level, though the disease is hyper-endemic.

Conclusion

At present kala-azar is a re-emerging serious public health problem in our country. It is affecting mainly the poorest section of the society. The cost of treatment is very high which is very difficult for the patients to afford. Kala-azar can be prevented and controlled by early detection and prompt treatment of the cases in addition to adopting preventive measure. So emphasis has to be given to the prevention of kala-azar as the risk of infection can be reduced through health education and individual protective measures such as - avoiding sleeping in the floor, repairing cracks and crevices in the floor and walls of mud houses, using fine - mesh nets around the bed, insect repellents in the form of lotion and cream etc. keeping environment clean, not sleeping in cow shade to avoid bite of sand fly vector.

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Dry eye followed by diarrheal disease, is preventable

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The ORION 2006 ; 24 : 376-377

Abstract

Objective - Effect of acute diarrheal dehydration on cornea is studied. *Method* -This was a descriptive type of cross sectional study conducted on 27 patient attended on OPD Moulana Bhasani Medical College peadiatrics OPD. Data were collected through periodic observation and examination using a structural check list. *Result*-In acute diarrhea, blindness prevented by medication on eye and with the correction of dehydration was 81.5% [n-22] and 18.6% [n-5] patient were not possible to follow up due to severe dehydration, they were referred to hospital for correction of dehydration with I.V. fluid. *Conclusion* - In this study it was found that due to acute diarrheal disorder, large amount of fluid and electrolyte's loss from the body. Due to generalized dehydration cornea become dry, the natural protection of the cornea is lost. Cornea is invaded by bacteria and keratitis is developed. So in this study it was found during rehydration theraphy cornea also should be treated with artificial tear and antibiotic ointment to protect from dehydration followed by infection.

Introduction

Cornea is a transparent organ through which we can see the part of the brain; it has got 5 layers from out wards to inwards :

1. Corneal epithelium
2. Bowman's membrane
3. Stroma
4. Desment's membrane
5. Endothelium

Corneal epithelium is covered by tear film. Tear film have 3 layers-

1. Outer lipid layer prevent evaporation and lubricate the cornea.
2. Middle aqueous layer supply oxygen and acts as antibacterial function.
3. Mucous layer make corneal epithelium from a hydrophobic to a hydrophilic surface.

The main lacrimal gland produces about 95% of the aqueous component of tears and the acccessory lacrimal glands of Krause and wolf ring produce the remainder.[1] Diarrhea is defined as an increase in the frequency, fluidity and volume [>200g/d] of bowel movement.[2] Basically, diarrhea is the passage of loose or watery stools that may contain blood, pus or mucus. It is fairly common in children. In fact, the American Medical Association (AMA) says that, in the U.S., there are 20 to 35 million episodes of diarrhea in children every year. When children do have diarrhea, they can also have other symptoms including nausea, vomiting, stomach aches, headache, and fever.

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Inflammatory diarrhea occurs because of damage to the intestinal mucosal cell so that there is a loss of fluid and blood. Following gastroenteritis, there is severe loss of body fluid due to diarrhea & vomiting which leads to dehydration. Along with other organs, eyes also suffers from dehydration, which is evident by sunken eyes, lusterless cornea, and this is followed by bacterial invasion, as the natural protection is lost. Along with involvement of other organs of the body eyes also suffers from dehydration so production of tears is markedly diminshed.

Patients suffers from generalized malabsorbation,[3] due to huge amount of fluid, electrolyte and mucous loss, there were develop severe dehydration, malabsorbtion. All the secretion of the body becomes decreased. Secretion of tear also decreased, Eye become sunken, lid movement become slow. There was unstability of the tear film. So cornea become dry, antibacterial protection of the tear film is lost. Which invade bacterial or virus cause keratities. In our practice we saw that due to dehydration cornea become dry, natural protection of the cornea was lost. Dry cornea invade the bacteria cause keratities and other complication in the eye and make the patient visual handicapped.

Methodology

This was a descriptive type of cross sectional study, during the study period 27 patient were selected in OPD for first time. Who reported to OPD with dehydration due to diarrhea with eye involvement. Study limited on pediatrics patients only [1 to 12 yrs]. Particularly in children as they are more vernerable to dehydration by the diarrheal disorders, their eyes are more involvement in children than adults.

Through history of the patient from his guardian or mother, particularly cardiovascular, respiratory, G.I.T, and urinary system were taken. Local examination was done as follows-

- Corneal examination by ophthalmic loupe.
- Schirmer test.
- Fundoscopy by direct ophthalmoscope [if needed]

General examiniation, which is done by a pediatrician [PRD, MASK]

- Dehydration moderate to severe
- Mode of onset, character of the stool.
- History of vomiting.
- CVS, RS, US, etc.

Following patients were excluded from our study-

- Severely dehydrated referred to other hospital for I.V. fluid replacement, so lost from our study
- Anuria
- Other diseases along diarrhea.

Placebo trail is not possible as because severely dehydrated patient may loss their eye. It is prospective single method study. Dry eye due to dehydration was treated by artificial tear and antibiotic ointment along with treatment of dehydration correction. Maximum patients were treated with frequent oral rehydration fluid. Only 5 patients were treated by intravenous fluid due to severely dehydrated by hospital admission. Follow up on 24 hours, 72 hours, 7 days, 21 days, upto 3 months.

Results

Out of 27 patient, 22 patient were treated by artificial tear and antibiotic ointment and their cure rate was 81.5% [n-22] but other 5 patients attended OPD with severe dehydration, they were referred to hospital for correction of dehydration about 18.6% [n-5]. [Those cases were not look by Opthalmologist] At the end of follow up on 21 days -all eyes of patient treated with the protocol mentioned-found healthy & the normal cornea.

Discussion

Diarrhea is common in our country, among them cholera is highly endemic in Banglaesh. An estimated 100,000 to 600,000 cases occur every year in the country.[5]

Clinical manifestation of dehydration : Table-1

Clinical signs	Degree of dehydration		
	Mild	Moderate	Severe
Decrease in body wt	3-5%	8-10%	12-15%
• Skin Turgor Color Mucous membrane • Hemodynamics Pluse BP Perfusion	 Normal [+/-] Normal Dry Normal " "	 Decreased Pale → → → →	 Markedly decreased Molted or gray Parched. Tachycardia Low Circulatory collapse
• Fluid loss Urinary output Tears	Mild oliguria Decreased	→ →	Anuria Absent

Current physiologic changes induced by diarrhea

1. Acid-base disturbance, fluid loss.
2. Electrolyte depletion [hyponatremia], hypokalemia, hypocalcaemia, hypomagnesemia.
3. Malnurition, vitamin deficiencies.

Signs of hypokaelemia are apathy, muscle weakness, parasthesia's, and tetany. So diminish of normal blinking reflex also. Tear are evaporated from the cornea due to long time exposure to open air, on the other hand decreased secretion of tear is another cause for dryness.

On above such condition normal natural protection of the cornea was diminish. Cornea become infected, keratitis developed followed by corneal ulcer and perforation or it may be turn into endophthalmitis, which lead to blindness. Mucous secretion by globet cell diminished. Generally dry eye syndrome was treated by systemic steriod but in this study it was not necessary as the pathology of cornea was due to fluid & electrolytes imbalance. Along with rehydration therapy patient's cornea should be prevented by our protocol-i.e. use of artificial tear & antibiotic ointment. So treatment of dryness should be urgent as well as treatment of the eye.

Conclusion

In conclusion our recommendation is that, during diarrheal attack children should be corrected his dehydration as well as eye care by artificial tear and antibiotic ointment even in mildly dehydrated cases.

Aknowledgement

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Adult onset Still's disease (AOSD) : A case report

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Abstract

A 30 years old male was admitted in BIRDEM hospital with fever, sore throat, cervical lymphadenopathy. Investigations failed to establish a microbial etiology of fever and empirical treatment with numerous antibiotic failed to resolve fever. Patient became a typical case of PUO. Later, the development of evanescent skin rash and polyarthritis pointed to a possible rheumatological diagnosis. With the help of very high serum level of ferritin and fulfillment of diagnostic criteria- a final diagnosis of Adult onset Still's disease was made. Patient was treated with combinations of NSAID and DMARD leading to remission. AOSD is one of the causes of PUO and early and aggressive treatment can herald possible fatal deformity and sufferings.

Introduction

Adult onset Still's disease is a recently recognized systemic inflammatory disorder of unknown etiology and pathogenesis. It is likely to be the continuum of systemic onset juvenile arthritis. It was initially described in 1897 by George F. Still, a pathologist. The characteristic features of this illness have subsequently been reported in adults, as detailed by Eric Bywaters in 1971[1]. No etiopathogenesis has been acceptably proven for AOSD. An infectious etiology has been inferred based upon the prodromal sore throat, reflecting non specific cytokines mostly IL-5, IL-6, IL-18, TNF-α. Although the disease is a sero-negative chronic poly-arthritis, the initial presentation is almost always with fever and other non-specific manifestation . Most of the patients (about 75 %) are between 16-35 years age. Most striking manifestations are - quotidian fever, evanescent rash, prodromal sore throat, arthritis/arthralgia, malaise, weight loss. Because arthritis is typically late onset, patient had already under gone numerous investigations and courses of antibiotics for presumed infections , till it became a case of PUO. 5-6% of patients being evaluated for PUO may be diagnosed eventually as Adult onset Still's disease[2]. AOSD remains a clinical diagnosis of exclusion; with typical clinical features, laboratory abnormalities and absence of other explanations. Various diagnostic criteria have been proposed. Among them Yamaguchi criteria has the greatest sensitivity and specificity.

Case history

The 30 years old non diabetic, normotensive, non-smoker, married male developed fever, which was high grade with maximum temperature of 104°F, intermittent in nature, associated with chill and rigor, subsided by sweating . Fever occurred mostly at late night, persisted for 2-4 hours and then subsided. During fever patient felt extremely weak and tired. During that time patient was treated with oral antibiotics, initially Cephradine, then Azithromycin and Ciprofloxacin; keeping in mind differential diagnosis of-pharyngitis and enteric fever. Patient had neutrophilic leucocytosis, high ESR. Blood C/S, urine C/S, throat swab C/S, ICT for Malaria, triple antigen all were negative. With antibiotics fever decreased but without complete remission. About 2 wks of fever, patient developed rash with high swinging temperature. The rash was pink colored, maculo-papular, distributed on upper chest, back and upper limb. The rash was most noticeable at the height of temperature. The investigations revealed persistent neutrophilic leucocytosis, raised hepatic enzymes with normal bilirubin. All the microbiological tests were again negative. Chest X-ray, USG of whole abdomen was normal. At that moment, left cervical lymphnodes were palpable. They were 2 in number, firm , tender, discrete. A lymph node biopsy was done to exclude tuberculosis, it showed chronic non specific lymphadenitis. During that period patient was treated with I/V antibiotics-ceftriaxone, gentamycine, but there was no response. An echocardiogram was done to exclude infective endocarditis, revealed only minimal pericardial effusion. About one week after admission, patient developed arthralgia followed by arthritis involving multiple big joints, e.g. shoulder, hip, wrist, elbow. This pointed to a possible rheumatological diagnosis. Because of the combinations of high fever, arthritis, evanescent rash, sore throat and lymphadenopathy-Adult onset Still's disease was assumed to be a possible diagnosis. Serum RA, ANA, both were negative, CRP was positive and serum ferritin level was found to be significantly elevated. So with fulfillment of diagnostic criteria (yamaguchi criteria) and exclusion of other causes-a final diagnosis of Adult Onset Still's disease was made.

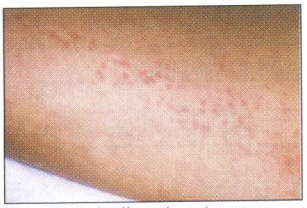

Fig-1: Typical still's rash on forearm

Patient was treated with NSAID. Aspirin was chosen and given in high dose - 2400 mg daily along with a proton pump inhibitor.[3] 4 wks after starting the treatment, most of the systemic features were improved with subsidence of fever, improvement of appetite & weakness. But the arthritis did not subside completely. Investigations showed persistent neutrophilic leucocytosis, high ESR, raised hepatic enzymes & serum ferritin level higher than before. So decision to start DMARD was taken. Hydroxy chloroquine was preferred over Methotrexate considering safety profile. 4 wks after starting Hydroxy chloroquine 200 mg daily along with Aspirin, the patient had complete clinical & biochemical remission.

Discussion

This multisystem inflammatory disease has some common articular and non-articular manifestations together with typical laboratory findings. Most common clinical features of AOSD are - arthralgia (98 -100%), fever > 39°c (83-100%), Myalgia (84 - 90 %), rash (87 - 90%), sore throat (50 - 92%).[4] Fever is an early feature, quotidian or diquotidian in pattern with rise of temperature in early morning/late afternoon. Patient with AOSD generally feel very ill while febrile & feel well when body temp is normal. This poses a dilemma for the

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physicians because hospital rounds usually do not occur during the times when the patient is febrile. Also here in this case the young male looked absolutely fine during morning rounds but the temperature chart showed high spikes at midnight associated with severe myalgia. So the patient received a number of antibiotics for presumed sepsis.

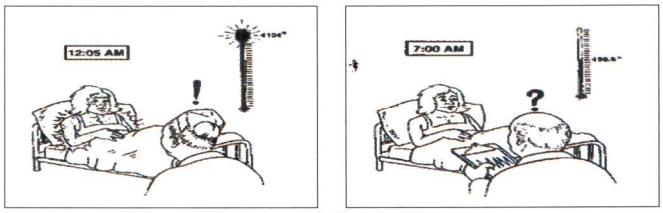

Fig-2: Temperature variation in Adult Still's disease

The rash of Still's disease is a salmon-pink colored evanescent rash, particularly on upper part of the body. It is often unappreciated unless specifically sought and may be seen only when the patient is febrile. The rash shows Koebner phenomenon and dermatographism. The patient also stated that he had similar rash for a few days before it could be particularly sorted out on careful examinations. Arthritis is often late onset and over shadowed by systemic features. This may be responsible for the disease being often categorized as PUO. The joints most commonly involved in decreasing frequency are - wrist, knee, ankle and elbows. Erosion & fusion of the carpal bones (50%), tarsel bones (20%), cervical spine (10%) may also be seen. A destructive arthritis is seen in up to 20-25% cases. Our patient developed arthritis more than 3 wks after the onset of fever & was characterized by large joint polyarthritis. Other clinical features include - lymphadenopathy (48-74%) splenomegaly (45-55%), hepatomegaly (29-44%), pleuritis (23-53 %), pericarditis (24-37%). Patients may present with complications like acute hepatic failure, aseptic meningitis, DIC etc. The characteristic findings in investigations are - elevated ESR>50 (90-100%), neutrophilic leucocytosis (71-97%), anaemia (59-92%), hypo albuminaemia (44-85%), thrombocytosis (52-62%), negative RA, ANA (90-100%). Our patient had almost all the above mentioned biochemical features. There is no single diagnostic test for AOSD. An extremely elevated serum ferritin level is suggestive of AOSD.[7] Although ferritin level may rise in other diseases and patient with AOSD may also have a normal ferritin level. A value of ≥1000 ng/dl in proper clinical setting being confirmatory of the diagnosis; specially if associated with low glycosylated ferritin level.[6]

Diagnosis of AOSD is one of exclusion, made in the setting of proper clinical features & laboratory abnormalities with the absence of other explanations such as infection or malignancy. Several diagnostic criteria have been proposed for the diagnosis of AOSD. Among them Yamaguchi criteria and Cush criteria are most popular.[7,8]

Yamaguchi criteria

Major criteria	Minor criteria
• Fever > 39°C. • Arthralgia /arthritis > 2 wks. • Still's rash. • Neutrophilic leucocytosis.	• Sore throat • Lymphadenopathy/Splenomegaly. • Hepatic dysfunction • RA/ANA negative.

Total > 5 criteria with 2 major criteria.[6]

Our patient fulfilled all the major & minor criterias of Yamaguchi criteria-along with fever, arthritis, rash, lymphadenopathy, sore throat, he had persistent neutrophilic leucocytosis, hepatic dysfunction and seronegativity. Because the disease is a inflammatory one, treatment is anti-inflammatory drugs. NSAIDs are the mainstay of treatment. Indomethacin/aspirin in high dose are mostly adequate to control the articular and systemic features. However more than 60 % patients require systemic steroid therapy with prednisolone, specially if systemic features are not adequately controlled by NSAID. DMARDs-Methotrexate, Hydroxy chloroquine are required if there is persistent articular features. TNF-α receptor blockers-etanercept, infiximab are the recent advances in therapy but costly and not available everywhere.[9,10] Resistant cases may be treated with I/V gamma globulin/Interferon-γ, plus cyclophosphamide, cyclosporine, mycophenolate mofetil.

Treatment of our patient was started with aspirin in high dose which was adequate to control the systemic features but not the articular features. So hydroxy chloroquine was added as disease modifying drugs.

Prognosis of AOSD is variable[2]. The median time to achieve remission with therapy is 10 months. One third patients have self limited disease with remission in 6-9 months. One third have intermittent features & one third have chronic progressive disease. There are some poor prognostic features such as - poly arthritis or large joint involvement at the onset, hepatic dysfunction & very high serum ferritin level >3000ng/dl. Though our patient had a number of poor prognostic features, he went into remission within 2 months of starting treatment & is still in remission 1½ year after initial diagnosis.

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Launching of New Products

Goldage

High Potency 32 Multivitamin & Multimineral

Gold standard for golden life

Goldage is a high potency multivitamin-multimineral supplement that containts 32 elements from vitamin A to Zinc. Goldage is a specially formulated preparation to fulfill the nutritional requirement to keep the body sound and healthy. It is indicated for the prevention and treatment of vitamins and minerals deficiencies. The usual dosage for Golden age (people of 11 to 50 years of age): 1 tablet daily or as directed by the physician. It is presented in a child lock plastic container as 15's and 30's pack size. MRP of 15's is TK. 90.00/ph and 30's is TK. 180.00/ph.

Silvage

Specially formulated multivitamin & multimineral supplement for 50+ adults

50 is the new forty

Silvage is a specially formulated multivitamin- multimineral supplement for Silver age (over 50 years of age) that contains 30 vitamins and minerals. This is specially adjusted with higher levels of certain age essential nutrients like calcium, B-vitamins and antioxidants to keep pace with age changing nutritional needs. Silvage is free from Iron and Tin, which has made it appropriate for geriatric patients. Silvage is indicated for the prevention and treatment of vitamins and minerals deficiencies. The usual dosage for Silver age (over 50 years): 1 tablet daily or as directed by the physician. It is presented in a child lock plastic container as 15's and 30's pack size. MRP of 15's is TK. 90.00/ph and 30's is TK. 180.00/ph.

Newage

Multivitamin- Multimineral Supplement

Blessings for the beginners

Newage is a specially formulated prenatal multivitamin and multimineral preparation. It contains 20 elements to fulfill the requirement throughout the pregnancy and during postnatal period for both the lactating and non-lactating mother. It also improves nutritional status prior to conception. Newage is enriched with Quercetin and Inositol which is essential for pregnant women. The usual dosage before, during and after pregnancy: 1 tablet daily or as directed by the physician. It is presented in a child lock plastic container as 15's and 30's pack size. MRP of 15's is TK. 75.00/ph and 30's is TK. 150.00/ph.

Pep plus

Zinc & Vitamin B-complex syrup

An ideal supplement for the growing children

Orion introduced the combination of Zinc & Vitamin B-complex under the brand name "Pep plus". Pep-plus syrup is a developed formula of Zinc and Vitamin B-complex. Zinc and Vitamin B-complex are the most vital micronutrients as they play crucial role in child's physical growth, mental growth & immunity. In Pep-plus Zinc is present as Zinc sulphate monohydrate and Vitamin B-complex comprises of Thiamine (B1), Riboflavin (B2), Pyridoxine (B6) and Nicotinamide (B3). Zinc is an essential trace element required for human nutrition and involved in a number of body enzyme system and Vitamin B-complex participates in many metabolic reactions to maintain good health and vitality. Pep-plus is indicated for the correction of Zinc deficiency problems like growth retardation, decreased taste and smell, alopecia, dermatitis, diarrhoea, immulogical dysfunction, failure to thrive and Vitamin B-complex ensures energy utilization from food, proper function of nervous system and facilitates RBC formation. Doses and administration: Adult 10 ml (2 teaspoonful) 2-3 times daily, Children 10 ml (2 teaspoonful) 1-3 times daily, Infant 5 ml (1 teaspoonful) 1-2 times daily.

Zoana

Nitazoxanide powder for suspension (100 mg/ 5ml)

The novel drug for childhood diarrhoea

Orion has introduced Nitazoxanide under the brand name "Zoana". Zoana (nitazoxanide) is a novel broad-spectrum antiparasitic agent for oral administration. Nitazoxanide is effective in broad range of protozoal and parasitic infections including 1. Giardia lamblia 2. Cryptosporidium parvum 3. Entamoeba histolytica 4. Ascaris lumbricoides 5. Hymenolepis nana 6. Enterobius vermicularis 7. Trichuris trichiura etc. Zoana is indicated in A) Diarrhoea caused by protozoa Giardia lamblia and Cryptosporidium parvum B) Amoebiasis and helminth infections. The usual dosage for Children (Age 1 to 3 years old): 5 ml (100 mg) every 12 hours for 3 days. Children (Age 4 to 11 years old): 10 ml (200 mg) every 12 hours for 3 days. It is important to take nitazoxanide with food. It is also very important to shake suspension well before measuring each dose. Zoana is highly palatable with orange flavour. The available pack size of Zoana is 32 ml & 62 ml powder for suspension. MRP of Zoana is Tk. 35.00 for 32 ml and Tk. 50.00 for 62 ml suspension.

Alve

Alverine citrate 60 mg Tablet

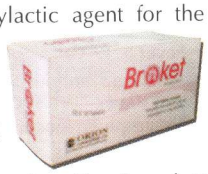
New treatment option for IBS

Alverine citrate is an antispasmodic which has a specific action on the smooth muscle of the alimentary tract and uterus. It is equally effective in reducing the muscular contractions induced by acetylcholine, histamine or 5 hydroxytryptamine. Alverine citrate also acts as an antagonist of calcium on the level of the cellular membrane and raises the cAMP by inhibition of the phosphodiesterase causing the relaxation of smooth muscle of gut. Orion has introduced Alverine under the brand name "Alve". Alve is available as 60 mg tablet form. Alve is indicated for Irritable Bowel Syndrome (IBS), Diverticular disease, and Primary dysmenorrhea. The usual dosage in adults: 60-120 mg tablet 1-3 times daily. MRP of Alve is TK. 4.00/Tablet.

Broket

Ketotifen tablet , 1mg/5ml syrup

Excellent prophylactic agent for asthma



Orion has introduced ketotifen under the brand name "Broket". Broket (ketotifen) is an orally active prophylactic agent for the management of bronchial asthma and allergic disorders. Broket is indicated in prophylactic treatment of bronchial asthma, symptomatic treatment of allergic conditions including rhinitis and conjunctivitis. It is presented in tablet and syrup form. Each tablet contains 1 mg ketotifen & each 5 ml syrup contains 1 mg ketotifen. The usual dosage in adults and children above 2 years of age: 1 mg tablet twice daily with food. It is presented as 100 tablets in one box, and 100 ml syrup in amber glass bottle. MRP of Broket is TK. 1.50/ tablet & TK. 40.00/ph.

MSD NEWS

Medical Services Department (MSD) of ORION Laboratories Limited successfully arranged significant number of Scientific Seminars, Internee Doctors Reception Program, Round Table Meeting etc. in different venues of all over Bangladesh in first quarter of 2006 as a part of their CME activities. Some snapshots of those programs are as follows.

Scientific Seminars

Scientific Paper Session-BMA Bhaban, Chittagong

A grand seminar was organized by Scientific Sub-Committee, Chittagong BMA, sponsored by Orion Laboratories Limited on 24th February, 2006 at Dr. Samiuddin Auditorium, BMA Bhaban,Chittagong. Prof. P. B. Roy, Surgery dept. & Prof. Mamoon Ur Rashid Safdar, Medicine dept., CMCH were chaired the session. Dr. Omar Faruque Yusuf, Scientific Secretary, BMA Chittagong was the convenor of the program. Prof. Md. Margub Hussain, Professor of Surgery, CMCH; Dr. Wazir Ahmed, Asso. Prof. of Neonatology,Chittagong Ma-O-Shishu General Hospital; Dr. S.A Karim, Registrar, Medicine, CMCH; Dr. Rokeya Begum, Asso. Prof. of Gynae & Obs. CMCH; Dr. Chowdhury Chiranjib Barua, Consultant Pediatrics; Dr. Md. Mahtabuddin Hassan, Asso. Prof. of Medicine, CMCH presented their scientific papers.

Prof. A.Z.M. Zahid Hossain, General Secretary, Central BMA delivering speech in the seminar

Disseminating Meeting on Community Based Training - RH Steps, SSMCH, Dhaka

A Disseminating Meeting On Community Based Training was held on 20th March, 2006 which was organized by the department of Gynae & Obstetrics, SSMCH, Dhaka and was sponsored by Orion Laboratories Limited. Prof. Mahmuda Khatun, Head, Dept. of Gynae & Obs. was the chairperson of the session.

Pediatric Surgery Department, BSMMU

Orion laboratories limited arranged a scientific seminar at Samad seminar hall, BSMMU that was organized by 'Association of Pediatric Surgeon of Bangladesh' on 21st January `06.

An Interesting Case of Jaundice with Anaemia - Gallery -I, Moulana Bhashani Medical College & Hospital, Dhaka

A seminar was organized by Medicine department, Moulana Bhashani Medical College & Hospital on `An Interesting Case of Jaundice with Anaemia' on 15th December 2005. Prof. Mokhlesur Rahman, Head of the Dept. of Medicine, Moulana Bhashani Medical College & Hospital was chaired the session. Total participant were about 125.

Documentary Video Show on Ceftriaxone

Conference Room, Cox`s Bazar Sadar Hospital, Cox's Bazar

A nice Video on `Vertex' was shown by Orion Laboratories Limited at Conference Room, Sadar Hospital, Cox`s Bazar on 17th December 2006. Doctors of Sadar Hospital were participated in that show. Dr. Abdul wadud Miah, Civil Surgeon was chaired the session.

Documentary video show - Hotel Media, Cox`s Bazar

Video show on `Vertex' was shown by OLL on 18th December at Conference Hall, Hotel Media International, with the general practitioner of Cox`s Bazar. Dr. A.K.M. Sirajul Haque, Ex-Civil Surgeon, Cox`s Bazar was the guest of honor.

Round Table Meeting

Pediatric Room, SBMCH, Barisal

Orion Laboratories Limited arranged a Round Table Meeting on `Management of Neonatal Infection with Zidim' on 15th March 2006 at Pediatric Room, SBMCH. Prof. Zahid Hossain, Head, Dept. Of Pediatrics, SBMCH was the chairperson of the session.

Dhaka Hospital (Pvt.) Limited, Dhaka

A round table meeting was held on `Sefin & Pep' on 19th February`06 at duty doctors room, Dhaka Hospital (Pvt.) Ltd. Dr. Ismail Hossain, Chairman of Dhaka Hospital (Pvt.)Ltd. Chaired the session.

Medicine & Cardiology Dept. Bogra Medical College Hospital, Bogra

Orion Laboratories Limited arranged a round table meeting on `Clognil Plus' at Northway Motel, Bogra on 13th February`06. Dr. Gazi Saiful Alam Chowdhury, Asst. Register, CCU, Bogra Medical College Hospital was chaired the session.

Surgery Department, Bogra Medical College Hospital, Bogra

A round table meeting on `Vertex' was held with the doctors of surgery department, Bogra Medical College Hospital on 14th February`06 at Northway Motel, Bogra. Dr. Samir Hossain, Asst. Register, Surgery, Bogra Medical College Hospital was chaired the occasion. Dr. G. M. Raihanul Islam, Medical Associate, MSD, Orion Laboratories Ltd. Was the speaker of the session.

Women's Medical College Hospital, Uttara, Dhaka

A round table meeting was conducted by Orion Laboratories Limited (OLL) on `Vertex' with the doctors of WMCH, Uttara on 7th December`05. Dr. Jesmin Akhter, Ass. Prof. of Gynae & Obstetrics, WMCH; Dr. Aktarunnessa, Asst. Prof. of Gynae & Obstetrics, WMCH were present on the occasion.

Medicine Seminar Room, MU-III, SBMCH, Barisal

A round table meeting on `Management of IBS' was held on 11th March`06 was organized by MU-III, SBMCH. Dr. Parvez Sumon, Asst.Register, MU-III, SBMCH was the chairperson of the occasion.

Medicine Seminar Room, MU-II, SBMCH, Barisal

A round table meeting on `Management of IBS' on 13th March`06 was organized by MU-II, SBMCH. Dr. Ferdous Wahid, Asst. register, MU-II, SBMCH was the chairperson of the occasion. Dr. Saidul Islam, Medical Associate, MSD, OLL was the speaker of the session.

Fatickchari Upazilla Health Complex, Chittagong

Orion Laboratories Ltd. arranged a round table meeting on `Reactin' organized by doctors of Fatickchari Upazilla Health Complex on 23rd February`06. Total participant of that program were about 25.

Amena Hospital, Bonpara, Natore

A RTM was held on 'Role of Multivitamin & Multimineral in Human Body' on 4th March `06 at Amena hospital, Natore. Dr. Ansarul Haque, MO, Gurudashpur THC, Natore was the chairperson of the meeting.

The rest of the MSD news at page -362

Medi News

What is the most essential elements...vital to our health?

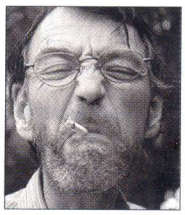
Surprisingly ZINC ! That's right..surprisingly..zinc! it's one of nature's most vital, essential elements. Humans, animals, plants and even the smallest micro-organisms need zinc to function. Zinc deficiency is a serious problem in many developing countries. Lack of zinc is ranked as the 5th leading risk factor in causing disease, especially diarrhea and pneumonia in childen, which can lead to high mortality rates in these under developed regions. Zinc supplementation and fortification programs could help overcome these problems as well as help growth among stunted children, another phenomenon associated with severe zinc deficiency.

There is no life without zinc. Zinc is found in all parts of our body ; it is in our organs, tissues, bones, fluids and cells. Because zinc is used to generate cells, it is especially important during pregnancy, for the growing fetus whose cells are rapidly dividing. And zinc is vital in activiting growth (height, weight, and bone development) in infants, children and teenagers. Zinc helps keep us going ..and enjoying our healthy, active lifestyles! Among all the vitamins and minerals, zinc shows the strongest effect on our immune system. Zinc has proven effective in helping fight infections and can even reduce the duration and severity of the common cold and more zinc enhances our memory and thinking by interacting with other chemicals to send messages to the sensory brain center. Zinc can also reduce fatigue and mood swings. Zinc is vital for taste and smell, it is needed for the renewal of skin clls and helps keep our hair and nails healthy. Zinc creams are used for babies and to heal cuts and wounds. Zinc also plays a vital role in fertility. In females, zinc can help treat menstrual problems and alleviate symptoms associated with pre-menstrual syndrome. In males, zinc protects the gland and helps maintain sperm count and mobility. Primarily we get zinc from our food- especially meat, poultry, fish and seafood, whole cereals and dairy products. A zinc supplement may be taken if your nutritional zinc intake is insufficient.

www.zincworld.org

Significant association between smoking and erection

Men who smoke a pack or more of cigarettes daily are 40% more likely to be impotent than non-smokers, finds research in Tobacco Control. The research team analysed the questionnaire responses of over 8000 men aged between 16 and 59 who were taking part in Australia. Almost one in 10 of the men said that they had had erectile problems lasting a month or more during the preceding year. More than a quarter of the respondents were smokers, one in five of whom smoked 20 or fewer cigarettes a day. Just over 6% smoked 20 or more a day. The results pointed to a significant association between smoking and erectile problems, which became stronger with increasing numbers of cigarettes smoked. When compared with non-smokers, those who smoked 20 or fewer cigarettes a day were 24% more likely to report difficulties maintaining an erection. Those smoking more than a pack a day were 39% more likely to report erectile difficulties.



www.bmjjournals.com

New malaria treatment guidelines issued

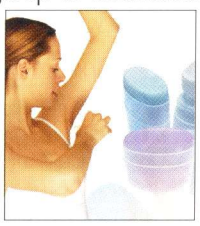
The World Health Organization (WHO) has issued new guidelines on malaria treatment and requested pharmaceutical companies to end the marketing and sale of "single-drug" artemisinin malaria medicines, in order to prevent malaria parasites from developing resistance to this drug. Malaria, causing acute illness in more than 350 million people each year. It can be cured by combined treatment with artemisinin, a medicine derived from the sweet wormwood plant, and a second anti-malarial drug. When used correctly in combination with other anti-malarial drugs in Artemisinin Combination Therapies (ACTs), artemisinin is nearly 95% effective in curing malaria and the parasite is highly unlikely to become drug resistant. ACTs are currently the most effective medicine available to treat malaria. "It is critical that artemisinins be used correctly," said Dr LEE Jong-wook, WHO's Director-General. "We request pharmaceutical companies to immediately stop marketing single-drug artemisinin tablets and instead market artemisinin combination therapies only. "According to the new malaria treatment guidelines, uncomplicated falciparum malaria must be treated with ACTs and not by artemisinin alone or any other monotherapy because the use of single-drug artemisinin treatment, or monotherapy, hastens development of resistance by weakening but not killing the parasite. "So far, no treatment failures due to artemisinin drug resistance have been documented, but we are watching the situation very atten tively," said Dr. Arata Kochi, the newly appointed director of WHO's malaria department. "We are concerned about decreased sensitivity to the drug in South-East Asia which is the region that has traditionally been the birthplace of anti-malarial drug resistance." If we lose ACTs, we'll no longer have a cure for malaria, and it will probably be at least ten years before a new one can be discovered."

Right, PAHO Deputy Director, Dr. Joxel Garcia, and left, Dr. Arata Kochi, the director of WHO's malaria department.

www. paho.org

Deodorants - a risk factor for breast cancer?

Underarm deodorants or antiperspirants are an essential part of the modern day hygiene routine, but most underarm hygiene products contain chemicals that work to disguise odour and reduce wetness. They also contain preservatives which ensure the product continues to work for a long period. For years, the rumours surfaced that using underarm deodorant or antiperspirant can cause breast cancer. Scientists are now researching some of the chemicals in underarm hygiene products and parabens are one particular group of chemicals being studied. Scientists found that parabens behave as weak forms of the hormone estrogen. Parabens prompted the growth of breast cancer cells and the growth of uterine cells in mice in test tubes. A new report raises that the aluminum salts contained in many underarm deodorants could possibly increase a woman's risk of breast cancer. The researchers say they found six different kinds of parabens in the breast cancer tissue samples and all of the samples contained some parabens. They say the average concentration of all types of parabens in the samples was about equal to the amount that had prompted breast cancer cells to grow in test tubes in earlier studies.



Journal of Applied Toxicology

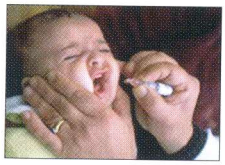
Medi News

More than a billion suffer from vitamin D deficiency

More than a billion may suffer from vitamin D deficiency. Consequences may be more severe than thought. Clinicians estimate that about half of the European population is suffering from mild vitamin D deficiency. Now a prominent European clinician has called for international action to address the problems which may lead to increased osteoporosis, cancer, and other diseases. The elderly and immigrant populations with darker skin are even the populations most seriously and most frequently deficient. Moreover insufficient vitamin D may have broader health consequences than previously thought. 2/3 of the UK Pakistani and Bangladeshi population is deficient of vitamin D. Vitamin D can either be obtained from food but natural food sources except fatty fish has a low vitamin D content. Exposure to sunlight can also produce vitamin D but the very same ultraviolet light is also responsible for accelerated ageing and cancer of the skin. Therefore, vitamin D intake should be increased by food supplementation. www.endocrinoloy.org

Diarrhoea vaccine tests 'hopeful'

Promising findings from two studies are offering the hope of a safe and effective vaccine against the most common cause of childhood diarrhoea. Rotavirus kills about 500,000 children a year in developing countries, and accounts for a third of hospital admissions from diarrhoea worldwide. The New England Journal of Medicine reports on tests of vaccines Rotateq and Rotarix involving 130,000 children. The studies found them to be 98% and 85% effective respectively, it says. The first study - involving more than 68,000 infants aged six to 12 weeks - found a vaccine called Rotateq, could safely prevent 98% of severe cases of viral diarrhoea and vomiting. Rotateq targets five major strains of rotavirus, which account for 90% of rotavirus disease. There were no more side effects seen in the vaccine group than their peers. The results of a trial of another oral vaccine called Rotarix, showed it was effective against the most common strain of rotavirus and able to prevent 85% of severe cases. www.bbc.com/health



Drug overdoses in feverish children

More than 50 per cent of feverish children are given incorrect doses of medicine by parents and overdoses have almost trebled in the last two decades, according to a research review in the latest issue of the British-based Journal of Advanced Nursing. Health professionals are also concerned about the increasing number of parents who give their children alternate doses of paracetamol and ibuprofen without leaving sufficient gaps between them. "Our review found that overdosing with ibuprofen is now a particular concern, both in terms of dosage and frequency " says researcher Anne Walsh. "We also discovered that some parents are giving their children one fever-reducing drug and then trying another type within a few hours if the first one doesn't have the desired result." "Overdoses have sharply increased over the last 20 years and recent studies have suggested that parents are giving children higher than recommended doses in about a third of cases.

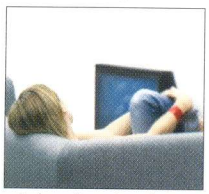
"Other parents under dose their children and, when their temperature hasn't reduced to a level they consider satisfactory, they seek professional assistance, placing burdens on already strained healthcare systems. Caring for a feverish child is emotionally challenging for parents and the limited improvements in knowledge, attitudes and practices highlighted by our research point to the need for a closer examination of the subject" says Anne Walsh. "Fever management education needs to highlight the benefits of mild fever and equip parents with the knowledge and skills they need to manage mild to moderate fevers. " www.journalofadvancednursing.com

Ceftriaxone may help fight dementia in HIV patients

An antibiotic commonly used to treat a variety of serious infections may also help prevent dementia in HIV patients, according to a test-tube study of human brain cells by Johns Hopkins University School of Medicine neurologist Jeffrey Rumbaugh, M.D., Ph.D. Rumbaugh added that, although ceftriaxone is FDA approved and could be used at any time by patients suffering from HIV dementia. The study looked at two proteins, called Tat and gp120, that are part of the virus that causes HIV infection and that are implicated in the development of HIV dementia, according to Dr. Rumbaugh. HIV is the only virus that makes Tat and gp120, which are produced during its normal life cycle, though other viruses make similar proteins. According to Rumbaugh, Tat and gp120 are believed to cause dementia by reducing the expression of a brain chemical called EAAT-2 (excitatory amino acid transporter-2). EAAT-2 absorbs the neurotransmitter glutamate from the space between neurons (the synapse), thereby preventing excess neuronal excitation, which in turn can cause cell death and brain damage. The dose of ceftriaxone needed for protection was well within the range currently used for treatment of bacterial infections. "These results indicated that this class of drugs may prove effective in treating HIV patients with dementia," Rumbaugh says. www.hopkinsmedicine.org

Watching too much television lead to extra weight

In a national study of more than one thousand preschool-age children, those who were exposed to more than two hours of television per day were more likely to be overweight at ages 36 and 54 months than those who were exposed to less than two hours of television per day, according to a study in the April issue of Archives of Pediatrics & Adolescent Medicine. The American Academy of Pediatrics recommends that children aged 2 years and older be limited to less than two hours of total TV time per day. Studies have linked excessive television viewing to a variety of problems, including risk of being overweight. Study shows that Less than one-third (31.7 percent, 322 children) were exposed to less than two hours of television per day, while 694 (68.3 percent) were exposed to more than two hours. About 5.5 percent of the children were overweight at the beginning of the study. Television exposure could contribute to increased weight in many ways, including through the advertising of unhealthy foods or the tendency of children to snack while watching TV. www.bbc.com/health



Information for Authors

The followings are the minimum requirements for manuscripts submitted for publication

The **MANUSCRIPT** should be prepared according the modified Vancouver style as proposed by the International Committee of Medical Journal Editors (ICMJE). The entire uniform requirements document was revised in 1997 which is available in the Journal of American Medical Association (JAMA. 1997; 277:927-934) and is also available at the JAMA website. Sections were updated in May 1999 and May 2000. A major revision is scheduled for 2001. The following section is based mostly on May 2000 update.

THREE COPIES of the manuscript should be sent in a heavy paper envelope. Manuscripts must accompany a covering letter signed by all authors. This must include (i) information on prior or duplicate publication or submission elsewhere of any part of the work as defined earlier in this document; (ii) a statement of financial or other relationships that might lead to a conflict of interest; (iii) a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship have been met; and (iv) the name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs. The letter should give any additional information that may be helpful to the editor.

A 1.44 MB 3.5 inch good quality **FLOPPY DISK** or **CD** must accompany the printed copies of the manuscript containing an electronic copy of the manuscript prepared in Microsoft Word 6.0 or later version.

PREPARE MANUSCRIPT AS PER THE FOLLOWING GUIDELINES

DOUBLE-SPACE all parts of manuscripts. TYPE or PRINT on only side of the paper. Number pages consecutively, beginning with the title page. Put the page number in the upper or lower right-hand corner of each page.

BEGIN, ON A NEW PAGE, each section or component with following sequence: title page, abstract and key words, text, acknowledgments, references. Tables, figures and illustrations may be positioned within the text where they should appear.

The **TEXT** of observational and experimental articles is usually divided into sections with the headings of Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections (especially within the Results and Discussion sections) to clarify their content. Other types of articles, such as case report, review, and editorial, are likely to need other formats.

The **TITLE PAGE** should carry (i) the title of the article, which should be concise but informative; (ii) the name by which each author is known, with his or her highest academic degree and institutional affiliation; (iii) the name of the department and the institution to which the work should be attributed; (iv) disclaimers, if any; (v) the name and address of the author responsible for correspondence concerning the manuscript; and (vi) sources of support in the form of grants, equipment, or drugs.

The **ABSTRACT** should be in second page and should usually be not more than 150 words for unstructured abstracts or 250 words for structured abstracts. The structured abstract should have following sections: (i) objective(s), (ii) methods, (iii) year and place of work, (iv) results, and (v) conclusion. The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations.

Below the abstract, authors should provide 3 to 10 KEY WORDS or short phrases that will assist indexers in cross-indexing the article and that may be published with the abstract. Terms from the medical subject headings (MeSH) list of Index Medicus should preferably be used.

Introduction should state the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

In **METHODS,** describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly. Identify the age, sex, and other important characteristics of the subjects. Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Precisely identify all drugs and chemicals used, including generic name, dose, and route of administration. Reports of randomized clinical trials should presents information on all major study elements including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatmen method of masking (blinding). Authors submitting review manuscripts are advised to include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

In **Results** section, when data are summarized, specify the statistical methods used to analyze them. Present your results in a logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alterative to tables with many entries; do not duplicate data in graphs and tables. Number tables consecutively in the order of their first citation in the text, and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Identify statistical measures of variations such as standard deviation and standard error of the mean. Do not use internal horizontal and vertical rules. Be sure that each table is cited in the text. Figures should be professionally drawn and photographed. Supply raw data in separate page so that the figures may be redrawn. For x-ray films, and other material, send sharp, glossy, black-and-white photographic prints, usually 127 x 173 mm (5 x 7 in) but no larger than 203 x 254 mm (8 x 10 in).

In **DISCUSSION** emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies.

Link the **Conclusions** with the goals of the study, but avoid unqualified statements and conclusions not completely supported by the data. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Acknowledgments may go as an appendix to the text, one or more statements may specify (i) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chair; (ii)acknowledgments of technical help; (iii) acknowledgments of financial and material support, which should specify the nature of the support.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

Use the style of the examples below, which are based on the formats used by the NLM in Index Medicus. The titles of journals should be abbreviated according to the style used in Index Medicus. Consult the List of Journals Indexed in Index Medicus, published annually as a separate publication by the library and as a list in the January issue of Index Medicus. The list can also be obtained through the library's web site (http://www.nlm.nih.gov/).

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the sources.

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Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be given in degrees Celsius. Blood pressures should be given in millimeters of mercury. All hematological and clinical chemistry measurements should be reported in the metric system in terms of the International System of Units (SI)

Use only standard **ABBREVIATIONS**. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

The **Chief Editor** reserves the right to style and formet and to determine the priority and time of publication of the accepted article. An edited copy of the manuscript is to be sent to the corresponding author for approval. The author is responsible for all changes in the manuscript. Articles are to submit to **Executive Editor : The ORION.**

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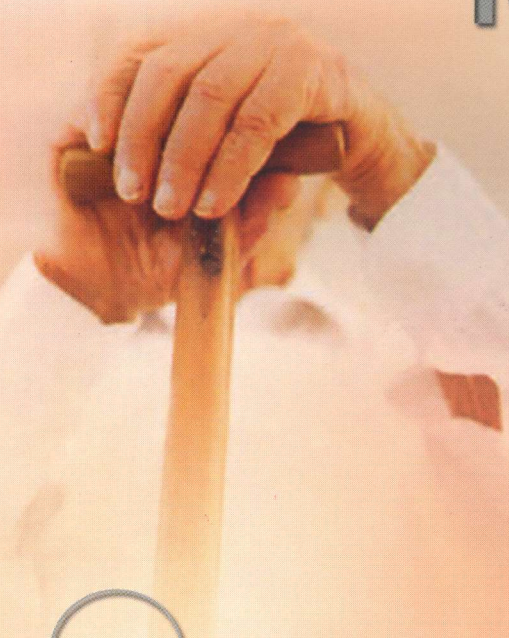

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