



IMSA

INTERNATIONAL MEDICAL SCIENCES ACADEMY

October - December 2009

Vol. 22 No. 4

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PRESIDENT WRITES

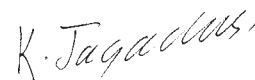
Dear Fellows and Members,

Our editor Prof. P. D. Gulati has chosen Type II diabetes as the topic for this issue of JIMSA. India is rapidly becoming the capital of this disease. Irrespective of this, it is a burning problem for patients, physician and the nation alike.

Uncontrolled diabetes affects every body system. So the management is directed at preventing these all important visceral complications. Our efforts must be directed to a cure for this condition. There are claims that Islet Cell Transplant, Pancreatic Transplant etc. will give relief to these patients. Work is in progress in many centres on gene manipulation. Hopefully, the efforts of various research groups will address this vital problem.

It has been decided to hold IMSACON 2010 on the 11th and 12th September 2010 at the Royal Society of Medicine, London. I am sure all fellows and members will participate with new thoughts and results to share with others.

Warm Greeting for a Happy & Prosperous Year 2010.



Dr. K. Jagadeesan
President, IMSA



IMSA/ JIMSA WEBSITE



www.imsaonline.com
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All fellows and members of IMSA can have access to the site and get information about its objectives, benefits to the fellows/members, chapters and their activities including seminars, refresher courses, rural CME;s etc. and also IMSACON - a regular annual event of international standard; *application form for enrollment as fellow/member can also be downloaded. Fellows - members and even not fellows - members can have access to full text in the quarterly journal - jimsa from July - Sept. 2003 onwards by putting their E-mail address under 'user name' and using the password 'UserJimsa'.*



Dr. P. Narasimha Rao

Ex. President, IMSA World H.Q.

Dr. Pinnamaneni Narasimha Rao International Award

Appeal by Vice-President IMSA



Dr. R.R.Thukral

Vice President IMSA World H.Q.

Dear Fellows and Members

You are aware late Dr. P. Narasimha Rao, an international figure both in academic and teaching had been the President of this prestigious organization for more than a decade from 1990 to 2002. He was President of Medical Council of India and Vice Chancellor of various Universities. He had to his credit several outstanding contributions to the medical fraternity till his death. He had been in close association with IMSA since its very inception in 1981. The Academy has flourished tremendously during his tenure as President. Keeping in view his status, services rendered to the mankind and on the insistence of senior Fellows, the Academy has established an International Award in his honour named 'Dr. Pinnamaneni Narasimha Rao International Award', on the lines of Dr. B.C. Roy National Award. Substantial funds are needed for this prestigious award. Initially, the family of Dr. P. Narasimha Rao has contributed a fair amount of money and has also assured to contribute more.

I appeal to all our Fellows and Members to contribute generously for this noble cause in the memory of this dedicated acadamecian - Dr. P. Narasimha Rao. A separate account has been opened for this Award.

(R.R.Thukral)

IMSA Chapter Activities

RCME Tamil Nadu Chapter

22-11-2009 : Dr. P.S. Sreemathi, "Cardiothorasic Emergencies in Pediatric Practice".

22-11-2009: Dr. C.R.Anand Moses, "Life Style Modification and New Drugs in Diabetes Mellitus".

Election of Fellows and Members (October-December 2009)

Fellows:

Dr. Ashok Kumar Janmeja, *Chandigarh*
 Dr. Swami Dass Mehta, *Chandigarh*
 Dr. V.S. Randhawa, *New Delhi*
 Dr. Krishna Dutt H Chavali, *Chandigarh*
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 Dr. Sudhir Kumar, *Chandigarh*
 Dr. Ravineet Kaur, *Chandigarh*

Members:

Dr. P.Venkata Krishnan, *Noida, U.P.*
 Dr. Himansu Pundir, *New Delhi*
 Dr. Rajinder Kaur, *New Delhi*
 Dr. Sukhvinder Singh Saggi.

Honour

Prof. N.S. Neki has been elected Fellow of Royal College of Physicians of Edinburg.

Announcement

Dr. Kamlesh Chopra has taken over as Secretary General, IMSA WHQ, in place of Dr. H.K.Chopra w.e.f. 01-12-09.

Dr. J.B. Sharma has been appointed as Treasurer, IMSA WHQ, in place of Dr. Kamlesh Chopra w.e.f. 09-12-09.

President & Board of Trustee, IMSA

Suggestions to Enhance Image of Medical Profession and Improve Doctor-Patient Relationship

President, Vice President and Trustees of IMSA have stressed that IMSA must engage itself in enhancing the image of Medical Profession by organizing seminars/conferences on various issues relating to medical profession, medico legal, patient—doctor relationship protocol of drug trials and research etc. It was also desired that suggestions be invited from all fellows and members, for improving relationship among doctors and patients. The Fellows and Members are, therefore, requested to send their suggestions & ways and means to IMSA World Headquarter at New Delhi, for enhancing image of medical profession and improving doctor—patient relationship.

Secretary General, IMSA

Change in Address

If the address of any Fellow/Member of IMSA has been changed, he may please intimate his latest address to IMSA, WHQ, New Delhi for future communication.

Dr.R.R.Thukral, Vice - President IMSA,WHQ

IMSACON – 2010 at London, U.K.

IMSA is pleased to inform its Fellows and Members that Annual Conference - IMSACON – 2010 will be held on 11th & 12th September 2010 (Saturday & Sunday), in London, U.K. Kindly confirm your participation in IMSACON- 2010.

For further details please contact:

Dr. Kamlesh Chopra, Secretary General, IMSA, WHQ, New Delhi, e-mail: imsawhq06@gmail.com



JIMSA

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October - December 2009

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Inland	Rs. 500
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FROM EDITOR'S DESK

Dear Colleagues

From time to time, it is important to ponder about the past, look at the present critically and also make an attempt to get a glimpse of the future; it is with this objective that every issue of JIMSA focuses on topics of current interest belonging to different disciplines of medicine through scientific editorials, updates, symposia, special issues. JIMSA instituted "best published article award" in the year 2005, so as to attract the medical professionals to contribute quality articles in JIMSA. The members of Editorial/Advisory boards of JIMSA planning to bring in more such incentives for contributors.

There is a growing and justified concern about the public health and economic impact of increasing population of diabetics in the country; India is emerging as the "Diabetics capital of the World". Oral hypoglycemic agents (OHA) have all along been the sheet anchor of drug treatment, especially for the large number of Type diabetic. During the last decade certain path breaking discoveries of new molecules have revolutionized the overall treatment and outcome of diabetes. An editorial by **Prof. Dinesh Dhanwal** contains an excellent critical appraisal of the new developments in OHA therapy. I am extremely grateful to him for his pains-taking efforts Published in the issue, is an update on "Anomia Management" which has adverse social implications; Another article describes a relatively complex surgical procedure which is perhaps the only hope for restoring sight in desperate cases of corneal blindness. Critical analysis of the 'Dangers from polluted water supply' provided in the article by Prof. D.S. Bhargava is quite relevant from public health point of view. A series of interesting original articles and case reports from different specialities appearing in this issue will, undoubtedly, provide useful reading. The issue also contains a **Symposium on Menorrhagia: Management Strategies** by **Professor Shubha S. Trivedi** of Lady harding Medical College New Delhi; I am extremely grateful to Prof. Trivedi and other contributors to the Symposium for brilliantly highlighting important aspects like diagnostic workup, medical and surgical treatment, of this common gynecological condition.

I take this opportunity to thank editorial/advisory board members for their help and suggestions; I am also thankful to various pharmaceutical firms for their help without which this publication will not have been possible.

*Wish to extend my good wishes to all readers of JIMSA for a
Happy, Healthy and Prosperous Year 2010*

P. D. Gulati

JIMSA BEST PUBLISHED ARTICLE AWARDS

Journal of International Medical Sciences Academy has instituted award for **three (3)** best original articles published during the previous 3 years; **guidelines** are as below:

- (1) **Original articles** belonging to any discipline of medicine published in JIMSA during the calendar year.
- (2) Award will be given to the Principal author/main researcher (co-author) of the selected article.
- (3) Number of awards: Three (3) annually, carrying a gold plated medal, citation and cash prize (1st Rs. 3000/-, 2nd Rs. 2000/-, 3rd Rs. 1000/-)
- (4) Awardee should preferably be a fellow/member of IMSA; non-fellows/ non members can also be considered for the award if the original work is outstanding; and if selected for the award will be required to apply for fellowship/membership of IMSA.
- (5) Awardees should preferably plan to receive the award at the annual IMSA conference - IMSACON.

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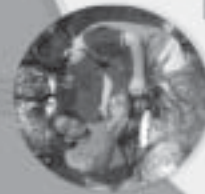
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ORAL HYPOGLYCEMIC AGENTS IN 21ST CENTURY: A CRITICAL APPRAISAL

India is in the grip of epidemic involving lifestyle diseases such as diabetes mellitus, hypertension, obesity and cardiovascular diseases. Diabetes in particular has caught the attention of world as India has become world capital of this disease. The profile of Indian diabetic patients is different from that seen in west such as they are thinner, younger and metabolically obese having low BMI. The management of diabetes mellitus has evolved with time since the discovery of disease. The race to reach the most appropriate glycemic goal has been attended by consequent development of multiple agents in the armamentarium of treating physician. Oral hypoglycemic agents are available to treat diabetes since 1956 when first generation sulfonylurea was introduced in form of tolbutamide followed by biguanides a year after. Since the introduction of these agents there have been additions of numerous oral hypoglycemic agents such as third generation sulfonylurea, glitazones, alpha glucosidase inhibitors. As of today physicians have choice for treating DM including new generation sulfonylurea (glipizide, gliclazide, glimepride), metformin, pioglitazone, rosiglitazone, acarbose, miglitol, voglibose, netiglinide and repaglinide. Latest in the armamentarium of physicians are dipeptidyl peptidase inhibitors which have come in clinical practice in last two years. Future looks bright as in the 21st century physicians will not only have access to newer antidiabetic drugs from existing classes of drugs but also have novel agents like glycosuric agents which are being researched vigorously.

The pathogenesis of type2 diabetes involves three primary defects: insulin resistance, beta cell dysfunction and hepatic glucose overproduction. None of the currently available treatment options address the problem of islet cell dysfunction and they have their attending problems of lack of efficacy and side effects, hence there remain critical unmet medical needs in the treatment of this disease. Beta cell function is lost more than 50%, once hyperglycemia is diagnosed and unattainable glycemic control is often the result of ongoing deterioration of beta cell function. A novel approach in treating diabetes mellitus is to utilize the physiological actions of endogenous incretin hormones; glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), the intestinal hormones released in response to nutrient ingestion. Although the incretin defect was noticed long ago its therapeutic value has been recognised very recently. GIP is secreted by K cells from upper small intestine and GLP-1 is by L cells located in distal intestine when stimulated by intraluminal glucose. Incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose in the gut. The observation that an oral glucose load was more effective at releasing insulin compared with the same amount of glucose given intravenously led to this theory. Studies prove that both GIP and GLP-1 stimulate insulin release in glucose dependent manner in humans, contributing 50 – 70% of the postprandial insulin response and both are necessary for maintenance of normal glucose tolerance. Incretins stimulate insulin secretion only in presence of hyperglycemia with no response in normal or low glucose levels. Pathophysiology of diabetes mellitus also encompass a recently understood defect in incretin effect with decreased insulinotropic effect of GIP and decreased

blood levels of GLP-1. Research shows a 15% reduction in post prandial levels of GLP-1 in patients with diabetes mellitus. Although hyperinsulinaemia is a hallmark of the first years after diagnosis, the first-phase insulin response (peak after a glucose load) is impaired or absent early in the disease. This first-phase insulin response is caused by incretins secreted from the small intestine after an oral glucose load. GIP and GLP-1 are rapidly inactivated by dipeptidyl peptidase 4 (DPP 4), a member of serine peptidase family. Different pharmacologic strategies to enhance incretin effect in management of diabetes include continuous administration of GLP-1, DPP4 resistant GLP-1 analogues and DPP4 inhibitors. The DPP-4 inhibitors approach GLP-1 insufficiency by enhancing incretin instead of mimicking it. By inhibiting DPP-4, the enzyme responsible for the breakdown of GLP-1, agents such as sitagliptin and vildagliptin can prolong the action of GLP-1 and increase circulating levels. One of the major differences between the GLP-1 analogues and the incretin enhancers is that the former are proteins that must be injected, and the latter are chemicals that can be taken in pill form. Also, exenatide, being a protein must be kept in the refrigerator, while sitagliptin doesn't require any special storage. DPP-4 inhibitors tend to be weight neutral with no effect on appetite and gastric emptying, while GLP-1 analogues seem to cause weight loss in overweight individuals owing to their unique action of delayed gastric emptying and suppression of appetite by a yet unknown central action.

Other favourable effects of incretin hormones may have a therapeutic role in type 2 diabetes mellitus like inhibition of glucagon release, decreased hepatic gluconeogenesis, slowing of gastric emptying, central action in suppressing appetite with consequent weight loss, stimulation of replication and neogenesis and inhibition of apoptosis of beta cells of pancreas, later quality signifying importance as potential agent for the prevention of type2 diabetes. As incretin receptor activation is only coupled to stimulation of insulin secretion in the presence of elevated blood glucose, therapies that are based on incretin enhancement have a low risk of hypoglycemia, which is a problem with current therapies. As confirmed from studies, DPP4 inhibitors increase meal stimulated active GLP-1 and GIP levels by two to three fold, increase insulin and c-peptide levels, reduced plasma glucagon levels, reduced glycemic excursion following glucose tolerance test, dose dependently reduced HbA1c and fasting plasma glucose. DPP4 inhibitors may have a beneficial disease modifying effects of attenuating loss of beta cell mass and function and normalizing beta-alpha cell ratio on chronic therapy for 2-3 months. Thus, DPP4 inhibitors have the potential both for assisting in achieving glycemic goals in anti-diabetic therapy and for modifying underlying disease course by correcting the islet cell dysfunctions characteristic of the disease.

Studies have proven their role as monotherapy and as complementary adjuncts to ongoing oral therapy for diabetes mellitus. DPP4 inhibition have demonstrated even delay in the onset of overt diabetes, improvement in insulin sensitivity and reversal of glucose toxicity speculating their use in humans as a potential agent for the prevention of type 2 diabetes. Because of the efficiency, safety, tolerability and oral route of administration, it is expected that DPP4 inhibition may

be the first-line treatment of the early stage of type 2 diabetes, particularly in combination with metformin or thiazolidinediones. Concerns have been raised on selectivity of DPP IV inhibitors and side effect profile as inhibition of DPP8 and DPP9 (enzymes of same family as DPP4) have evoked severe toxicities in animal species. Thus, pharmaceutical efforts focused on identifying a highly selective DPP4 inhibitor for clinical development. Optimization of this series led to the discovery of sitagliptin (MK431) and vildagliptin (LAF237), highly selective DPP4 inhibitors for the treatment of type 2 diabetes, others in final stages of development are saxagliptin (BMS477118), alogliptin, demiglipitin, SYR322, PHX1149, GRC8200, ilethiozolidide. DPP4 inhibitors may have the greatest impact in patients who are early in the disease process; however, whether these agents are enough to get more patients to reach their target HbA1c levels or they simply delay the start of insulin therapy remains in question. GLP-1 analogue, exenatide is available in injection form only and its cost is prohibitive for average Indian diabetic patient. However it scores over other oral drugs such as sulphonylurea by reducing weight in obese diabetic patients and not causing hypoglycaemia. Oral DPP4 inhibitors available in India for patients include Sitagliptine and vildagliptine. Both these agents are equally effective and comparable in their adverse effect profile. The emerging aspect of these agents is their potential role in beta cell preservation. In patients with type 2 diabetes mellitus who had moderately severe hyperglycemia inadequately controlled by metformin alone, the addition of sitagliptin 100 mg once daily or vildagliptine 50 mg twice daily provided significant and sustained improvements in HbA1c and other glycemic endpoints, including fasting glucose and post prandial glucose. In addition, sitagliptin provided statistically significant improvements in markers of β -cell function. Overall, the addition of sitagliptin to ongoing metformin therapy was well-tolerated with neutral effects on body weight relative to placebo, low incidence of hypoglycemia, and no worsening of gastrointestinal adverse events. Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy was effective and well tolerated in these patients with type 2 diabetes who had not achieved adequate glycemic control with pioglitazone alone. Another study provides add-on efficacy and safety results for sitagliptin, compared with a standard sulphonylurea agent, glipizide, in patients with inadequate glycaemic control on metformin monotherapy. The study results demonstrate that sitagliptin was non inferior to glipizide in HbA1c-lowering efficacy. Although both treatments were generally well tolerated, sitagliptin had a considerably lower risk of hypoglycaemia relative to glipizide and produced weight loss compared with weight gain with glipizide. In one study sitagliptin 100 mg once daily significantly improved glycemic control and beta cell function in patients with type 2 diabetes with inadequately controlled on glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy. Sitagliptin is not currently indicated for use with insulin although there are clinical trials in progress evaluating this combination. While consensus agrees that there is a strong scientific rationale of sitagliptin use even in patients taking insulin, proactive promotion of DPP4 inhibitors use in combination with insulin should be avoided until we have the phase III clinical trial on this combination.

The addition of vildagliptin to on-going metformin therapy produced clinically meaningful dose-related reductions in HbA1c and fasting plasma glucose and appeared to reduce metformin-related GI adverse effects. Metformin patients who added vildagliptin (50mg qd or bid)

also experienced a beneficial effect on blood pressure, relative to placebo. Although suggestive, the influence of vildagliptin on blood pressure remains to be clarified. Two 24-week studies examining the combination of vildagliptin and pioglitazone showed that vildagliptin produces clinically meaningful reductions in HbA1c when combined with reduced-dose pioglitazone in drug-naïve patients and when added to full-dose glitazone treatment. A comparative trial versus rosiglitazone showed that vildagliptin produced a similar reduction in HbA1c, improved lipid measures, and did not produce weight gain compared with rosiglitazone. The addition of vildagliptin to insulin treatment produced a significant reduction in HbA1c that was particularly marked in older patients and appeared to reduce the frequency and severity of hypoglycaemia.

The most common adverse effects with the use of DPP4 inhibitors are upper respiratory tract infection (6.3% in the sitagliptin-pioglitazone group vs. 3.4% in the pioglitazone-only group), nasopharyngitis (5.2% in the sitagliptin group vs. 3.3% in the placebo group), urinary tract infections and headache (5.1% in the sitagliptin pioglitazone group vs. 3.9% in the pioglitazone-only group). Gastro intestinal side effects including nausea, abdominal pain, and diarrhoea have also been reported in some studies. DPP4 is a ubiquitous cell-membrane protein, expressed in many tissues, including lymphocytes, which has raised some concerns about the long-term effects of DPP4 inhibitors especially on immune function. It has been classified as schedule 4 prescription only medicine in poison schedule. DPP4 enzyme family also includes other members such as DPP8, DPP9 and QPP, and selective inhibition of DPP4 is highly desirable, because inhibition of two other enzymes, DPP8 and DPP9 has resulted in fatal toxicities in animal studies. The DPP 8/9 selective inhibitor produced alopecia, thrombocytopenia, reticulocytopenia, multiorgan histopathological changes, enlarged spleen and mortality in rats. This inhibitor also produced gastrointestinal toxicity in dogs. Furthermore, the DPP2 selective inhibitor produced reticulocytopenia in rats. The reported incidence of hypoglycemia in subjects receiving sitagliptin or vildagliptine is similar to that in control subjects.

Vildagliptin was generally well tolerated in phase III trials. One case of significant peripheral edema was reported. The most common adverse events reported with vildagliptin were mild and included nasopharyngitis, headache, and dizziness. Vildagliptin has been associated with very few episodes of hypoglycemia when used as monotherapy or in combination with other antihyperglycemic medications. No significant laboratory abnormalities have been observed during or resulting from trials involving vildagliptin. Potential of DPP4 to also cleave other bioactive may cause adverse events on administration of DPP4 inhibitors related to increased blood pressure, neurogenic inflammation, and immunological reactions however, no such adverse events have been reported in animal studies or in humans using DPP4 inhibition. Other reported adverse reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay. Isolated case reports of renal failure and rhabdomyolysis with sitagliptin and simvastatin exposure are quoted.

Very few case reports from Philippines also report fatal haemorrhages, leukaemia, eosinophilia, erythema, skin exfoliation during sitagliptin use raise suspicion.

There are few unsettled issues about DPP4 inhibitors. There are reports that commonly used antidiabetic drugs can affect circulating DPP4 activity. Metformin has been reported to reduce DPP4 activity in patients with type2 diabetes and in diabetic animal models. Metformin increased active levels of GLP-1 in obese, non-diabetic human males and reduced inactivation of exogenously administered GLP-1 in obese-diabetic (*ob/ob*) mice. There are reports of reduced serum DPP4 activity brought about by the thiazolidindiones, meglitinide, and nateglinide. There is theoretical risk of aggravation of hypertension. Sitagliptin, by blocking dipeptidyl peptidase IV, prevents metabolism of neuropeptide Y₁₋₃₆ and thereby increases the effects of neuropeptide. Y₁₋₃₆ released from renal sympathetic nerves on Y₁ receptors leading to augmentation of neuropeptide Y₁₋₃₆ induced enhancement of the renovascular effects of angiotensin II. The renal effects of dipeptidyl peptidase IV inhibitors in hypertensive diabetic patients merit a closer examination. To add to debate, a study in non diabetic hypertensives shows a decrease in blood pressure on administration of sitagliptin. Although presently not indicated for use in type1 diabetes, benefits have been suggested in combining DPP4 inhibitors with insulin therapy.

FUTURE ORAL AGENTS FOR DIABETES MELLITUS

Glycosuric agents: The kidney is important for the body's energy control. Glucose filtered from the blood in the glomerulus is reabsorbed mainly in the S1 segment of the kidney's proximal tubule, but when the capacity for glucose reabsorption reaches saturation, excess glucose is excreted in the urine. Two types of sodium glucose cotransporters mediate this reabsorption. The low-affinity sodium glucose cotransporter (SGLT2) is found almost exclusively in the kidney, and several mutations in the human SGLT2 gene can cause renal glucosuria. Although the high-affinity sodium glucose cotransporter (SGLT1) is expressed to some extent in the kidney and contributes to glucose reabsorption, it is mainly expressed in the small intestine. Although several reports concerning genetic mutations in human SGLT2 suggest that this molecule plays some role in glucosuria, pharmacological validation in intact animals is needed to support SGLT2 playing a critical role in renal glucose reabsorption. Several researchers have focused on the renal glucose reabsorption system as a way of improving hyperglycemia in type 2 diabetes mellitus, and SGLT inhibitors have been developed. Enhancement of urinary glucose excretion via SGLT2 inhibition leads to a negative energy balance, which is not really achieved by any existing clinical pharmacological inventions. Phlorizin lowers blood glucose without increasing insulin secretion and thus a SGLT2 inhibitor might improve hyperglycemia without hypoglycemia being caused by excessive insulin secretion. Thus, KanjuKastuno et al attempted to obtain compounds without unwanted properties of phlorizin (selectivity, bioavailability, and GLUT1-inhibitory effect of its aglycon). In this study, to elucidate the role of SGLT2 in renal glucose reabsorption, authors investigated the potency and properties of sergliflozin as a selective SGLT2 inhibitor in vitro and in vivo, and also evaluated the potency and properties of sergliflozin as an antidiabetic drug. In an oral glucose tolerance test in diabetic rats, sergliflozin exhibited glucose-lowering effects independently of insulin secretion. Any

glucose excretion induced by sergliflozin did not affect normoglycemia or electrolyte balance. These data indicate that selective inhibition of SGLT2 increases urinary glucose excretion by inhibiting renal glucose reabsorption. As a representative of a new category of antidiabetic drugs, sergliflozin may provide a new and unique approach to the treatment of diabetes mellitus.

Scientists in Australia (unpublished reports) have produced results that could silence the current debate about exactly how fat molecules clog up muscle cells, making them less responsive to insulin. The finding is an important milestone in understanding the mechanisms of obesity related insulin resistance, a precursor of Type 2 diabetes. These scientists have added to evidence that fat molecules clog up the cytosol, but not the mitochondrion, Kraegen and colleagues made one small change to a single muscle in one leg of a rat, allowing that muscle to burn fat molecules better. To do this, they overexpressed a protein (CPT1) that acts like a "gate" or "tap" to control entry of fat molecules into mitochondria.

The changed muscle burned more fat molecules and became significantly more responsive to insulin than the equivalent muscle in the opposite leg, which had not been re-engineered.

There is continuous interest in glucagon receptor antagonists, glucokinase activators, inhibitors of gluconeogenesis and glycogenolysis and activators of insulin signal pathways and coming few decades could see some new agents emerging from these. To conclude, in 21st century sulfonylurea are arguably the most cost effective glucose lowering agents either as monotherapy or in combination with insulin sensitizers. If incretin mimetics and DPP4 inhibitors are proven to have beta cell preservation then these agents could play an important factor in how the prescriptions for type 2 DM are written. For other future therapies such as glucosuric agents, GPPR 119 agonists, glucagons receptor antagonists etc. we need to wait and watch for their possible role in management of diabetes mellitus.

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THREE MONTHS COMPARATIVE STUDY OF EFFICACY AND SAFETY OF METFORMIN PLUS GLIBENCLAMIDE VERSUS ROSIGLITAZONE PLUS GLIBENCLAMIDE IN THE TREATMENT OF DIABETES MELLITUS

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Abstract: The objective of our study was to make a three months comparative assessment of the efficacy of metformin plus glibenclamide versus rosiglitazone plus glibenclamide in the control of glycemic status of patients suffering from type 2 diabetes with moderate hyperglycemia and to make a comparative assessment of safety profile of these drugs by monitoring their adverse drug reaction profile. In this single centre, single blind parallel group study patients were randomized to receive either metformin 500 mg twice daily and glibenclamide 5mg (gr1, n=30) or rosiglitazone 2 mg twice daily glibenclamide 5 mg once daily (gr2, n=30). All patients were thoroughly examined clinically and all biochemical parameters were recorded at screening and at termination of the study. HbA1C was reduced by 2.01% in group 1 and 1.99% in group 2. Fasting plasma glucose was reduced by 57.96 mg/dl and 52.04 mg / dl in the respective groups. PPG was also glucose was reduced by 93.50 mg/dl and 105.10 mg/dl respectively. A mean weight gain of 1.87 kg was observed in the rosiglitazone plus glibenclamide group compared to a reduction of 2.60 kg in the metformin plus glibenclamide group over 12 weeks. Metformin addition to glibenclamide significantly reduced triglycerides (-4.98% vs -1.31%) and increased HDL cholesterol (6.37% vs 4.19%) compared with rosiglitazone and glibenclamide. The significant reduction of total cholesterol (-5.36% vs -30.02) and LDL cholesterol (-6.05% vs -3.02) was also noted in the respective groups, both combinations were well tolerated. The double drug therapy demonstrated early and sustained reduction in fasting and post-prandial glucose levels; as also in glycosylated haemoglobin levels. Compared with rosiglitazone plus glibenclamide, addition of metformin to glibenclamide resulted in a better reduction of LDL, total cholesterol and significantly greater improvement in triglycerides level and HDL cholesterol level. Both combinations were significantly effective.

INTRODUCTION

Type 2 Diabetes is often characterized by hyperglycemia as a result of increased insulin resistance, in addition to deficit in insulin secretion, pancreatic B-cell dysfunction^{1,2} and is manifested in adipose tissue, skeletal muscle and the liver. Excess visceral adiposity, dyslipidemia and hypertension often accompany insulin resistance. This defect increase lipolysis in adipose tissue, elevates free fatty acid and leads to raised triglycerides levels. The inability to suppress hepatic glucose production is a major contributor to the fasting Hyperglycemia³. Post prandial hyperglycemia can precede fasting hyperglycemia. Hyperglycemia itself exacerbates insulin resistance and impairs insulin secretion. Thus interacting defects in multiple organs of pancreas, muscle, adipose tissue and liver generate the pathogenic milieu which results in diabetes. Various oral glucose lowering agents are now available that target the different pathophysiologic factors contributing to diabetes but once, initial monotherapy starts to lose its effect, long term management with combination therapy with two groups of oral antidiabetics having different mechanisms of action is often necessary⁴. Metformin improves glucose tolerance by lowering both fasting and post prandial plasma glucose. It decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization⁵. Metformin also reduced the cardiovascular complications of diabetes.

Studies have shown that thiazolidinediones, when used as monotherapy^{6,7} or in combination with either nsulfonylureas⁸ or with Metformin⁹ improve glycemic control. Rosiglitazone, a TZD, is a peroxisome proliferators activated receptor (PPAR) – γ agonists, that enhances the action of insulin mainly by suppressing gluconeogenesis in the liver and increasing glucose utilization in peripherals tissues, in particular, in skeletal muscle^{10,11}. Rosiglitazone reduces FPG, PPG, HbA1C, insulin and C-peptide and prevents the onset of

hyperglycemia. Clinical studies suggests that rosiglitazone has the potential to sustain a improve B-cell function in type 2 diabetes. Glibenclamide works by inhibiting ATP sensitive potassium channels in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening of voltage dependent calcium channels, thus triggering an increase in intracellular calcium into the beta cell which stimulates insulin release^{10,11}. The study was conducted to compare efficacy and safety of Rosiglitazone added to Glibenclamide with the commonly used combination of Metformin and glibenclamide over 12 weeks in the control of glycemic status of patients suffering from type 2 diabetes with moderate hyperglycemia.

MATERIALS AND METHODS

This was a prospective e, randomized, single blind, parallel group study conducted on 60 patients of type II diabetes. All patients gave written, informed consent to participate in the study which was conducted with the approval from Institutional ethical committee and in accordance with the good clinical practice guidelines of Govt. of India. The study was also carried out in accordance with the principles in the Declaration of Helsinki for Biomedical Research¹² on human subjects. The screening for the eligibility of the patients with type 2 diabetes were performed based on 3 major criteria.

- 1) Male and female patients in the age group of 25-65 years. (provided they would adopt contraceptive methods during study period)
- 2) Fasting plasma glucose level (FPG) ≥ 7.2 mmol/L or
- 3) Two hour post prandial plasma glucose level (PPG) 10 mmo /l. Exclusive criteria included patients with type I diabetes or ketoacidosis, type 2 diabetes with severe hyperglycemia (FPG 15 mmol/L or above,) transient ischemic attacks or stroke in the previous six months, pancreatitis, a history of myocardial infarction, symptomatic heart failure, polyposis, malignant disease in the previous

12 years, known hypersensitivity to the trial drugs, history of chronic alcohol intake, impaired renal function, acute or chronic liver disease and impaired liver function elevated, AST/ALT level; pregnant or breast feeding woman, were also excluded.

The **trial patients** received the test drugs for a total period of 3 months comprising of three monthly follow up visits. Eligible patients were randomized in two groups to receive combination therapy of either metformin and glibenclamide or rosiglitazone and glibenclamide. Patients of group 1 received metformin 500 mg twice daily and glibenclamide 5 mg once daily. The patients were followed up every month for 3 months. At each visit, thorough clinical examination was conducted and FPG, PPG levels were estimated. Routine blood biochemistry was done at baseline and at study and visit. Adverse events, as elicited from the history, clinical examination and review of the trial diary being maintained by the patients were recorded to assess the safety parameters.

Statistical analysis was performed using statistical version 6 software. Mean differences between groups were calculated with 95% CI and A two sided student's 't' test ($\alpha=0.05$) was performed. Data were presented as mean SD; p value < 0.05 was considered statistically significant.

RESULTS

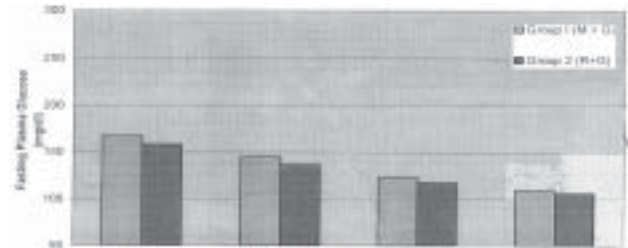
In total 60 patients received study treatment in two groups (n=30 with metformin plus glibenclamide; n=30 with rosiglitazone plus glibenclamide). Both the groups were evenly matched with respect to baseline demographic, disease duration and disease severity profile. The baseline glycemic indices i.e. fasting, post prandial plasma glucose and glycosylated haemoglobin levels were not significantly different (P>0.05) in the two groups. A mean weight gain of 1.87 kg (mean increase in BMI 0.77 kg/m²) was observed in the rosiglitazone plus glibenclamide group 1 metformin plus glibenclamide) and group 2 rosiglitazone plus glibenclamide) were inadequately controlled as evident by the mean baseline glycosylated haemoglobin levels of 8.19 + 0.89% and 8.08 + 0.65% respectively. After medication of three months, the mean glycosylated haemoglobin levels of group 1 and group 2 reduced to 6.18% and 6.09% respectively. The mean FPG level of group 1 reduced to 109.07 + 16.51 mg / dl from 167.03 + 25.79 mg / dl and that of group 2, reduced to 106.13 + 23.52 mg dl from 158.17 + 22.79 mg/dl when compared study end levels with baseline values. The mean PPG level reduced from 254.57 + 42.10 mg / dl to 161.07 + 36.50 mm / dl and from 260.13 + 28.99 mm / dl to 155.03 + 35.88 mg / dl for group 1 and Group 2 respectively when compared study end level with baseline level (table-I fig. 1,2,3, changes in total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol and VLDL cholesterol from baseline to 12 weeks are shown in Table 2 (Fig. 4-5). No serious adverse events were encountered during the entire course of the present study. In the rosiglitazone plus glibenclamide group, only one patient complained of vertigo but the clinical signs and plasma glucose level showed no substantial derangement. In the metformin plus glibenclamide group several patients had initial nausea and diarrhea episode, however they were non-serious and disappeared with therapy continuation. Although rosiglitazone is reported to cause hepatotoxicity. We did not detect any significant hepatotoxicity with rosiglitazone plus glibenclamide group therapy. There was no significant change in AST, ALT and ALK levels in both groups. They were found to be within normal ranges at study end.

No rescue medicines were used on any patient to control glycemic status as the study drug achieved the required glycemic control over the study period. Of other concurrent ailments present, only one patient in rosiglitazone plus glibenclamide group, had associated hypothyroidism and hypertriglyceridemia which was well controlled with levothyroxine and statin supplementation. Twelve (12) patients

Table -1: Serial Changes In Efficacy Parameters

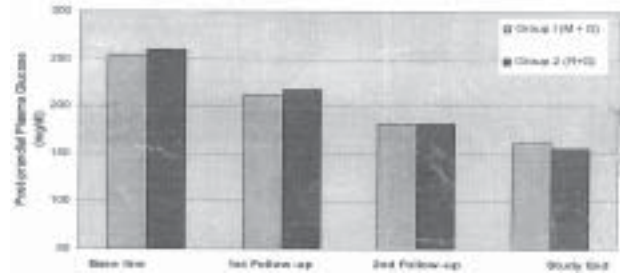
Item	Group	Baseline	1 st Follow up	2 nd Follow up	Study End
FPG (mg / dl)	Group 1 (M+G)	167.03 ±25.79	144.67 ± 20.57	122.93 ± 16.75	109.07 ± 16.51
	Group 2(R+G)	158.17± 22.79	136.70 ± 22.14	117.60 ± 20.03	106.13 ± 23.52
PPG (mg / dl)	Group 2(R+G)	254.57± 42.10	212.67 ± 40.91	181.80 ± 38.52	161.07 ± 36.50
	Group 2(R+G)	260.13± 28.99	218.33 ± 30.29	181.70 ± 32.23	155.03 ± 35.88
HbA1C	Group 1 (M+G)	8.19± 0.89			6.18 ± 0.71
	Group 2(R+G)	8.08 ±0.65			6.09 ± 0.72

All values are Mean ± SD; N=30 in each group FPG = fasting plasma glucose PPG = postprandial plasma glucose HbA1C = Glycosylated hemoglobin. Denotes p < 0.001 in comparison with baseline values in respective groups (paired test).



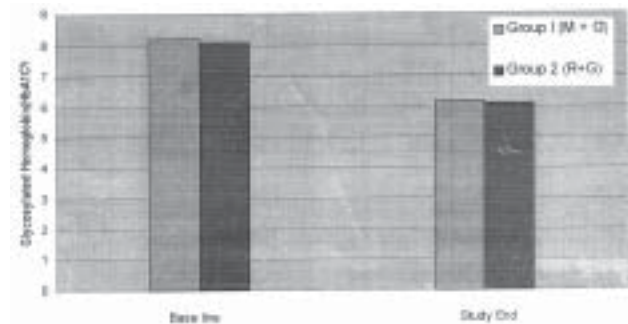
All values are mean ± SD of n=30; values are expressed in mg/dl

Figure 1: Serial Changes in fasting plasma glucose levels in both groups.



All values are mean ± SD of n=30; values are expressed in mg/dl

Figure 2: Serial Changes in Post-prandial plasma glucose levels in both groups.



All values are mean ± SD of n=30; values are expressed in %

Figure 3: Serial Changes in Glycosylated Hemoglobin levels in both groups.

belonging to group Metformin plus Glibenclamide and thirteen patients of rosiglitazone plus glibenclamide group were hypertensive and were on Enalapril with doses ranging from 5-10 mg daily. Their blood pressure levels were adequately controlled throughout the study period.

Table 2 Effects On Lipid Profile

Parameters	Group	Baseline	Study End
Total Cholesterol (mg/dl)	Group 1	174.80 ± 11.84	165.43 ± 10.53
	Group 2	170.17 ± 10.86	165.03 ± 8.45
Serum LDL (mg/dl)	Group 1	86.67 ± 10.35	81.43 ± 8.14
	Group 2	83.73 ± 6.99	81.20 ± 5.62
Serum HDL (mg/dl)	Group 1	41.30 ± 1.97	43.93 ± 2.33
	Group 2	40.57 ± 1.94	42.27 ± 2.02
Serum Triglyceride (mg/dl)	Group 1	130.50 ± 7.15	124.00 ± 8.61
	Group 2	127.60 ± 9.26	125.93 ± 16.89
Serum VLDL (mg/dl)	Group 1	23.60 ± 2.82	21.23 ± 2.11
	Group 2	23.57 ± 4.00	22.43 ± 4.53

All values are mean ± SD of n = 30 for both groups

Group 1: Metformin + Glibenclamide; Group 2: Rosiglitazone + Glibenclamide; HDL = High – Density Lipoprotein; LDL=Low Density Lipoprotein; VLDL =Very low – Density Lipoprotein

DISCUSSION

This study provides evidence supporting the use of combination therapy (metformin plus glibenclamide or rosiglitazone plus glibenclamide) in patients with type 2 diabetes mellitus with moderate hyperglycemia. The double drug therapy method used in this study demonstrated early and sustained reduction in fasting and post prandial glucose levels, followed by similar reductions in glycosylated haemoglobin levels. Rosiglitazone enhances insulin sensitivity in adipose tissue, liver and skeletal muscle and thus lowers blood glucose^{13,14}. This study also tried to assess the responders and their relationship with the other clinical characteristics such as body weight and BMI. The mean weight gain of 1.87 kg observed in rosiglitazone plus glibenclamide group may be observed in rosiglitazone plus glibenclamide group may be attributed to increased adipocyte differentiation¹⁵, fluid retention or increased appetite¹⁶ which suggests that Rosiglitazone treatment leads to increased energy storage in the subcutaneous adipocytes. Weight gain in type 2 diabetes is generally associated with worsening of insulin resistance and deteriorating in glycemic control. However, in this case, despite of weight gain of 1.87 kg over 12 weeks, there was an improvement in glycemic control. In the metformin plus glibenclamide group, there was a mean reduction of 2.01% in HbA1C after 12 weeks of treatment, similar to the reduction of 1.99% observed in the rosiglitazone plus glibenclamide group. The patients of both groups achieved an HbA1C < 7.0% after 12 weeks of treatment. The glycemic status of patients of both controlled in both the groups (GR.1 – paired difference 2.01 ± 0.55, Gr. 2 1.99 ± 0.47, p<0.01, in comparison with baseline, paired ‘t’ test). Mean fasting plasma glucose were reduced by 57.96 mg / dl and 52.04 mg / dl in the respective groups over study period. Similarly mean PPG was also reduced by 93.50 mg / dl and 105.10 mg / dl in the respective groups over study period. The mean reduction of FPG, PPG and HbA1C of both the groups were highly significant (p< 0.01). With metformin plus glibenclamide, the mean HDL Cholesterol was increased by 2.63 mg / dl and by 1.70 mg / dl in the rosiglitazone plus glibenclamide group. In the metformin plus glibenclamide group, mean triglycerides were reduced by 6.50 mg / dl and by 1.67 mg / dl in the rosiglitazone plus glibenclamide group. The significant reduction of mean total cholesterol (-5.36% vs -3.02%) and mean LDL Cholesterol (-6.05% vs -3.02%) was also noted in respective groups. Mean VLDL levels of patients of both the groups were reduced (-10.04% vs. -4.84%) at the study end. Improvements in HDL cholesterol, triglycerides, total cholesterol, LDL cholesterol and VLDL cholesterol with Metformin plus glibenclamide group were much better compared to rosiglitazone plus glibenclamide group. The total cholesterol to HDL cholesterol ratio (3.77 vs 3.90 of group 1 and group 2 study end respectively) gives an indication of the overall changes in the lipid profile and has been found to be a useful indicator of cardiovascular risk.

Both Metformin and rosiglitazone (when used with glibenclamide as

combination therapy) were highly efficacious oral anti diabetic agents. The three months duration of the study was intended to provide sufficient exposure to demonstrate the maximal therapeutic effect, as assessed by reduction in glycosylated haemoglobin levels, FPG and PPG levels. Various previous studies have shown that Thiazolidinediones used in combination with sulphonylurea or Metformin improved glycemic control. Analysis of the result of this study also shows that Thiazolidinedione (Rosiglitazone) is effective and well tolerated when used with sulphonylurea (glibenclamide). The other combination therapy of Metformin and Glibenclamide is equally effective in treatment. Use of intensive and demanding combination therapy for type 2 diabetes over a three months period if feasible and in the present study, it resulted in significant attainment of efficacy. The study also achieved control of FPG, PPG and HbA1C levels. No patients of the study group withdrew because of the therapy. Body weight was stable over three months intervention period.

CONCLUSION

This study was made to determine the best combination of drugs (either Metformin plus Glibenclamide or Rosiglitazone plus glibenclamide) for achieving target glycemic control in Type 2 diabetic patients. However, at the end it has been found that both combination of drugs are significantly effective but there is no significant advantage of one group of drugs over other in controlling efficacy and safety parameters of type 2 diabetes mellitus patients. These agents can, therefore, be prescribed (as combination therapy of metformin and glibenclamide or rosiglitazone and glibenclamide) as effective oral anti diabetic agents for control of mild to moderate degree of hyperglycemia in subjects of type 2 diabetes mellitus.

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EFFICACY OF ISOTRETINOIN IN ACNE VULGARIS

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Abstract : Isotretinoin was first introduced in India just over 5 years back. In this prospective study, efficacy and side effects of isotretinoin are evaluated in Indian subjects managed in a mid sized service hospital. Cases of nodulocystic acne, therapy resistant severe acne received 0.5 mg of isotretinoin per kg per day for a period ranging from 4 to 10 weeks, a total mean cumulative does of 24.2 mg per kg. A total of 14 subjects were treated with isotretinoin 12(86%) patients achieved the therapeutic goal and 2 (14%) had poor compliance or significant side effects forcing their withdrawal from the study. Adverse effects occurred in all the patients, but led to discontinuation of the drug in only one case. The clinical side effects were similar to those reported in literature except for minor differences in prevalence. Elevation of plasma triglyceride levels was the most significant laboratory adverse effect. The drug induced prolonged remission of active acne from lesions occurred in all cases that completed the therapy.

INTRODUCTION

Acne vulgaris is a common skin disease affecting nearly 80 percent of all people between the age of 11 and 30 years¹. Increased sebum production abnormal keratinization, Propionibacterium acne proliferation and inflammation affect the pilosebaceous follicles especially on the face, neck and upper trunk². Most cases are mild but it can persist and result in disfigurement and permanent and permanent scarring in over 50% of cases³. It is often associated with serious adverse effects on psycho-social development resulting in emotional stress, withdrawal from society and depression⁴. Modes of treatment include topical anti inflammatory and peeling agents, oral and topical antibiotics, hormonal agonists antagonists⁵. The introduction of 13 cis retinoic acid or isotretinoin has revolutionized the management severe cases of can to routine treatment. Isotretinoin is a synthetic vitamin A analogue belonging to the class of retinoids. Isotretinoin is the only drug that acts on all the pathogenic factors of acne. It was first used to treat severe recalcitrant nodulocystic acne and has gradually been accepted for other forms of severe acne as well⁶ It has recently been launched in India and we report our experience with this drug in the Armed forces in the Indian setting.

MATERIAL AND METHODS

In this prospective study, 14 subjects treated with Isotretinoin at MH Secunderabad were evaluated. The aim of the study was to establish the place of Isotretinoin in the treatment of acne and to note its clinical and laboratory side effect in our setting. Inclusion criteria were a) severe nodulocystic acne b) fulminans c) acne resistant to conventional therapy. All subjects were subjected to detailed clinical assessment including details of earlier therapy and advised removal of provocative / aggravating factors (Table 1). The drug was administered in the standard dose of 0.5 mg / kg body wt vis 20-40 mg / day as OD/BD schedule with meals rounded off to the nearest available preparation⁷. Topical antibiotics were the only other medications used during Isotretinoin therapy. The end point of therapy was reduction of more than 80% inflammatory lesions, a total cumulative does of 120 mg / kg body wt or side effects warranting stoppage of the drug.

Relevant hematological and biochemical investigations were done prior to the Institution of the drug and after completion of therapy. Subjects were assessed at 1-2 weeks interval while on therapy and at 2-4 week intervals after completion of the treatment. Patients were cautioned about the side effects of the therapy and asked to report back immediately if they developed any untoward problem. Women of child bearing age were warned against conceiving and advised suitable contraceptive measures prior to initiation of therapy, during treatment and for one month after

completion.

RESULTS

Twelve (12) of the 14 subjects were males with mean age of 21 years. All subjects had received conventional therapy earlier in the form of doxycycline and topical erythromycin / clindamycin or benzoyl peroxide / retinoic acid.

Table-1: Patient profile and Indication of Isotretinoin Therapy

S.No.	Age	Sex	Diagnosis	Previous Therapy
1	17	M	Resistant Acne	Doxycylice+Tretinoin Gel
2	24	M	Resistant Ac	Doxycylice+Tretinoin Gel
3	19	M	Resistant Ac	Doxycylice+Tretinoin Gel
4	16	M	Nodulocystic Acne	Mino cycline+Adalplene Gel
5	18	M	Nodulocystic Acne	Mino cycline+Adalplene Gel
6	25	M	Resistant Ac	Doxycylice+Tretinoin Gel
7	26	M	Nodulocystic Acne	Mino cycline+Adalplene Gel
8	22	M	Resistant Ac	Doxycylice+Tretinoin Gel
9	21	M	Resistant Ac	Doxycylice+Tretinoin Gel
10	22	M	Resistant Ac	Doxycylice+Tretinoin Gel
11	18	M	Resistant Ac	Doxycylice+Tretinoin Gel
12	17	M	Acne Fulminans	Minocycline / Amoxycillin/Clarithromycin+ clindamycin / Benzoyl peroxide Gel
13	31	F	Nodulocystic Acne	Mino Cycline + Oral Contraceptive + Adalplene Gel
14	18	F	Resistant Ac	Dopxycline + Tretinoin Gel

Response to therapy was seen in all patients after 2-3 weeks. Decreased oiliness of skin due to reduction of sebum was the first change. Pustules and papules decreased in a few weeks with decrease in appearance of new lesions and diminution of existing lesions. 2 subjects were required to be administered the drug for 4 weeks, 8 for 6 weeks and 1 for 8 weeks depending on the clinical response. The maximum duration of therapy was 10 weeks in one patient. The drug was stopped in one subject after one week as compliance could not be assured. In our study, on an average isotretinoin was required to be taken for just over 6 weeks to achieve good therapeutic results. The cumulative does in the majority of cases was only 15-35 (mean 24.2) mg/kg much below our initial anticipation. Improvement continued after stoppage of the drug establishing an overall response of 86% of our patients reaching the end point of our therapeutic goal (table 2) An occasional fresh papule appeared especially after stopping therapy in most subjects but regressed spontaneously or with topical erythromycin / clindamycin or benzoyl peroxide. None of the subjects required a second course of isotretinoin in a follow up period of 6 months -11/2 years.

Table 2 Clinical Effects of Isotretinoin Therapy

S.No.	Isotretinoin dose (mg / d)	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	Duration of therapy (weeks)
1	30	Dryness	Lesions Reduced*	Lesions Reduced*			04
2	40	"	No new Lesions				06
3	30	"	Lesions Reduced*				04
4	30	"	No new Lesions	Lesions Reduced*06			06
5	30	"	No new Lesions	Lesions Reduced*06			06
6	40	"	Dryness	Lesions Reduced*			06
7	30	"	Poor compliance therapy stopped				01
8	40	"	Increased Triglycerides – therapy stopped				02
9	30	"	No new Lesions	Lesions Reduced*			06
10	30	"	No new Lesions	Lesions Reduced*			06
11	30	"	No new Lesions	Lesions Reduced*	Lesions Reduced*		08
12	30	"	Dryness	No new lesions	Lesions Reduced*	Lesions Reduced*	10
13	30	"	No new Lesions	Lesions Reduced*			06
14	20	"	No new Lesions	Lesions Reduced*			06

*End point reached

Cheilitis of varying degree was observed in all subjects. 12 to 14 subjects developed dryness of face and lips within 2 weeks of drug therapy. 2 of these 12 patients developed xerostomia. All subject required petrolatum application on the lips after the first few weeks of therapy and was recommended to all subject as a routine. Side effects observed with lesser frequency were palmoplantar desquamation headache photophobia and arthralgia¹. Blood counts were within normal limits in all subjects. Serum triglycerides were raised in 1 subject (450 mg dl) 2 weeks after initiation of therapy which led to discontinuation of the drug (Table 3). The effect of the drug at is 8 weeks after stopping the drug some of the earlier cases prolonged effect on a follow up of one to one and a half years (Table 4).

Table 3: Side Effects of Isotretinoin Therapy

S.No.	Cumulative dose (mg / kg body wt)	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks
1	16.0	Cheilitis	Cheilitis / Xerostomia	Cheilitis / Dryness	Cheilitis / Dryness	Regressed
2	25.0	Cheilitis	Cheilitis	Controlled with Petrolatum	Regressed	Regressed
3	17.0	Cheilitis	Cheilitis	Regressed		
4	24.2	Cheilitis	Palmoplantar desquamation	Controlled with Petrolatum	Controlled with Petrolatum	Regressed
5	21.0	Cheilitis	Dryness	Dryness	Dryness	Controlled with Petrolatum
6	24.0	-	Cheilitis / Dryness	Xerostomia	Regressed	
7	Poor compliance	-	Therapy stopped	-	-	-
8	07.4	Increased Tr.	Therapy stopped			
9	23.3	Dryness / cheilitis	Photophobia	Regressed		
10	23.3	Dryness / cheilitis	Cheilitis	Regressed		
11	30.2	Dryness / cheilitis	Headache	Palmoplantar desquamation	Dryness / cheilitis	Regressed
12	35.0	-	Dryness	cheilitis	Palmoplantar desquamation	Dryness / cheilitis
13	27.0	Dryness cheilitis	Arthralgia	Arthralgia	Regressed	
14	24.0		Dryness	Headache	Regressed	

Table 4: Follow up of Isotretinoin Therapy

S.No.	3 months	6 months	9 months	12 months	15 months	18 months
1	No fresh lesions	Occ fresh lesion	Occ fresh lesion*		Occ fresh lesion	Occ fresh lesion*
2	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion		
3	No fresh lesions	Occ fresh lesion	Occ fresh lesion*			
4	"	Occ fresh lesion		Occ fresh lesion		
5	"	Occ fresh lesion*				
6	Occ fresh lesion	Occ fresh lesion*				
7	No follow up withdrawn from study					
8	No follow up withdrawn from study					
9	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*
10	No fresh lesions	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*	
11	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*
12	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*	
13	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*		
14	No fresh lesions	Occ fresh lesion	Occ fresh lesion*			

* follow up lost thereafter

DISCUSSION

Of all the therapeutic modalities now available only isotretinoin alters the natural course of the disease. It reduces the sebum secretion and this effect persists long after stopping the drug. Prolonged remission has been noted after isotretinoin therapy

Isotretinoin therapy was only initiated in the most recalcitrant cases of acne. An excellent to good response was observed in all our subject. Some of our earlier disillusioned cases dramatically improved with this modality. The cumulative does in the majority of cases was only 15-35 (mean 24.2) mg/kg much below the recommended schedule^{7,8}. Peak improvement was seen at 4-8 weeks after cessation of therapy. The efficacy persisted fairly long after stopping the drug. Our earliest cases continued to sustain the effects even more than one and a half years after stopping the drug. This outcome is not observed with any other treatment and also decreases the total cost of therapy. Initial literature gives a long term remission rate of 61% at the end of nine years with only 23% requiring a second course of therapy. It is difficult to predict the future requirement of a course of isotretinoin as factors related to relapse include long duration of complaints, presence of severe truncal acne, and is higher in females older than 25 years. Higher relapse rates are also noted to be within the first 3 years and patients administered isotretinoin < 0.5 mg/kg per day or cumulative does < 120 mg / kg Recently prospective studies have shown isotretinoin to be equally effective in lower doses in combination with other topical / systematic drugs Intermittent isotretinoin therapy has also emerged as a viable alternative to control milder forms or relapses in acne¹¹ Unfortunately follow up in our patients was only possible for an over a year on an average inadequate to clearly envisage the future requirements of isotretinoin. However, our results are in accordance with current recommendations of low dose isotretinoin therapy to avoid its side effects.¹² No significant side effects were noted in any of our patients. Xerosis and cheilitis are extensions of the therapeutic effects of the drug and were easily controlled by moisturizing agents. These were corresponding to those mentioned in literature being limited to skin and mucus membranes. Metabolic changes and arthralgia were detected early and reversed on stopping therapy. The risk benefit ratio was clearly in favour of our patients in view of the low total dose, male sex predominance and short duration of therapy.

It is thus concluded that isotretinoin is a safe and highly effective therapy, capable of producing remission in severe forms of acne. However, its optimum dose and ideal therapeutic regimen scheme are still under discussion and many long follow up studies in different groups of patients would finally decide the best schedule for long remissions with the least adverse effects.

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CORRELATION OF UMBILICAL CORD LIPID LEVELS AND ANTHROPOMETRY AT BIRTH IN TERM NEW BORN

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Abstract : This study was conducted to assess the cord blood lipid profile and its correlation with anthropometric measurement in newborns. One hundred (100) newborns delivered by spontaneous vaginal route and elective LSCS at term gestation were included in study. Umbilical cord blood was evaluated for cholesterol, low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) and triglycerides. Present study showed no correlation of LDL with either abdominal girth, birth weight and head circumference in term newborns ($p=0.221$ and $p=0.978$ respectively). Similarly no correlates were found for total cholesterol, HDL, triglycerides and VLDL with weight, length, abdominal, girth, ponderal index or head circumference respectively of term newborns at birth in present study.

INTRODUCTION

The imprints programmed during fetal growth in mothers womb manifest as substantial behavioral and metabolic findings in childhood. Many longitudinal studies have now established the interest in programmed changes during fetal life as origins of many diseases¹. The hypothesis of such imprinting was put forward by DJP Barker and numerous studies have evaluated various parameters in fetal and neonatal life and subsequent emergence of adult diseases^{2,3}. Many human fetuses have to adapt to limited supply of nutrients and in doing so they permanently change their physiology and metabolism⁴ Though fetus behaving as a parasite extracts the required nutrients from mother and certain part of metabolic needs fulfilled by placenta itself, yet a shortfall of nutrients may impair fetal growth and low blind major Species, which are relatively heavy at birth such as guinea pigs and humans, have placentas, which are relatively permeable to fatty acids and related molecules in late gestation. Fatty acids may thus form a small but important component of fetal diet in these species at end of pregnancy⁵.

The initial epidemiological studies linked birth weight to subsequent disease risk. Later studies examined these risks in relationship to various body proportions at birth such as Ponderal Index [thinness], abdominal circumference etc^{6,7,8,9}. This appears to have occurred because in many cases these measures are more closely related to disease risk than the actual birth weight itself. A fetus can reach a given birth weight via a variety of possible different growth trajectories.

Among various body proportions that can be studied *Ponderal Index* is important. It is defined as statistically, babies, may be divided as those having ponderal index more or less than 10th percentile. Another variable used in studies is abdominal circumferences at birth. Reduced abdominal circumference has been assumed to reflect reduced liver size^{10,11,12} one has been used as possible explanation of relationship observed between abdominal circumference at birth and lipid metabolism in childhood. Studies in Sheffield showed that the neonate with a small body in relation to head size and the neonate with small abdominal circumference, though within the normal range of birth weight, have persistent disturbances of cholesterol metabolism and blood coagulation¹¹. These results suggest that certain persons at increased risk for cardiovascular disease can be identified in infancy

and that early stages of atherosclerosis begin in childhood¹³.

More corroboration of liver programming during fetal life comes from animal experiments where it has been shown that under nutrition in rat fetuses in utero can permanently alter balance of two liver enzymes phosphoenolpyruvate carboxykinase and glucokinase. In support of fetal programming hypothesis most studies till date have been done in growth restricted fetuses or IUGR babies correlating the body proportions with cord blood lipid levels^{15,16}. Studies have also shown racial and gender variabilities in cord lipid concentration¹⁷ Studies to determine correlation in lipid profile at birth and abnormal body proportions in normal birth weight babies i.e. birth weight more than 2.5 kg are rarer¹⁵ A study done in Israel has shown dysanthropometry at birth in correlation with cord blood lipid levels¹⁸. The aims of the present study were to determine relationship of umbilical cord lipid levels with anthropometry of baby at birth as measured by Ponderal index, abdominal circumference, head circumference, birth weight and length of baby at birth in babies born appropriate for gestational age between 37 to 40 weeks of gestation.

MATERIAL & METHODS

One hundred new borns delivered by spontaneous vaginal route and elective LSCS at 37-40 weeks of gestation would be included in study. Umbilical cord blood will be collected for measurement of lipid profile. Exclusion criteria were congenital anomalies, chromosomal disorders, chronic congenital infections, major placental lesions, multiple births, infant of diabetic mothers, maternal hypertension, mothers with polyhydramnios, or oligohydramnios, maternal hypertension, toxemia of pregnancy, birth asphyxia [defined by Apgar Score<7 at 1 minute, persistent fetal heart rate abnormalities during labour]. Standardized records were kept for study group. Maternal and neonatal data were collected which included relevant maternal history and neonatal birth data including neonatal anthropometry and cord blood lipid profile. Mixed umbilical arterial and venous blood was obtained after clamping of umbilical cord post delivery and prior to delivery of placenta {5ml of cord blood in plain tube}. The lipid profile was done by centrifugation. The lipid fractions cholesterol, low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) and triglycerides were measured using fully automatic BECKMAN-SYNCHRON CX5 PRO. The

method used for measurement was ELIMINATION METHOD using enzymes and subsequent COLORIMETRIC analysis of lipid fraction isolated. For statistical analysis Subject were segregated as per sex and PEARSON COEFFICIENT was used to analyze relationship between lipid concentration and anthropometric measurements. Each variable would be evaluated and a p value < 0.05 was considered significant. To study any correlation between abdominal girth and lipid fractions ANOVA was used after dividing abdominal girth into subgroup.

This study was conducted after clearance from hospital ethics committee and the written consent of the parents/guardians.

RESULTS

Mean values of various lipid fractions in term newborns found in present study are shown in: Table-1

Table-1: Lipid profile of present study in term newborns

	Mean Value	Std Deviation
Total Cholesterol	62.31 mg/dl	19.15
LDL Fraction	27.46 mg/dl	10.79
HDL Fraction	26.98 mg/dl	11.57
Triglycerides	32.50 mg/dl	19.34
VLDL Fraction	7.460 mg/dl	4.77

Further to study any difference in male and female newborns, they were segregated and sex wise lipid parameters studied, which were as: Table -2 and Table-3.

Table-2 Data showing Lipid profile characteristics in female newborns.

	Minimum	Maximum	Median	Mean	Std Dev.
Total Cholesterol (mg/dl)	29	102	63.5	61.95	16.29
LDL fraction (mg/dl)	4.8	49.5	26.4	26.45	9.09
HDL Fraction (mg/dl)	10.6	64	26.1	29.03	11.5
Triglyceride (mg/dl)	2.0	49.8	28	28.01	12.23
VLDL fraction (mg/dl)	0.4	16	5.8	6.2	3.25

Table -3: Data showing Lipid profile characteristics in male newborns

	Minimum	Maximum	Median	Mean	Std Dev.
Total Cholesterol (mg/dl)	32	120.73	57	62.56	20.98
LDL fraction (mg/dl)	91	58.6	26.05	28.20	11.84
HDL Fraction (mg/dl)	8	68.4	22.1	25.61	11.47
Triglyceride (mg/dl)	5	118	31	35.49	22.49
VLDL fraction (mg/dl)	1	32.4	7.3	8.25	5.44

Except slight triglyceride fraction all other lipid fractions were similar in both males and females. To look for correlation of lipid fractions with different fraction the tests of correlation were used. Pearson's coefficient was used to determine any strength of correlation and p values 18 had shown a negative correlation of LDL, cholesterol with abdominal circumference, birth weight and head circumference. Barker⁶ originally noted 14 that smaller abdominal circumference at

birth is associated with higher lipid levels. Based on this observation he suggested that, since abdominal circumference at birth is thought to reflect liver size, and cholesterol metabolism is regulated by the liver, impaired liver growth in uterus re-sets present study showed no correlation of LDL with either abdominal girth, birth weight and head circumference in term newborns (p=0.875, p=0.221 and p=0.978 respectively). Similarly no correlates were found for total cholesterol, HDL, triglycerides and VLDL with either weight, length, abdominal girth, Ponderal Index or head circumference respectively of term newborns at birth in present study (Table 4)

Table-4: Correlation of anthropometry variables with lipid fractions

WEIGHT	r	.049	.124	-.140	.013	.056
	p	.625	.221	.164	.900	.583
O.F.C	r	-.033	-.003	-.019	.015	.032
	p	.743	.978	.855	.879	.749
LENGTH	r	.059	.078	0.35	.061	-.004
	p	.557	.439	.729	.544	.971
POND INDEX	r	-.007	.050	-.160	-.042	.052
	p	.943	.623	-.113	.677	.604
ABD. GIRTH	r	.179	-.016	.163	.002	-.014
	p	.074	.875	.104	.985	.892

To further test the hypothesis of variability of lipid fractions as per abdominal girth, which was purported to correlate with liver size, lipid fractions were correlated to abdominal girths after dividing subjects into 4 groups based on abdominal girth (table 5).

Table-5 Lipid fractions distribution based on abdominal girth

Abd Girth	Total cholesterol	LDL fraction	HDL fraction	Triglycerides	VLDL fraction
>30 cm	58.94	27.91	24.15	33.60	8.07
30-30.5 cm	58.10	24.79	26.64	29.48	6.69
30.5-31 cm	70.00	27.71	34.71	31.69	7.07
>31 cm	64.85	28.58	26.29	33.54	7.47

ANOVA test was used to find significance of lipid fraction distribution within the 4 groups divided as per abdominal circumference (Table-6).

Table -6: ANOVA test

	p value
Total cholesterol	0.163
LDL fraction	0.662
HDL fraction	0.023
triglycerides	0.877
VLDL fraction	0.762

To study the seemingly significant HDL distribution (p value 0.023) as per abdominal girth groups Bonferroni multiple comparison test (post hoc) was used to find HDL fractions distribution across the abdominal girth groups and each group was compared with 3 other groups to find whether the distribution of HDL fraction was significant. In this analysis the distribution was not found to be behaving significantly across all the groups.

DISCUSSION

The magnitude of association between birth parameters and later disease risk, requires assessment in comparison with those attributed to behaviors and lifestyle. A WHO paper in 2002²² concluded that intrauterine programming is likely a third underlying factor of cardiovascular disease and major markers of risk, along with genetic predisposition and lifestyle. Studies have previously demonstrated altered lipid profiles in small for gestational age or IUGR newborns. Though such association has not been seen in term babies. Mainly by work of Barker and colleagues the lipid profile in newborn and possible risk of adult diseases has been brought to fore¹⁴. The study in full term newborns in Israel¹⁸ showed disproportionate body size at birth in full term newborns is associated with disturbance of

cholesterol metabolism. It is known that many factors are associated with lipid characteristics in new born. In a study of 303 newborns and their mothers at the mean value of cholesterol was 72 mg/100 ml for the newborns and 253 mg/100 ml in the mothers. By multiple regression analysis it was shown that a significant independent correlation exists between cord blood cholesterol and the cholesterol of the mothers, birth weight, sex and the blood group of the ABO system of both the newborn and the mother. This demonstrates that several factors known to influence cholesterol in adult life are already operating at birth. Lipid profile in newborns has been studied in ethnically diverse populations and similar distribution has been noted in various populations. (table 7)

Table -7: Comparison of studies from different countries

	CHILE(20)	CHINA(19)	INDIAN(21)	ISREAL(18)
Total Cholesterol	64 mg/dl	65.91 mg/dl	76.6 mg/dl	88.4 mg /dl
LDL Cholesterol	30 mg/dl	31.59 mg/dl	20.7 mg/dl	61.7 mg/dl
HDL Cholesterol	27 mg/dl	22.62 mg/dl	22.5 mg/dl	21.6 mg/dl
Triglycerides	35 mg/dl	20.47 mg/dl	---	31.09mg/dl

Table 7 clearly shows that despite diverse ethnic backgrounds the metabolic milieu of newborn remain constant across the globe. The correlation of lipid profile with anthropometric measurement, however, showed no correlation in present study. A study of term newborns in Israel 18 had shown a negative correlation of LDL cholesterol with abdominal circumference, birth weight and head circumference. However present study showed no correlation of LDL with either abdominal girth, birth weight and head circumference in term newborns (p=0.875, p=0.221 and p=0.978 respectively.) Similarly no correlates were found for Total Cholesterol, HDL, Triglycerides and VLDL with Weight, Length, Abdominal Girth, Ponderal Index or Head Circumference respectively of term newborns at birth in present study.

Barker¹⁴ originally noted that smaller abdominal circumference at birth is associated with higher lipid levels. Based on this observation he suggested that, since abdominal circumference at birth is through to reflect liver size, and cholesterol metabolism is regulated by the liver, impaired liver growth in uterus re-sets cholesterol concentration towards more atherogenic profile. This view is supported by one other study that shows a negative association between abdominal circumference and TG in growth-retarded human fetuses²³. However, more research is needed to show whether the association between abdominal circumference and lipids exists in other populations, and how accurately measurement of abdominal circumference reflects the size of the liver in a new-born baby. The concordance between the size of the liver and abdominal circumference in humans is so far weak 10. Present study also shows no significant correlation between abdominal girth with lipid fractions in cord blood sera. A statistically significant correlation was found to be emerging after ANNOVA analysis of HDL among four abdominal girth groups (p=0.023), however the HDL values which seemingly behaved positively with abdominal girth as it increased from 30cm to 31cm fell as girth rose above values of 31cm. However, larger study with inclusion of maternal lipid profile, maternal anthropometry, maternal macro and

micronutrient intake with placental weight and neonatal anthropometry may prove useful in studying the concept of fetal programming and impact of maternal variables in this context.

Moreover, study of atherogenic lipoprotein fractions mainly Apo E, other fractions Apo B & Apo C may probably elucidate more interesting data. More important studies is long-term follow up; to study whether those with altered lipid profiles at birth manifest the chronic disease of adulthood independent of lifestyle variables.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognized. It has acquired a new sense of urgency as the ethical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory clinical trials on new drugs, a number of diagnostic procedures, therapeutic interventions and preventive measures including the use of vaccines, are being introduced which involve human subjects. Further the advent of new medical devices and radio-active materials and therapeutic benefits of recombinant DNA products have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in mind the following principles of: (i) essentiality, (ii) voluntariness, informed consent, (iii) non exploitation, (iv) privacy and confidentiality, (v) precaution and risk minimization, (vi) professional competence, (vii) accountability & transparency, (viii) maximisation of public interest and distributive justice (ix) institutional arrangements (x) public domain (xi) totality of responsibility and (xii) compliance.

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OXIDATIVE STRESS IN PATIENT WITH DIFFERENT HISTOPATHOLOGICAL TYPES OF IDIOPATHIC GLOMERULONEPHRITIS

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Abstract: The present study was carried out to evaluate oxidative stress/status in idiopathic glomerulonephritis and to find out its correlation with degree of histopathological lesions in patients with different types of glomerulonephritis (GN). Thirty three (33) adult patients of idiopathic glomerulonephritis with nephritic range proteinuria and twenty one adult healthy controls (Group-I) were enrolled in the study. The patients in study (group II) were divided into two subgroups on basis of histopathological diagnosis. Group IIA included patients with histopathological diagnosis consistent with minimal change disease. Group IIB, included twenty three patients with significant glomerular changes on histopathology. This subgroup included 6 patients each of membranous GN, membranoproliferative GN, mesangioproliferative GN and 5 patients of focal segmental glomerulosclerosis, respectively. Informed written consent was obtained from all the subjects. Serum levels of malondialdehyde (MDA) glutathione peroxidase (GPX) superoxide dismutase (SOD) and Vitamin C were measured in all subjects. For comparison between Study group, group II Group IIA, Group IIB and Control Group I, unpaired t-test was applied and p value was calculated. Patients with idiopathic glomerulonephritis showed a significant increase in MDA and decrease in SOD, GPX and vitamin C levels, as compared to controls ($p < 0.05$). Significantly increase levels of MDA, and decrease in SOD, GPX and vitamin C levels were observed in patients with significant glomerular changes disease as compared to minimal change disease and controls ($p < 0.05$). A positive correlation between serum MDA ($r = +0.354$), vitamin C level ($r = +0.047$) and the number of patients with histopathological lesions was observed in patients with significant glomerulonephritis ($p > 0.05$). Patients with significant change glomerulonephritis showed a negative correlation between serum glutathione peroxidase ($r = 0.19$), superoxide dismutase ($r = 0.28$) and the numbers of histopathological lesions ($p < 0.05$). **Conclusion:** Oxidative stress levels are significantly higher in idiopathic glomerulonephritis, the levels were much higher in significant, suggesting that more is the histopathological damage, the higher were the levels and vice versa.

INTRODUCTION

Glomerulonephritis is the leading cause of end stage renal disease world wide and immune mechanism is the most accepted pathogenetic mechanism. Reactive oxygen species have been proposed to be primary mediator in glomerulonephritis and has been blamed for modification of glomerular permeability to proteins, alteration of glomerular hemodynamic and development of morphological lesions. This process results in imbalance between oxidants and antioxidants and raised levels of oxidants results in increased oxidative stress¹. Oxidative stress is involved in a variety of clinical and experimental renal disease in which a spectrum of seemingly unrelated diseases from minimum change lesion to obstructive nephropathies are known. An impaired antioxidative system has been observed in patients with nephritic syndrome, lupus nephritis and IgA nephropathy^{2,3}. Recently Markan et al⁴ evaluated oxidative stress status in patient with different primary glomerular diseases (PGD) which were grouped in to non proliferative glomerulonephritis and proliferative glomerulonephritis and found significantly higher oxidative stress in proliferative glomerulonephritis.

Various studies show that oxidative stress is increased in various glomerulonephritis. However, there is only single study available where oxidative stress has been evaluated in different histopathological types of glomerulonephritis⁴. Therefore in this study we have assessed the level of oxidative stress in different histopathological types of glomerulonephritis using malondialdehyde, super oxide dismutase, glutathione peroxidase and vitamin C as markers of oxidative stress.

MATERIAL AND METHODS

A total of thirty three histopathologically proved adult patients of idiopathic glomerulonephritis with nephritic range proteinuria with normal renal functions were enrolled in study group (II) Twenty one adult healthy volunteers were also included as control in study procedure and with associated disease which are likely to influence oxidative stress or cases on steroids / immunosuppressant drugs, were excluded from study.

The patient in study group (II) were divided in to two subgroups on basis of histopathological diagnosis. Group IIA included 10 patients with histopathological diagnosis consistent with minimal change disease, where a Group IIB, included twenty three patients with significant glomerular changes on histopathological examination, including 6 patients in each of membranous glomerulonephritis, membranoproliferative GN, mesangioproliferative GN and 5 patients of focal segmental glomerulosclerosis, respectively. Informed written consent was obtained from all the subjects.

The mean age of patients was 31.45 ± 14.4 years and that of control was 35.14 ± 13.1 years. There was 24 males and 9 females in study group. Besides routine biochemical parameters, oxidative stress was assessed in all subjects by estimation of lipid peroxidation – Malondialdehyde, ascorbic acid and glutathione peroxidase, superoxide dismutase.

Statistical Analysis: For comparison between study group (Group II), IIA, Group IIB and Control Group I, unpaired t-test was applied and p value was calculated. Correlation coefficient – r was also calculated to find any correlation between oxidative stress markers

and number of histoathological lesions.

RESULTS

Biochemical parameters in the various groups of patients, including creatine clearances, were comparable and were within normal limits (Table -1). Patients with idiopathic glomerulonephritis had significantly increased level of serum MDA, and decreased levels SOD, GPX and vitamin C as compared to healthy volunteers (p<0.05 Table 2).

Table 1: Showing baseline renal profile and other investigations

Parameter	Group A	Group B	Control	Total cases
Hemoglobin (gm%)	10.78± 1.54	10.33 ±0.89	13.04 ±0.80	10.64 ±1.38
Serum bilirubin (mg%)	0.99± 0.15	0.92 ±0.13	0.95 ±0.15	0.96 ±0.15
Blood Sugar (mg%)	88.6 ±10.38	87.2 ±8.8	91.85 ±8.79	88.18 ±9.81
Blood urea (mg%)	24.52± 8.62	27.2 ±4.91	33 ±4.2	28.82 ±7.68
Serum Creatinine (mg%)	0.95± 0.16	0.87± 0.12	1.27± 0.15	0.93± 0.15
Serum Calcium (mg%)	8.4 ±0.8	9.35 ±0.68	9.16 ±0.17	8.38 ±0.76
Serum phosphate (mg%)	4.67± 0.99	4.79 ±0.75	4.36 ±0.24	4.70 ±0.95
Serum protein with A/G ratio	6.32 ±0.95 / 1.07± 0.32	6.29 ±0.83 / 1.07 ±0.32	7.1 ±0.1 / 1.17 ±0.1/	
SGOUT (IU)	32.47± 6.57	37.8 ±5.37	31.04±4.12	34.09 ±6.63
SGPT (IU)	30.52 ±7.63	33.2 ±4.54	24.71 ±3.05	37.33 ±6.88
Serum cholesterol (mg/d)	302.43± 126.54	232.88 ±56.9	147.09±4.38	281.33 ±113.91
Proteinuria (gm/day)	5.9± 2.07	5.11 ±1.51	4.36 ±0.24	5.57 ±1.93

Table II: Oxidative stress markers in patients with idiopathic glomerulonephritis, minimal change disease, significant change glomerulonephritis and controls

	Contyrol Goup I (n=33)	Study Group II (n=33)	Group IIA (n=10)	Group IIB(n=23)
MDA(nmol/l)	2.431± 0.213	3.206± 0.334	2.99± 0.242	3.3± 0.329
SOD(uit/ml)	49.010 ± 2.527	35.112 ± 7.391	42.618 ± 4.649	31.848 ± 5.819
GPX (unit / ml)	0.0710 ± 0.0367	0.0453 ± 0.014	0.0598± 0.014	0.0391 ± 0.0092
VIT.C (mg %)	1.242 ± 0.092	0.893 ± 0.149	1.057 ± 0.109	0.821± 0.098

MDA Malondialdehyde, GPX Glutathione peroxidase, SOD: Superoxide distumase.

Patients with significant change glomerulonephritis (group IIB) had significantly increased levels of serum MDA and decreased levels SOD GPX and vitamin C as compared to minimal change disease (group II A) (p <0.05) and healthy volunteers (Table II). Within various histopathological types, the mean MDA levels were found highest in MPGN and lowest in MCD group, and mean SOD, GPX and vitamin C levels were lowest in MPGN and highest in MCD group.

A positive but statistically non significant (p>0.05) correlation was found between serum MDA (r=+0.35) vitamin C level (r=0.047) and the numbers of histopathological lesions in patients with significant glomerulonephritis (Table 3). Patients with significant change glomerulonephritis showed a negative correlation (p>0.05) between serum glutathione peroxidase (r=0.19), superoxide dismutase level (r=0.28) and the numbers of histopathological lesions.

Table III: Oxidative stress markers in patients with significant change Glomerulonephritis with numbers of histopathological lesions

Number histopathological of lesions	One lesion (n=10)	Two lesions (n=9)	Three lesions (n=3)	Four lesions (n=1)	Pearson's correlation coefficient	P-value
MDA(nmol/l)	3.17± 0.35	3.35± 0.24	3.37± 0.27	3.68	R=+0.35	P>0.05
SOD(uit/ml)	33.08 ± 4.52	31.72 ± 6.7	31.5 ± 7.79	22.96	r=-0.28	P>0.05
GPX (unit / ml)	0.04 ± 0.007	0.04 ± 0.011	0.035± 0.009	0.03	r=-0.19	P>0.05
VIT.C (mg %)	0.81 ± 0.08	0.83 ± 0.07	0.87 ± 0.21	0.73	r=+0.047	P>0.05

DISCUSSION

Oxidative stress plays a key role in pathophysiological processes in various renal disease, including inflammatory lesions such as glomerulonephritis and interstitial nephritis, ischemic reperfusion injury, hemolytic uremic syndrome and toxic nephropathies, and possibly in progression of chronic renal failure². Malondialdehyde is product of lipid peroxidation, which normally occurs at low level in all cells and tissues. But this process is accelerated by increase oxidative stress, causing increase production of Malondialdehyde^{9,10}. Significantly higher MDA levels in significant change glomerulonephritis as compared to minimal change disease and controls indicate an increased production of Reactive Oxygen Species (ROS) and severe lipoperoxidative damage in these patients. ROS react with polyunsaturated fatty acid in lipids, which are highly susceptible to oxidation, producing lipid hydroperoxides. Most of the lipid hydroperoxides are unstable and undergo decomposition through peroxy radical dependent chain reaction to smaller and more stable lipid hydroperoxides products, such as malondialdehyde¹¹. This process is accelerated by increased production of reactive oxygen species, causing increase production of malondialdehyde. Increased MDA levels might be due to lipoperoxidative damage caused by excessive amount of reactive oxygen species generation by infiltrating inflammatory (neutrophils, monocytes) or proliferating glomerular cells (mesangial and endothelial cells and podocytes) as a result of different sites of glomerular damage and cellular proliferation, and their propensities to generate reactive oxygen species in these patients.

We also observed significantly decreased level of SOD, GPX (anti oxidant enzymes) and vitamin C (non enzymatic anti oxidants) in Patients with significant change glomerulonephritis, thus indicating an increased oxidative stress in patients with significant glomerulonephritis. Glutathione peroxidase is a selenoenzyme which catalyzes the reduction organic hydro peroxides and hydrogen peroxide by using glutathione as reducing agent and play an important role of extra cellular fluid component and cell surface against peroxide mediated damage¹². The exact mechanism of decreased glutathione peroxidase levels in patients with significant glomerulonephritis as compared to minimal change disease is not known, but these different levels of glutathione peroxidase in different histopathological types or lesions might be result of increased utilization of enzymes to cope up with reactive oxygen species, which might be generated in excessive amount by proliferating glomerular cells (mesangial cells, endothelial cells and podocytes) which are a source of ROS or could be due to infiltration of the macrophage and the neutrophils or impaired synthesis of extra cellular GPX in the damaged kidneys^{13,14}.

Superoxide dismutase is one of the key antioxidant enzymes that participates in the cellular defense system against oxidative damage by catalyzing the dismutation of superoxide (O₂⁻) to oxygen and H₂O₂¹⁵, and ascorbic acid is one of the most effective water soluble antioxidants (non enzymatic anti oxidants) in biological fluids and can scavenge physiologically important reactive oxygen species and

reactive nitrogen species. However, the significant decrease in SOD and vitamin C levels in patients with significant glomerulonephritis might be the result of inactivation of enzyme by reactive oxygen species, could have been generated in excessive amount due to the rapid proliferation of the glomerular cells (mesangial cells, endothelial cells and podocytes) which are a source of ROS or could be due to infiltration of the macrophage and the neutrophils in the patients with significant change glomerulonephritis. Superoxide dismutase inactivation by hydrogen peroxide (H_2O_2), a dismutation product of O_2 through destruction of histidine residue has been reported by Bray and Cockle. Like in present study, significant increase in oxidative stress also has been supported by various other studies: Markan S et al⁴ reported that mean serum MDA levels were significantly higher ($p < 0.05$) and lower SOD levels ($P < 0.05$) in patients with proliferative glomerulonephritis (MPGN and RPGN) as compared to non proliferative glomerulonephritis (MCD, MGN and FSGS).

Kuo HT et al¹⁸ also reported increased plasma malondialdehyde (MDA) levels in the patients with FSGS as compared to patients with MCD which were associated with the degree of glomerulosclerosis, suggesting that oxidative stress occurs early and may play an important role in the pathogenesis of glomerulosclerosis. Hung Chun C et al¹⁹ reported that plasma glutathione peroxidase levels were significantly lower (both $p < 0.01$) in FSGS patients than in either MCD patients or normal control subjects.

From the observations made in this study, it can be concluded that oxidative stress levels were significantly higher in idiopathic glomerulonephritis; the levels were much higher in significant change glomerulonephritis (membranous glomerulonephritis, membranoproliferative glomerulonephritis, mesangio proliferative glomerulonephritis and focal segmental glomerulosclerosis) as compared to minimal change disease. Suggesting that more is the histopathological damage, higher were the levels and vice versa. Also the oxidative stress difference in different histopathological types can be used for clinicopathological correlation and perhaps is a prognostic indicator in different histopathological types. Thus future research should focus on decreasing oxidative stress by using various antioxidants, to halt the disease process and improve survival.

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LITERATURE REVIEW

Initiation of dialysis at higher GFRs: Is the apparent rising tide of early dialysis harmful or helpful?

Steven Jay Rosansky et al. *Kidney International* 2009;76,257-261.

Over the past decade a trend of increasing estimated glomerular filtration rate (eGFR) at the initiation of dialysis for treatment of end-stage renal disease (ESRD) has been noted in the United States. In 1996, only 19% of patients began dialysis therapy with an eGFR of greater than 10 ml/min/1.73m² (denoted as 'early start'), but by 2005 the fraction of early start dialysis patients had risen to 45%. This review examines US dialysis data, national guidelines, and publications relevant to the early start phenomenon. It is not known whether early start of dialysis is beneficial, harmful or neutral with respect to the outcome of dialysis treatment for ESRD. Available data indicate that mortality while on dialysis therapy may be higher in those subjects with early start. Comorbidities present at the time of dialysis initiation do not appear to be a major driving force for early start patients. As well, residual kidney function in these patients is a major contributor to total urea or creatinine clearance. This can be a positive factor for patient outcomes and might be compromised by early start. Finally, we estimate the dollar cost of early start to the US Medicare-supported ESRD program. Properly designed, prospective and randomized studies may help to clarify the benefit or harm of early start of dialysis for ESRD.

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MODIFIED FISH MEAL EXTRACT AGAR: A NEW MEDIUM FOR THE SELECTIVE ISOLATION OF PSEUDOMONAS AERUGINOSA – A PRELIMINARY REPORT.

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Abstract : A new bacteriological medium Modified Fish Meal Extract A(FMEA) agar was tested for its efficacy in promoting the growth of *P aeruginosa* normally encountered in clinical specimens. 50 specimens each of sputum, pus and urine were cultured on Modified Fish Meal Extract Agar and the results were compared with normal Nutrient agar and Blood agar. There was 100% conformity in the results compared with the other selective media for *Pseudomonas aeruginosa*. One of the greatest advantages of this Modified FMEA was that no other organisms grew in culture other than *Pseudomonas aeruginosa*. **Conclusion:** The cost of consumable materials used in the preparation of fish meal extract agar being simple and cheap; this medium can be used successfully in the routine culture work for the isolation of *Pseudomonas aeruginosa* from clinical specimens like sputum.

INTRODUCTION

There has been continued effort in the recent years to improve the routinely used media in the bacteriological work. The aim has been to develop a simple and more economical medium for the isolation of *pseudomonas aeruginosa* from clinical samples. Here we compared the efficacy of modified fish meal extract agar with the conventional non selective and selective media for the effective isolation of *Pseudomonas aeruginosa*. Fish Meal Extract Agar (FMEA) has been already used in the cultivation of bacteria, *entamoeba histolytica*, non swarming of the proteus species, as antibiotic sensitivity test medium and also as a differential media for the lactose and non lactose fermenting organisms^{1,2,3,4,5}.

MATERIAL AND METHODS

Fish meal ordinarily available in coastal Karnataka is nothing but the dried and powdered residue of sardine fish after the extraction of oil. This was the basic substance used in the preparation of modified fish meal extract agar. 500 grams of fish meal (Raj fishmeal and Oil Co. Malpe) which was properly cleaned out of its gross impurities was boiled for 10 minutes in one liter of distilled water, with constant stirring. After cooling, the solution was allowed to stand over night and the supernatant was decanted. This was the fish meal extract concentrate obtained¹.

For the preparation of modified fish meal extract agar, for every 10 ml of fish meal extract 90 ml of distilled water was added making the final concentration of fish meal in the medium to 10%. Then 5% beef extract 1% sodium chloride and dettol 0.3% was added to make the medium selective. The pH of the medium was adjusted to 7.4 and 2% of the agar was added. The medium was sterilized by autoclaving at 121 C and poured into Petri plates⁶.

Fifty (50) specimens of each of sputum, urine and pus were cultured on modified fishmeal extract agar, blood, agar, nutrient agar, cetrimide agar and *pseudomonas* isolation agar and the results were compared.

RESULTS AND DISCUSSION

Pseudomonas aeruginosa grew on all the plates and there was cent

percent conformity in the isolation of this organism from the sputum, urine and wound specimens. This study was also used to compare this medium with the *Pseudomonas* isolation agar and cetrimide agar. It was noted that then isolation of *pseudomonas aeruginosa* when less in sputum samples were better in the modified fish meal extract agar as shown in the following compared to the cetrimide media but the intensity of pigment production was found to be less in the modified fish meal extract agar compared to the above two selective media. The two strains of *Pseudomonas aeruginosa* isolated from sputum produced pyorubin pigment in the modified fish meal extract agar. The colonies were more mucoid in nature after 24 hours of incubation on modified fish meal extract agar whereas the colonies were highly pigmented and irregular in nature on cetrimide and *pseudomonas* isolation agar.

Table: Comparison of different Culture Media in isolation of *Pseudomonas aeruginosa* from different clinical specimens.

Specimens (50 samples each)	Blood agar*	Nutrient Agar**	Cetrimide Agar **	<i>Pseudomonas</i> Isolation agar**	Modified Fishmeal Extract Agar **
Pus	12	12	12	12	12
Sputum	17	17	15	17	17
Urine	5	5	5	5	5

* in these media, along with the *Pseudomonas aeruginosa* other bacteria were also grown

** these were the selective media used for the selective isolation of *Pseudomonas aeruginosa*

The fish meal extract agar without any added ingredients were also tried in this study but none of the medically important bacteria grew in the medium in 24 hours. Only *pseudomonas aeruginosa* grew in the culture after 48 hours of incubation. The colonies here were very small and highly irregular in morphology. To isolate the organism at a faster rate, the fish meal extract medium was modified which had similar isolation rates at par to the common selective media used for the isolation of *pseudomonas aeruginosa*.

The cost of the consumable materials used in the preparation of 100 ml medium is very much lower than that of other selective media.

Hence this is a much cheaper medium than pseudomonas isolation agar and cetimide agars which are used for the selective isolation of Pseudomonas from clinical specimens and this could be successfully replaced with the former in routine bacteriological work.

Nutritionally, fish meal extract is as good as peptone and has been successfully used for formulating media to grow bacteria and to test their antibiotic susceptibility. The performance of the media with regard to growth characteristics were largely at par with each other. However bacteria isolated from clinical specimens produced large colonies than those used from stock cultures. The counts of growth on all these media were same. The growth character of the pseudomonas aeruginosa isolated from clinical specimens is more important than those subcultured from stock cultures. Upon storage, stock cultures usually tend to lose some of their growth characteristics. Unlike peptone, fish meal is non hygroscopic and do not become sticky when exposed to air. Like peptone, fish meal has a very low content of copper and is free from fermentable carbohydrates and able to support the growth of moderately exacting bacteria like S aureus. In addition, fish meal has higher amino acid nitrogen 2.62% and tryptophan 1.87% than peptone for which the values are 1.7% and 1.2% respectively.⁵ The cost of fish meal is much low that is approximately Rs. 16/kg as against peptone with a price of Rs. 1600/kg. In addition to the quality of growth in Microbiology, the important aspect is to obtain the raw material very cheaply for routine clinical investigations. Hence modified fish meal extract agar may be a suitable alternative compared to other selective media in the primary isolation of Pseudomonas aeruginosa from clinical samples like sputum which is often contaminated with normal oral flora which was observed on blood and nutrient agar.

According to the previous studies, none of the selective media produced the growth of pseudomonas species in the primary isolation and it is better to inoculate the specimen in a noninhibitory medium and the subculture on to the selective media for the proper isolation of Pseudomonas species⁷. In this study, we found that the Modified Fishmeal Extract Agar media is far superior to other selective media

which are commonly used for the isolation of pseudomonas aeruginosa from clinical specimens as even a very scanty growth of Pseudomonas aeruginosa could be observed in the Modified Fishmeal extract agar for the selective isolation of Pseudomonas aeruginosa.

CONCLUSION

In conclusion this study has proved that in the selective isolation of pseudomonas aeruginosa from clinical specimens, the modified fish meal extract was better in the isolation rate compared to the pseudomonas isolation agar and cetrimide agar. This media is also found to be very cost effective as the raw materials used is very cheap compared to the other selective isolation of Pseudomonas aeruginosa which is obtained as a pure growth on the agar and is within the reach of every microbiology laboratory for routine bacteriological investigations whenever pseudomonas infections are suspected.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the support and help of Pro. Subbannayya K, Department of Microbiology KVG medical college Sullia.

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DRUG PROFILE

Trospium Chloride

Indications and Usage: Trospium is an anticholinergic drug, indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. **Dosage and Administration:** The recommended dosage is 20mg twice daily. The drug should be given with water on an empty stomach, at least one hour before the meal. **Contraindications:** The drug is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions. **Warning and precautions:** The drug should be administered with caution to patients with clinically significant bladder outflow obstruction or gastrointestinal obstructive disorders due to risk of urinary or gastric retention. In patients with narrow angle glaucoma, it should be used only with careful monitoring. The drug is not recommended for use in patients with severe renal impairment (creatinine clearance < 30mL/Min). Alcohol should not be consumed within 2hrs of administration, of the drug. **Adverse reactions:** These include dry mouth (10.7%) and constipation (8.5%). **Drug Interactions:** Trospium is metabolized by ester hydrolysis and is excreted by kidneys through tubular secretion and glomerular filtration. Concomitant use with digoxin did not effect the pharmacokinetics of either drug. The oral bioavailability was reduced following a high fat-content meal. **Use in specific population: Pregnancy:** In the post-parturition animal studies, Trospium chloride was excreted to a limited extent into the milk. **Pediatric:** The safety and effectiveness of the drug in Pediatric patients have not been established. **Renal Impairment:** Trospium is not recommended for use in patients with moderate to severe renal impairment. Caution is advised when the drug is used in patients with severe hepatic impairment.

MELOXICAM INDUCED ACUTE THROMBOCYTOPENIC PURPURA

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Abstract : Thrombocytopenia is a well documented adverse reaction of many commonly used NSAIDs like diclofenac, nimesulide, piroxicam and other NSAIDs. With meloxicam, side effects related to gastrointestinal, cutaneous, cardiovascular and neurological systems are common; but thrombocytopenia is rarely reported with meloxicam⁴. A case of acute thrombocytopenic purpura in a female patient suffering from arthralgia is being reported here on account of its rarity.

INTRODUCTION

Cyclooxygenase-2 (Cox-2) inhibitors have been shown to be effective nonsteroidal antiinflammatory agents (NSAID's) with better gastric tolerability¹. The preferential Cox - 2 inhibitors include meloxicam, flosulide (CGP 2838), DUP 697, NS 398, nimesulide, nabumetone, etodolac² and these selective Cox-2 inhibitors block inflammation without blockage of Cox-1 dependent normal physiological house keeping prostaglandins. The most common causes of thrombocytopenia are bacterial or viral infections, immune disorders, collagen vascular disorders, drugs and idiopathic thrombocytopenic purpura³.

CASE REPORT

A 48 years old educated post-menopausal lady, a known case of bronchial asthma with history of generalised nonspecific arthralgia, presented with bleeding from the mouth with no evidence of melena. When questioned, she revealed that she was given 15 mg of meloxicam for relief of joint pains by the private practitioner. History of hypersensitivity to sulpha group of drugs was positive. On examination, all the vitals were normal. There were ecchymosis of varying sizes on the flexor aspects of both arms without involving other parts of body (See photograph). Lips and soft palate revealed active bleeding. There was no evidence of organomegaly/lymphadenopathy. Laboratory profile revealed Hb 10.3 gm/dl, TLC 11900/mm³, DLC-P68, L30, E2, B0, platelet count 65000/mm³, RA factor negative and S. uric acid 4.2 mg/dl. Peripheral blood film was non-contributory. BT, CT, coagulation profile was normal with negative ANA, LE cell and blood culture. Bone marrow aspiration revealed peripheral destruction of platelets.



A diagnosis of meloxicam induced acute thrombocytopenia was made. The drug was stopped and patient was put on prednisolone 1mg/kg body weight. On the third day, she had an episode of haemetemesis but no melena. Her Hb came down to 7 gm/dl with platelet count 60000/mm³. She was given 2 units of blood transfusion and immunoglobulins I/V in doses of 1 gm/kg body weight for 2 days. The bleeding stopped from gastrointestinal tract (GIT) and oral cavity. The endoscopic evaluation of GIT was normal. On 4th day, platelet count increased to 1.90 lac/mm³. She was continued on oral prednisolone from 40mg/day to tapering doses of 5mg/day for a period of six weeks after which, the platelet count improved to 2.52 lac/mm³. After 6 months of follow up, she was asymptomatic with normal platelet count of 2.74 lac/mm³.

DISCUSSION

The most common causes of thrombocytopenia are viral or bacterial infections, immune disorders, collagen vascular disorders, drugs and idiopathic thrombocytopenic purpura³. Most of the drugs are known to produce

thrombocytopenia by either suppressing platelet production or causing immunological destruction of platelets. Majority of the cases occur due to immune complex mediated mechanism. Current laboratory tests can identify the causative agent in 10% of patients with clinical evidence of drug - induced thrombocytopenia³. Thrombocytopenia is a well documented adverse reaction to many commonly used NSAIDs like diclofenac, nimesulide, piroxicam and other NSAIDs. No dose dependence or age preference factor is noted. From September 1996 when meloxicam was first marketed in UK till mid June 1998, the UK Committee on safety of medicines had received a total 773 reports of 1339 suspected adverse reactions with meloxicam⁵. The most adverse reactions with meloxicam pertain to various systems like GIT, cutaneous, CVS and CNS. Of all the reactions, 41% are gastrointestinal like perforation, ulceration, haemorrhage and or bleeding pruritis, erythema multiforme, bullous eruption, rash and urticaria are the most common cutaneous manifestations. Neurological adverse effects include nausea, vomiting and dizziness. Although thrombocytopenia has been reported in 2 patients, but no case of thrombocytopenic purpura has been reported in a study of 19087 patients using meloxicam in England⁴.

Meloxicam has been suggested to be a selective Cox-2 inhibitor based on in vitro studies⁶. However, when tested in vivo in human beings, its selectivity to inhibit Cox-2 compared to Cox-1 was only about 10 folds and there was some inhibition of platelet Cox-1 mediated thromboxane production after oral treatment with both 7.5 mg/day and 15 mg/day⁷. Patoria et al⁸ has proposed that the extent of inhibition of Cox-1 with meloxicam is largely a function of dose and interindividual variability of drug levels.

The best proof of a drug induced etiology is the clinical course and abrupt rise in the platelet count as observed in the present case. High dose intravenous gammaglobulin given in doses of 1 gm/kg body weight over 6-8 hours for two successive days is usually an effective treatment for any induced immune thrombocytopenia. Since thrombocytopenia usually develops within 12 hours in a previously sensitised individual, but in this patient, it appeared after 24 hours of drug ingestion with no history of previous sensitization. A similar case of acute thrombocytopenic purpura caused by meloxicam has been reported earlier also⁹.

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HYDROXYUREA INDUCED LEG ULCER IN A PATIENT OF CHRONIC MYELOID LEUKEMIA-A CASE REPORT

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Abstract : Dermatological side effects of long term hydroxyurea therapy used for chronic myeloid leukemia (CML) are not uncommon. But the development of leg ulcers is very rarely reported with its prolonged use. A 55 years old nondiabetic, non smoker male patient on long term use of hydroxyurea for the management of CML, who developed leg ulcer as complication, is being reported here for its rarity.

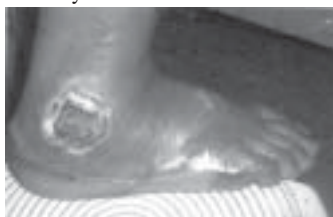
INTRODUCTION

Hydroxyurea is a hydroxylated derivative of urea which is recognised as an effective antineoplastic drug. It inhibits cellular DNA synthesis and promotes cell death in the S-phase of cell cycle through its action on enzyme ribonucleotide reductase¹. The common cutaneous side effects of hydroxyurea include hyperpigmentation, scaling, erythema and partial alopecia etc.² But the development of leg ulcers is a rare complication³. A patient of chronic myeloid leukemia who developed leg ulceration secondary to hydroxyurea therapy is being presented here.

CASE REPORT

A 55 years old male-non smoker and non-diabetic-presented with the complaints of weight loss, pain abdomen, lump in the abdomen and weakness for three months. On examination, he had pallor, massive splenomegaly of 14 cms, palpable below left costal margin and mild hepatomegaly. There was no lymphadenopathy. Examination of CVS, CNS and respiratory systems were normal. There was no past history of diabetes, hypertension, tuberculosis or syphilis. There was no history suggestive of drug hypersensitivity, autoimmune disorder or peripheral vascular diseases. His laboratory profile included Hb 9.8 gm/dl, TLC 105000/mm³, platelets 290000/mm³, ESR 90 mm at the end of first hour, FBS 90 mg/dl serum uric acid 6.2 mg/dl, Serum LDH 150 IU/L. Peripheral blood film examination revealed neutrophils 78%, lymphocytes 12%, basophils 2%, myelocytes 1%, metamyelocytes 2%, promyelocytes 3% and blasts 3%. The bone marrow was hypercellular with myeloid hyperplasia and 2% blasts. APTT was comparable with the control. ANA, antiphospholipid antibody and VDRL tests were negative. Liver and renal profile were normal. Cytogenetically he was Philadelphia chromosome positive. He was diagnosed to be a case of CML and put on hydroxyurea orally 1.5 g/day in divided doses along with hematinics. He was under regular follow up and doses of hydroxyurea were adjusted according to the WBC count.

Patient remained asymptomatic with this treatment for two and half years. Then he developed painful ulcer over right lateral malleolus with purulent discharge along with swelling of right lower leg (photograph). He was unable to walk. The ulcer was single, circular in shape with irregular crescentic border. There was black discoloration and extensive desquamation of the skin in the surrounding area. The skin around ulcer had normal temperature. There was no bleeding from the ulcer, varicosities involving the limb or evidence of stasis dermatitis. Peripheral pulses like posterior tibial and dorsalis pedis arteries were normally palpable. Biopsy of ulcer was negative for malignant infiltration. Patient was put on antibiotics and local dressing of wound. Culture from the wound did not reveal growth of any organism. X-ray of involved area did not show any abnormality.



Hydroxyurea was continued in the lower doses for 6 weeks but ulcer did not heal. Subsequently hydroxyurea was replaced by tablet Busulfan 4 mg orally daily and ulcer started healing progressively following the cessation of hydroxyurea within 8 weeks and patients improved symptomatically as well. The total leucocyte count was controlled on Busulfan. But he was lost on follow up.

DISCUSSION

Hydroxyurea is commonly used in the treatment of various types of hematological disorders. Dermatological side effects of hydroxyurea include diffuse hyperpigmentation, brown discoloration, acral erythema, scaling of nails, stomatitis, erythema and partial alopecia⁴. A rare complication of leg ulceration was described by Montefusco et al³, subsequently Nguyen reported four cases⁴ and Beast et al⁵ reported fourteen cases. All of them improved after cessation of offending drug. No consistent correlation between the dose or duration of hydroxyurea therapy and occurrence of ulcers has been reported⁶. The mechanism of action of hydroxyurea is inhibition of cellular DNA synthesis leading to cell death in the S phase of the cell cycle. Damage also occur from free radical nitroxide intermediates and inhibition of DNA repair¹. Basal keratinocytes are the most actively replicating cells of the epidermis and damage to keratinocyte by cytotoxic drugs is common. Epidermis atrophy may result from damage to basal keratinocyte⁷. Hydroxyurea induced leg ulcers could be due to impairment of normal wound healing in areas of common trauma resulting in non production of normal epidermis, stromal cells or epithelium⁸. Another mechanism of ulcer development may be cumulative toxicity of hydroxyurea on basal layer of epidermis due to inhibition of DNA synthesis¹. This is supported by the autoradiographic study, which revealed large areas of absent epidermal uptake of titrated thymidine⁹. Most patients who developed leg ulcers received over 1 gram of hydroxyurea per day for atleast one year. But our patient remained asymptomatic till two and half years after which he developed leg ulceration. few cases of reversible hydroxyurea induced leg ulcers in patients of CML have been reported in the Indian literature¹⁰ from various parts of the country. Probably this is the first case report from this part of the country to the best of our knowledge. Hence the case report.

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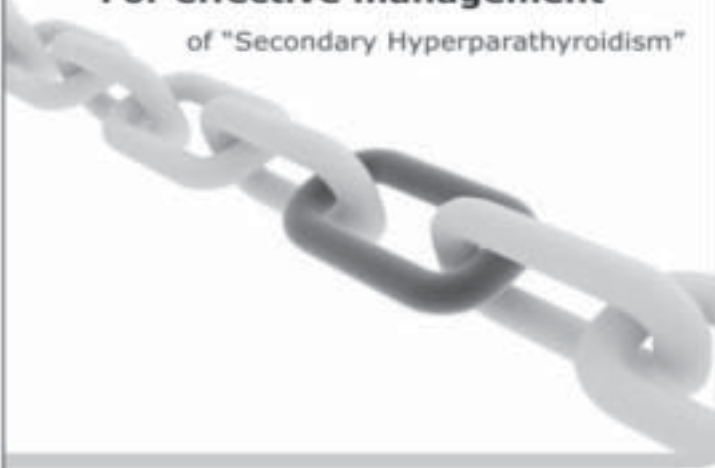
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FRACTURE OF LATERAL SESAMOID BONE OF THE GREAT TOE: A DIAGNOSTIC DILEMMA

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Abstract :Fracture of the lateral sesamoid bone of the great toe is rare, very few cases have been reported in the world literature, and none has been reported from this subcontinent. Recently, two cases of fractured lateral sesamoid bones of the great toe were treated initially as gouty arthritis, elsewhere. CT scan confirmed the diagnosis and should be mandatory. Conservative management with below knee plaster produced excellent result.

INTRODUCTION

In each half of the flexor hallucis brevis tendon there are two sesamoid bones. Sesamoid bones are like seeds, after which they are named. Despite their close association with articulations, the precise function of sesamoid bones are still uncertain. It has been opined that they may modify pressure, diminish friction, and sometimes later the direction of the muscle pull. Fractures of sesamoid bones of the great toe are rare, and not many cases have been reported in the world literature, and no cases have been reported from this sub-continent.

Fractures of the sesamoid bones can result from direct trauma or from repetitive stress. Of the two sesamoid bones of the great toe, the medial sesamoid is more prone to fracture than the lateral. As fractures of these sesamoid bones of great toe are uncommon, hence these cases may cause diagnostic dilemma. Recently two cases of fractured lateral sesamoid bones of great toe were treated by med both of them were initially managed as gouty arthritis.

CASE REPORTS

Case I A young female aged 23 years, slipped in the bathroom and injured her right great toe. After two days, when pain did not subside with analgesics, she consulted an orthopaedic surgeon, who promptly sent her for radiological investigation.

Routine X-ray showed no bony injuries, as the swelling was around the first metatarso – phalangeal joint, and the x-ray showed no bony injury, the history of trauma was taken as a red herring, and she was treated as a case of gouty arthritis, although her serum uric acid level was normal. However, even after taking the medicine for one week she did not experience any relief. On examine she had a painful, tender swelling around the first metatarso – phalangeal joint of right great toe. The maximum tenderness was on the planter aspect of the head of the first metatarsal of the right great toe. As the x-ray report was negative, a C.T. scan was done. C.T. scan clearly showed a fracture of the lateral sesamoid bone of the right great toe (*Photo 1*) CT scan showed fracture of the lateral sesamoid bone of right side. She was treated with a Short-leg walking plaster for six weeks, and she made an uneventful recovery.

Case-II A young male, aged 28 years, a long distance runner. After running a mini marathon he complained of a painful tender swelling, at base of his right great toe. Initial X-rays showed no bony injuries. So he was treated as a case of gouty arthritis, although his serum uric acid level was normal. After one week of medication, he did not have any relief, so he came to my clinic.

On examination it was noticed that his maximum tenderness was at

the planter aspect of the head of the first metatarsal of the right foot. A C.T. scan was done, which showed a stress fracture of the lateral sesamoid bone of the right great toe. He was treated conservatively with below knee walking plaster for six weeks. He made an excellent recovery (*Photo 2*). CT scan showed stress fracture of the lateral sesamoid bone of right side.

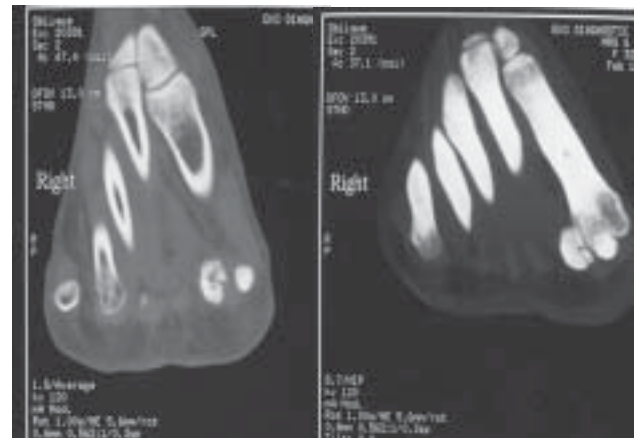


Photo1

Photo2

DISCUSSION

Fractures of the sesamoid bones of the great toe are rare, and very few cases have been reported in the world literature and no cases have been reported from this sub continent.

Fracture of the lateral sesamoid bone, of the great toe are extremely rare and ordinary x-rays may sometimes fail to reveal them, these fractures may be missed and can pose a diagnostic peril.

Two cases of fractures of the lateral sesamoid bone, reported in this article, were initially treated as gouty arthritis. Excessive tenderness on the planter surface of the first metatarsal joint, and swelling which increases on weight bearing and does not respond to uricosuric drugs should be taken as positive pointers for a possible fracture of the sesamoid bones. A.C.T. scan will finally clinch the diagnosis.

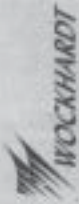
Although few workers 1,2 recommended surgical excision of the fractured sesamoid bone as a primary treatment, yet both the cases reported in this paper did very well with conservative management.

RECOMMENDED READING

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PERIPHERAL GANGRENE - A RARE PRESENTATION OF FALCIPARUM MALARIA

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Abstract :The occurrence of peripheral gangrene manifested by distal ischaemic damage in the absence of large vessel obstruction is a rare manifestation of falciparum malaria. A case of peripheral gangrene developed in a patient of falciparum malaria involving only one extremity (right foot) is being reported here for its rarity although few cases of symmetrical peripheral gangrene due to falciparum malaria have been described in the literature.

INTRODUCTION

Symmetrical peripheral gangrene (SPG) is defined as symmetrical distal ischaemic damage at two or more extremities without any evidence of obstruction or vasculitis of the relevant artery. This condition is usually seen as a complication of infection of bacterial, viral or rickettsial origin; low output states like myocardial infarction, shock, congestive heart failure; and use of vasopressors like dopamine. Less commonly it is described as a complication of paraneoplastic syndrome, ergotism, polymyalgia rheumatica, C-protein deficiency, Raynaud's phenomenon and sickle cell disease etc. In the literature only few cases of SPG have been reported in falciparum malaria². But asymmetrical peripheral gangrene (APG) involving only one extremity (in our patient right foot) has not been described in the literature so far.

CASE REPORT

A 28 years old unmarried male labourer by occupation, presented with blackish discolouration of all the toes of right foot since 10 days (*photograph*). Seven days before the development of black discolouration of the toes, he had high grade fever with rigors and chills and loss of consciousness for the last 24 hours. On physical examination, he was mildly anemic with no evidence of dehydration, cyanosis and edema. Pulse rate was 110/min regular, BP 100/70 mmHg, respiratory rate 23/min and altered sensorium. All peripheral pulses were palpable. Abdominal examination revealed hepatomegaly 4 cm below the right costal margin and splenomegaly just palpable below the left costal margin. Examination of rest of the systems was noncontributory. His laboratory profile revealed Hb 7.2 gm/dl; TLC 6800/mm³; DLC- N62, L34, E2, M2; ESR 20 mm at the end of 1st hour; platelet count 2.2 lacs/mm³; RBS-120 mg/dl; urine C/E -NAD; B.urea 32 mg/dl; Serum creatinine 1.1 mg/dl; Serum bilirubin 1.0 mg/dl; SGOT 30 IU/L; SGPT 35 IU/L; Serum alkaline phosphatase 170 IU/L; BT 1 min 40 sec; CT -2 min 10 sec; PTT -14 seconds; ECG -normal graph; Widal test -ve. Peripheral blood smear showed presence of asexual forms of P.falciparum. Blood and urine culture, HBsAg, anti HCV, antinuclear antibodies, LE cells, RA factor VDRL and Coomb's test were noncontributory. CSF examination was normal. G-6PD was not deficient. Echocardiography and colour doppler study of right limb vessels did not show any abnormality. Blood could not be tested for fibrin degradation products and cryoglobulins because of financial constraints. Local examination of the right foot revealed blackish discolouration of all the toes with definite line of demarcation without any local rise of temperature and ulceration (*photograph*). As the PBF revealed presence of asexual forms of P.falciparum, the patient was put on I/V quinine hydrochloride 600 mg given 8 hourly. The patient improved and regained consciousness after 48 hours of treatment.

DISCUSSION

The most common cause of SPG is septicemia⁹. But other conditions include asplenia, diabetes mellitus, renal failure, Raynaud's phenomenon, myoglobulinaemia, use of ergot and vasopressors like dopamine. Disseminated intravascular coagulation (DIC) is the most common pathogenic mechanism in majority of cases of SPG^{2,3,4,6,7,8}. The likely mechanisms for



DIC in falciparum malaria include activation of complement system⁸, marked parasitaemia triggering the coagulation pathway¹⁰, cytoadherence and rosetting resulting in micro-circulatory obstruction¹¹, alterations in the lipid disturbances across the surface membranes of the parasitised RBC's activating the coagulation pathway¹². Though our patient had no biochemical evidence of DIC, yet its presence could be possible in view of the finding of other workers²⁻⁸ where no manifestation of spontaneous bleeding was found. However in our patient, DIC could have been averted in the initial procoagulant stage with the effective treatment of quinine therapy before the development of consumptive coagulopathy. In the literature, SPG has been described as a complication of P.falciparum malaria by many workers²⁻⁸. But no reference in the literature with regard to asymmetrical peripheral gangrene as in our case involving only one extremity (right foot) could be found even after extensive review of the literature. So, it may be the first rare case of Plasmodium falciparum malaria manifesting as asymmetrical peripheral gangrene from this part of the country to the best of our knowledge. Hence the case report.

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MANAGEMENT OF ANOSMIA

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Abstract : Olfactory dysfunctions, in particular anosmia have been relatively ignored by the physicians despite being a major social harassment for an individual. Moreover, information about diagnosis is also fairly limited. The therapy of olfactory loss is cause specific; therefore each etiology will have to be considered separately and efficacy of each method of treatment has to be thoroughly evaluated. Mostly systemic corticosteroids or intra nasal corticosteroids are being administered. Besides natural supplementation including vitamin A may be considered in deficiency states.

INTRODUCTION

Although different cultures react to smell in different ways and there is no uniformity over our attitude to smell yet plainly speaking, smell not only can please, delight, arouse, comfort, intrigue and bring smiles but can also disgust and annoy. Hence, loss of sense of smell is a great blow and social harassment for a person suffering from anosmia.

Of the five senses, smell ranks fourth in importance for humans, although it is much more pronounced in other animals. Bloodhounds, for example, can smell an odor a thousand times weaker than humans. The sense of smell originates from the first cranial nerves (the olfactory nerves), which sit at the base of the brain's frontal lobes, right behind the eyes and above the nose. Inhaled airborne chemicals stimulate these nerves.

DEFINITION

Anosmia is the lack of olfaction, or a complete loss of the ability to smell. It can be either temporary or permanent. A related term, **hyposmia**, refers to a decrease in the ability to smell, while **hyperosmia** refers to an increased ability to smell or enhanced smell sensitivity. Some people may be anosmic for one particular odour. This is called "**specific anosmia**" and may be genetically based. There are other aberrations of smell beside a decrease. **Dysosmia** stands for distortion in odour perception that includes **parosmia** (distortion of perception of external stimulus) and **phantosmia** (smell perception with no external stimulus). **Troposmia** is thought to be associated with a reduced olfaction ability that could be linked to some cancers or may occur after an upper respiratory infection (URI), head trauma or after treatment with antibiotics¹. **Agnosia** is inability to classify, contrast or identify odour sensation verbally, even though the ability to distinguish between odorants or to recognise them may be normal². Smells can be distorted, intensified, or hallucinated. These changes usually indicate a malfunction of the brain.

ETIOLOGICAL WORK-UP

Anosmia is the most common type of smelling disorder. Loss of the olfactory sense is generally caused by nasal congestion or obstruction. Temporary partial anosmia often occurs when a person has a cold, the flu, or some types of rhinitis, especially hay fever (allergic rhinitis). During these conditions, nasal mucus membranes become inflamed. Other causes for anosmia are:

1) **Physiological:**

The aging process may cause the sense to lessen. In most cases, there is no other obvious cause for the disorder.

2) **Pathological:**

- a. **Atrophic rhinitis:** This condition causes mucus membrane to waste away. The person may experience some level of permanent anosmia. One symptom of this condition is that a person expels a foul-smelling discharge.

- b. **Hypertrophic rhinitis.** Mucous membrane thickens, covering the olfactory nerve endings. If not treated, hypertrophic rhinitis can lead to permanent anosmia. Smoking aggravates the nose's membrane and intensify nasal polyp symptoms.
- c. **Nasal polyps** and other disorders that prevent air from getting to the area in the nose where the smell receptors are found. Hay fever or an allergy may cause one or more polyps to show up.
- d. A **crooked nose** or a **deviated septum**, congenital abnormalities².
- e. **Viral:** Upper respiratory infection (e.g., sinusitis or the common cold)³, AIDS²
- f. In situations such as **head trauma, infections or nasal or sinus surgery, neurosurgery** when the olfactory bulbs, tracts, or central connections are destroyed.
- g. **Head injury.** If both olfactory nerves are torn during a head injury, permanent anosmia results.
- h. **CNS disorders** like Huntington's chorea, Parkinson's disease²
- i. A **tumor** behind the nose or in the membranes surrounding the brain.
- j. Many **systemic diseases** may cause anosmia, including hypothyroidism, diabetes, renal failure, hepatic failure, and pernicious anemia.
- k. **Radiation therapy**
- l. **Refsun's disease**
- m. **Tracheostomy**
- n. **Psychomotor epilepsy:** If the anosmia or unusual odour is intermittent.
- o. **Depression**²

3) **Deficiency States**

Zinc deficiency, Vitamin B₁₂ deficiency, malnutrition².

4) **Drugs and Chemicals**

- a. Drugs such as antihistamines and decongestants like naphazoline, phenothiazines, especially prolonged use of decongestants or overuse of nasal sprays.
- b. Drugs like amphetamines, estrogen, reserpine, captopril and penicillamine.
- c. Thyroid medications, antirheumatic and antiproliferative drugs.
- d. Overuse of alcohol or tobacco.
- e. Exposure to acid fumes and certain chemicals like acrylates, methacrylates,⁴ formaldehyde and insecticides.
- f. Lead poisoning.
- g. Cold-eeze products, over the counter homeopathic nasal sprays and other forms: sprays, pumps, tablets and gel swabs contained zinc gluconate with glycine and cadmium⁵ have reported to cause anosmia.

5) **Idiopathic**

Which means there is no diagnosable cause for the condition.

TREATMENT

Since the disorder is not life threatening, its importance is frequently

underestimated and that information about the diagnosis is also limited. Currently, there is no single therapeutic approach for all aetiologies. Therapy is to be tailored to individual needs and **cause specific**. Various treatable causes of anosmia relate to cause pertaining to nasal pathology. These should be treated by administering antibiotics, decongestants, steroid therapy, multivitamins etc⁷.

i) Nasal and/or Sinus Disease (NSD)

This aetiology is thought to be the most amenable to therapeutic interventions. Anosmic patients with allergic rhinitis and/or nasal polyposis can be successfully treated following administration of systemic corticosteroids and intranasal topical corticosteroids⁸. Alternatively, surgery may be carefully considered.

ii) Systemic corticosteroids

Systemic corticosteroids are potent anti-inflammatory substances that act by reducing inflammation of the nasal mucosa, allowing the odorant to reach the olfactory neuroepithelium⁹. Prednisolone is extremely effective in treating smell disorders and it is often used as a diagnostic tool. Adverse side effects associated with systemic corticosteroids include a raised blood pressure, therefore it is advisable to take only a short course of medication.

iii) Intranasal topical corticosteroids

Intranasal topical corticosteroids such as beclomethasone dipropionate, flunisolide, dexamethasone sodium phosphate are a reasonable alternative. They are believed to be more potent than systemic administrations, which rapidly metabolise into inactive or much less active metabolites. Local side effects are usually mild, for example mucosal dryness and sneezing¹⁰. Topical steroid therapy is effective for treating seasonal perennial rhinitis and nasal polyps.

Nasal sprays are also an effective method of treatment. The distribution of spray encourages maximum exposure of the drug to the nasal and paranasal sinus mucosa.

Administration of several natural supplements with the aim to rectify levels of trace elements including magnesium and zinc may help in isolated cases. However, whether this evidence can be credited, is debatable.

Alternative therapies such as herbal remedies have been proposed to improve smell sensitivity.

iv) Haloperidol in Phantosmia

As a neuroleptic, haloperidol controls hallucinations, thus inhibiting the phantom smells¹¹.

v) Surgical Interventions

Usually surgical measures are undertaken in presence of deformity. Surgical procedures including endoscopic ethmoidectomy, turbinectomy, septoplasty, polypectomy and excision of mass can restore symptoms and in some cases these can last for up to two years¹².

vi) Treatment for olfactory loss from Head trauma/ Post traumatic injuries

Though olfactory system has the ability to regenerate, indeed there is the potential for recovery after a head injury yet in humans the prognosis is much lower. It is generally believed that this aetiology can not be treated with drug therapy. Approximately a third of sufferers do recover¹³ owing to natural regeneration of the olfactory system. However, Ikeda et al¹⁴ in a series of head trauma patients reported that patients on a systemic oral dose of prednisone showed signs of recovery.

Levy et al.¹⁵ proposed the use of theophylline, a nonselective phosphodiesterase (PDE) inhibitor, as a therapeutic approach for relieving symptoms. Theophylline acts by blocking the PDE involved in the transduction process, therefore preventing cAMP metabolising into AMP. As yet this approach is controversial because toxic side effects have been reported at doses which are very close to therapeutic ranges.

vii) Prior Upper Respiratory Infection (URI)

Currently, there is no effective medical treatment to restore the olfaction ability in these patients^{16,17,18}. An alternative and some what controversial

treatment involves the administration of natural trace elements such as zinc and vitamin A. Evidence involving zinc is rather conflicting, hence the term 'zinc controversy'¹³. Evidence of spontaneous recovery is conflicting and that the mechanism and prognosis of the disorder is not fully understood. Approximately a third of patients do recover and in the majority of these cases, recovery occurs six months after onset¹⁶.

Treatment involving vitamin A is not generally supported although vitamin A acted by regenerating the olfactory cells of the mucous and serous glands.

GENERAL MEASURES

All patients should be subjected to *counselling* and *reassurance*, and be made aware of adjustments for everyday living, for example the installation of smoke and fire detectors, avoid gas stove and change to electric stove. When recovery does look unlikely, then it is important that patients develop *adaptive strategies* so that they can cope with personal hygiene, appetite, safety and health. Other areas that should also be considered are vocational, psychological and cognitive difficulties because to some patients they can lead to great anxiety. Some authorities have reported a link between olfactory impairment and sexual dysfunction, although this is disputed by others¹⁹.

Loss of the sense of smell leads to distress, anxiety, and significant impairment of the quality of life. The widespread trivialization of olfactory symptoms by clinicians is inappropriate, but has probably been perpetuated by the widely held but misplaced belief that all causes of smell loss are untreatable. Even if the condition is found to be irremediable after careful investigation, many patients express relief that no serious underlying cause has been found, and many also find it much easier to accept their disability and adjust to life ahead knowing that all avenues have been explored¹⁹.

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OSTEO-ODONTO-KERATOPROSTHESIS: A TOOTH FOR AN EYE

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Abstract : The OOKP (Osteo – Odonto – Keratoprosthesis), although described 40 years ago, is a complex two stage surgical procedure in which a patient's own tooth and surrounding alveolar bone is used to help restore their sight. A plastic lens cemented in to a section of decalcified tooth that is then stiched in to an opening cut in a totally opaque cornea to restore vision. Follow up is life long in order to detect and treat complications one of which is oral. Regular imaging with spiral CT or electron beam tomography can help detect bone and dentine loss. This article aims to describe this complex two stage procedure.

INTRDOUCTION

The Osteo-Odonto – Keratoprosthesis (OOKP) is a two stage complex surgical procedure which is used to replace damaged cornea in blind patients for whom cadaveric corneal transplantation is doomed to be a failure. This technique was developed about 40 years age by Strampelli and uses the patients own tooth root and alveolar bone to support an optical cylinder. Early British followers of this techniques reported poor retention results. Prof. Gian Carlo Falcinelli of Italy, a student of Prof. Strampelli has refined and improved the technique was re-introduced in Britain (UK) at the Sussix Eye Hospital in 1996. The Falccinelli OOKP is now recognized internationally be corneal surgeons worldwide as the treatment of choice for patients with end stage inflammatory corneal disease as in the case of severe dry eye. Because of its complexity the procedure is at present performed by less than 10 centres in the world. India for the first time surgery was performed in Maharashtra at Taparia Eye Institute of Bombay Hospitalo, New Marine Lines, Mumbai.

INDICATIONS (Table 1)

Table 1: Indications for OOKP surgery

- Bilateral corneal blindness resulting from severe end stage Stevens – Johnson syndrome
- Ocular cicatricial pemphigoid
- Chemical burns
- Trachoma, Dry Eyes
- Multiple corneal graft failure

CONTRAINDICATION (Table 2)

Table 2: Contraindication

- Previous history of retinal disease
- Glaucoma (advanced)
- Optic nerve disease
- Ocular perforation
- Pre-phthisis
- Children under age of 17
- Irreparable retinal detachment

Suitable persons who wants to undergo this complex two stage procedure should understand that surgery can be prolonged – they may require multiple procedures and that there is a significant risk of serious complications including loss of eye.

The patient must be able to commit to life long follow up and not

have unreasonable expectations of outcome and cosmesis.

COMPLICATIONS

Table 3: Potential complications of OOKP surgery

Eye
<ul style="list-style-type: none"> • Buccal mucous ulceration • Lid malposition and loss of fornix • Secondary glaucoma • Tilting of optical cylinder • Extrusion of keratoprosthesis • Retroprosthetic membrane formation • Retinal detachment • Endophthalmitis
Mouth
<ul style="list-style-type: none"> • Poor mouth opening • Damage to adjacent tooth • Oro-antral fistula • Jaw fracture
Systemic
Complications of cyclosporine treatment – Scleroderma / renal crisis

PATIENT ASSESSMENT

The patient assessment can be divided into:

- The ophthalmic assessment
- The oral assessment
- Psychological assessment

The patient assessment is a joint assessment by as ophthalmologist (CL) and a maxillofacial surgeon (JH) and a psychiatrist

In pre-operative assessment, a detailed history is recorded and the primary diagnosis and previous surgical interventions especially ocular perforations, glaucoma, or a history of amblyopia is obtained preoperative examination involves determining an intact and functioning retina and optic nerve, by relatively accurate projection of light in all quadrant a normal B scan and in selected cases flash Electroretinogram (ERG) and Visual Evoked Potential (VEP).

ORAL ASSESSMENT

The oral assessment must take in to account both the buccal mucosal graft donor site and selection of an appropriate tooth to form a dentine / bone lamina. Following oral examination and radiography a choice is made as to which tooth (usually a canine) to harvest depending on the length and girth of the root amount of gum recession, and it associated alveolar bone for fashioning a lamina.

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In the absence of suitable single rooted tooth the use of an HLA – matched relatives tooth is possible but prolonged immunosuppression with cyclosporine will be necessary.

The surrounding anatomy is assessed to avoid possible complications and to reduce to cosmetic defect to a minimum There also needs to be an adequate space between the teeth to harvest the tooth without damage to its neighbour. The overall oral health and particular reference to oral hygiene and periodontal bone loss must be assessed. Gingival disease with no bone loss can be easily reversed. Clinical assessment of bone loss can be useful but radiographs are essential. There is usually little to choose between upper or lower canine. Other single rooted teeth can be used in the absence of canine. The mainstay radiographic views are orthopantomograms (OPT) and intra oral periapical radiographs (IOPA) and CT scans. All other things being equal the choice of upper or lower canine depend on the proximity of maxillary sinus in the upper and the proximity of mental foramen in the lower. The lower canine harvesting is straight forward but the buccal plate is occasionally a little thin and the lingual mucoperiosteum is more difficult to procure. The upper canine occasionally gives too much bone palatally and there is a risk of violation of the antrum, however, technically the harvesting is easier. The patient's regular dental practitioner should be informed at this stage so that preparation to replace the missing tooth be made, also be oral hygiene and periodontal condition can be optimized pre operatively.

PSYCHOLOGICAL ASSESSMENT

The patient must be fully informed of the procedure and risks. The patient who has no undergo this complex surgical procedure must be psychologically assessed carefully and must understand that the formation of an osteo-odonto-keratoprosthesis involves multiple operations, usually over a period of months and sometimes years. During that time there will be multiple hospital admissions and follow up visits and these are likely to be setback along the day which may or may not be readily rectifiable, the patient must also appreciate the significant financial, time and emotional stresses that they and those close to them will encounter.

SURGICAL TECHNIQUE

The OOKP surgery is performed usually in 2 stages spaced 2 to 4 months apart. The gap allows soft tissue to grow around the osteo-odonto-lamina and for ocular surface reconstruction with buccal mucosa membrane grafting to become vascularized.

Each stage takes approx. 6 hours and special anesthetic precautions are necessary. Prior to OOKP surgery it is important to treat pre-existing glaucoma by cyclodestruction. Fornix reconstruction, where necessary, can be carried out before hand or at the time of stage I procedure.

Stage I

A monoradicular tooth is harvested to prepare as osteo – odonto – lamina. The root and surrounding jaw bone is sliced sagittally and then removed by cutting across the bridging bone. Whilst the crown is grasped with extraction forceps, the bone are pared down on either the mesial or outer surface with a diamond dusted fly wheel to expose pulp that is removed. The crown of the harvested tooth is used as a handle; whilst the attached tooth root and surrounding bone is worked into a lamina with dentine on one side and bone on the other. Periosteum is conserved and where possible glued back with fibrinogen adhesive. A hole is drilled through dentine through which the anterior part of PMMA optical cylinder is cemented in place. The crown is removed prior to drying with filtered O₂ and the

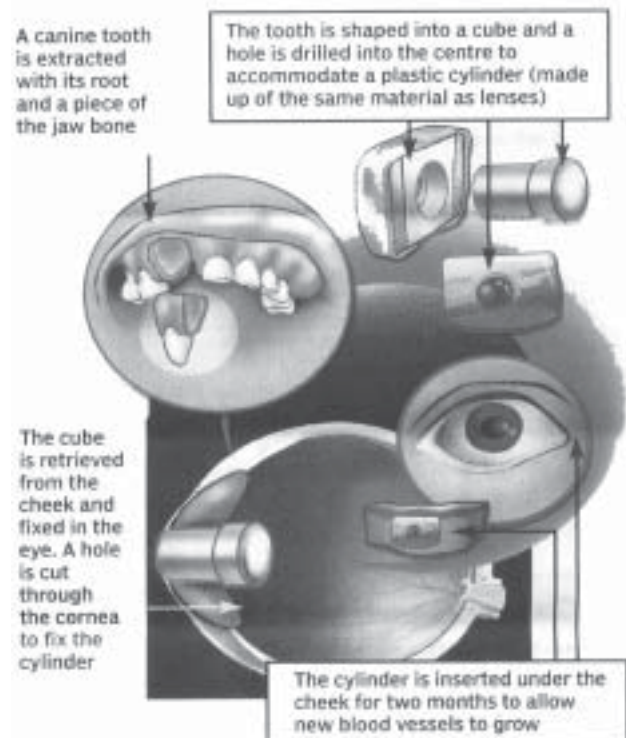
cementing of the optical cylinder. The saw, flywheel and drill and burtips are constantly irrigated with balanced salt solution to provide cooling. Where periosteum has been detached it is glued back with fibrin glue. The KprO is then implanted in to a submuscular patch (often the lower eyelid of fellow eye) for the period of 2-4 months.

Stage II

Stage II surgery is carried out two to four months after Stage I in order for soft tissue to invest in to the bone pores of the lamina. The interval also allows the lamina to recover from thermal damage, and any infection introduced from the oral cavity can be treated whilst the lamina is submuscular rather than on the eye. Stage 2 starts with retrieval of the osteo – odonto lamina from its sub-muscular pocket and excess soft tissue is removed from the bone surface. On the dentine surface, no soft tissue is allowed to remain. The lamina is reinserted in to its pocket until the eye is ready to receive. The buccal mucosal graft is reflected to allow access to the cornea. A Flieringa ring is sutured in place. The centre of the cornea is marked, and a small hole is trephined, the diameter of which corresponds to that of posterior part of the optical cylinder. Relieving incisions are made and total iridodialysis, lens extraction and anterior vitrectomy are performed.

The posterior part of the lamina is inserted through the central corneal hole and the lamina is sutured in to the cornea and sclera.

The eye is re-inflated with sterile filtered air. The mucosal flap is replaced after cutting a hole to allow the protrusion of the anterior part of the optical cylinder.



ANAESTHESIA FOR OOKP

The technique of general anaesthetic for OOKP surgery, both stage I and Stage 2 is similar. Both stages require the administration of antibiotics at induction of the anaesthesia. During the first stage the oral surgeon will require access to the mouth and so a nasotracheal tube is used, for the second stage a RAE or similar orotracheal tube

can be used. After placement of an 18 gauge intravenous cannula, anesthesia is induced; The conduct of the anaesthetic is aimed at obtaining good operating conditions for the surgeon; to this end a little "head up" position for the operating table and the maintenance of a hypotensive technique is employed.

POSTOPERATIVE CARE

After Stage I, a conformer is often in place over the buccal mucous membrane and daily glass rodding is carried out to the fornices to keep them open. The patient uses chlorhexidine and nystatin mouth washes.

Post Stage II, Diamox, steroids and antibiotics are continued. The optic is cleaned and the health of the buccal mucous membrane monitored. The skin sutures are removed after 5 days and the patient is admitted for 1 week for each stage.

FOLLOW UP VISITS

The follow up is life long and at weekly intervals for one month, then monthly for three months then every two months for six months, then every four months.

If stable then follow up can be at longer intervals possibly shared with the referring ophthalmologist.

At the follow up visits the vision is checked, unaided and with correction and pinhole, and a refraction performed. The intraocular pressure is checked digitally, the lids examined, the buccal mucous membrane assessed, including colour, dryness and presence of any areas of thinning or laceration. The optical cylinder is examined specifically looking at the cement, seeing if there is tilting or lengthening and the presence of a retroprosthetic membrane.

The stability of the optical cylinder is also tested by prodding with a cotton tipped stick. Fundoscopy is carried out to check the optic disc and macula, B-Scan to detect early peripheral detachments and visual field assessments are made 6 monthly for diagnosis and monitoring glaucoma. Resorption of the bone may be assessed clinically by palpating the mass and dimensions of the lamina, and radiologically using spiral CT, MRI or electron beam tomography, degeneration can affect statistical results for visual improvement.

CONCLUSION

OOKP surgery is complex and requires meticulous care at each step to ensure the overall success rate. Therefore, surgeons must not attempt to provide a service without first having undergone adequate training. Oral structures have to be sacrificed. All patients experience glare and a restricted visual field. The cost of OOKP surgery is high and formal cost benefit analysis has confirmed its cost effectiveness (un published data) Although it is far from perfect, modern OOKP surgery is the only hope for restoring sight in the long term for desperate cases of corneal blindness not amenable to conventional corneal surgery.

RECOMMENDED READING

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LITERATURE REVIEW

Renal outcome in patients with congenital anomalies of the kidney and urinary tract

Sanna-Cherchi et al Kidney International 2009,76,528-533

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are a major cause of morbidity in children. We measured the risk of progression to end-stage renal disease in 312 patients with CAKUT preselected for the presence of anomalies in kidney number or size. A model of dialysis-free survival from birth was established as a function of the renal CAKUT categories of solitary kidney; unilateral and bilateral hypodysplasia; renal hypodysplasia associated with posterior urethral valves; and multicystic and horseshoe kidney. Cox regression analysis took into account the concomitant presence of vesicoureteral reflux, year of diagnosis, and time-varying values of serum creatinine, proteinuria, and hypertension. By 30 years of age, 58 patients had started dialysis, giving a yearly incidence of 0.023 over a combined 2474 patient risk years. The risk for dialysis was significantly higher for patients with a solitary kidney or with renal hypodysplasia associated with posterior urethral valves (hazard ratios of 2.43 and 5.1, respectively) compared to patients with unilateral or bilateral renal hypodysplasia, or multicystic or horseshoe kidney, and was independent of other prognostic factors. Our study shows that sub-clinical defects of the solitary kidney may be responsible for a poorer prognosis compared to more benign forms of CAKUT. Prospective studies are needed to validate these results.

Special Issues

- Emerging Infections: Indian Perspective
- Challenges of Diabetes in the Developing World
- Ophthalmology Today
- Organ Transplantation: Current Scenario
- Critical Care: What is relevant to our needs
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DANGERS TO HEALTH FROM WATER SUPPLIES IN INDIA

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Abstract : Water serves every need of man. Drinking for quenching the thirst is, perhaps, the greatest use of water. Unsafe water drinking is associated with a variety of diseases besides other dangers to which the public is exposed. The use of polluted water can cause by lapses in administration before installation or, in the distribution system lapses and most importantly personal callousness. The article looks at these aspects in brief.

INTRODUCTION

Water is the elixir of life and there can be no life without water. The water serves every need of man. The water cleans man's environment to abate the spread of disease, gives aestheticity on the earth, provides all comforts and recreations to the man, serves the main in many beneficial ways such as in irrigation/ farming, fish cultivation, industrial (soft drinks production, processing of various products, cooling etc.) reception of huge amounts of water waters generated from the numerous human activities, and most importantly for drinking the great water use. The degree of usefulness for all uses is dependent on the quality status of the water. The public (literate the most) is most ignorant about the quality aspects of water and related direct or indirect impacts / implications. For example, the author has witnessed street eating shops (popularly called 'dhabas' in Delhi) using raw Hooghly river water (meant for street washings, fire fighting etc. in Kolkata) for dish washing etc. mistaking for culinary use the confused colour code of red and green painted taps carrying potable and raw river water many hotels of Kolkata (which had dual water supply system one for potable water and the other for a raw river water system) as a result the non kolkatains dwelling the Kolkata hotels invariably land up using the non potable water for culinary and drinking purposes and thus falling prey to the various water borne disease.

Almost 80% of the various diseases are caused through the use of unsafe water for drinking. The Indian public is almost totally ignorant of the dangers from the use of unsafe, contaminated and polluted waters. The public generally rely upon the aestheticity or palatability of the water, that is, a water that looks clean (turbidity free), that is at a comfortable temperature and that gives no feeling of any kind of taste and / or odour. But the concept of safety or wholesomeness is entirely different. The term wholesomeness applies to waters which do not contain any pathogens (disease causing organisms) or toxicants or excessive amounts of organic matter. It is therefore, the prime duty of environmental engineers to make public water supplies both palatable and wholesome. Apart from this, they should also ensure that the public water supplied do not become unsafe while flowing through the water distribution systems including the overhead service reservoirs. This paper discusses the many dangers to which the public is exposed so that appropriate awareness is created in the present situation.

HEALTH HAZARDS OF WATER

POLLUTION

The various dangers to which the public is exposed while deciding about any water's safety, can broadly be classified in to three

categories. Viz. (i) public administrative (ii) private and (iii) personal

Administrative lapses

These include those dangers which are caused due to the neglect of safety precautions by the various public officials at various places. The following is an account of such dangers.

- 1) The drinking water collected from a sources is made both palatable as well as wholesome at the water treatment plants. This involves several units including sedimentation, flocculation system (channel or mechanical flocculation tank), secondary sedimentation, filtration, clear water reservoir (where contact time is provided for chlorination to inactivate the pathogens) etc. All these units are open and generally constructed separately as individual units. In most situations, they do not have any security and one can easily have an uninterrupted entry in to them (on the pretext of having a look at them to know how their water gets treated) and easily add or throw some soluble poison or pathogen containing capsules in to any of the said water treatment units or at the water intake points. A terrorist act can not be ruled out. This can easily result in a mass killing of the population served by the said water treatment plant. Therefore the water treatment plants should have a very strict type of security arrangements preferably by well trained ferocious dogs as they can not be influenced (or bribed) through dubious means. Likewise the huge service reservoirs or clear water reservoirs (such as the one at the "Hanging Gardens" at Mumbai (Bombay) used also as picnic spots should have adequate foolproof security arrangements
- 2) From the service reservoirs the water is conveyed through distribution system to reach the various consumers. The stated distribution system has many joints all along the way to the consumers and many of them, in India, remain leaking due to the poor and neglected maintenance. Such leaking points also become the places where poison can be injected in to the water resulting in the mass killing of the consumers. The defaulting officers, engineers and / or water analysis keeping track of the desired water quality should be legally held responsible and answerable apart from being tried for mass murder.
- 3) The services pipe leading to individual houses in India, most often have leaking joints and the author has personally seen such joints occurring right in the middle of some open drains carrying the town's wastewater. In such situations, when the

water supply is suspended for any reason, a partial vacuum would result and the wastewater (containing pathogens) of the drain would enter the service pipe to directly reach the consumer. The danger is obvious. The responsible officials should be booked for mass murder in such cases. A surprise random water sampling at the various consumer points and treatment units should routinely be carried out faithfully and regularly.

- All public water supplies are invariably disinfected with chlorine to make the water free of pathogens. A small residual of chlorine is always provided for taking care of any future contamination that may occur on the way to the consumers. Therefore, a chlorine odor is an index of safety against pathogens and the consumer invariably places all his trust and reliance on the residual chlorine. Due to the various corrupt practices most prevalent in India. One hardly notices any residual chlorine any where in India. The involved officials make money through bogus vouchers showing the purchase of chlorine and / or bleaching powder at the cost of the safety of the public. Such offences should be considered very serious and treated as mass murdering.

Private lapses

Due to the lack of confidence for safety of the public water supplies and inadequate public supply of water, the consumers very often manage to have their own private supply of water. Following are some of the situation where the stated consumers become exposed to dangers.

- The consumers for their water supply may install hand pumps, tube wells etc. in their private areas/ premises. But such consumers are most often ignorant about the quality status of the ground water. The groundwater appearing palatable can never be wholesome due to the continuous contamination from the seepage of polluted waters from the surface and open drains carrying domestic and other (also toxic in some cases) waste waters. It is well known that in some areas (such as Mayapuri in Delhi in India), most households private carry out 'Plating' activities generating lot of toxic wastes which flows in open drains only to seep in to the ground and / or reach the nearby stream / river. As part of sabotaging and / or terrorist activities, poisons can even be forced to seep / percolate in to the ground. These toxicants contained in the waters continuously accumulate in some selected organs (s) of the human body only to result in the malfunctioning of such organs (requiring a need for organ transplant) or even death. Such consumers should be educated about the said dangers and to disinfect their waters before consuming.
- The consumers have to have installed a plumbing system (system of pipes from entry of water to exist of waste water) in their houses along with an overhead tank (which are most often, not kept clean, and the author, as a student, once detected a dead foul smelling crow in the overhead tank in his hostel) for storing water for toilet uses. In India, such plumbing jobs are most often carried out by untrained / unlicensed plumbers, as a result, the wholesome public water supply gets mixed up with the overhead tank's unsafe water due to some cross connection s/ inter connections etc. This exposes the consumers to dangers of using their own household water supply. The consumers therefore need education and awareness to get the plumbing work done only by licensed plumbers.
- The advanced countries started the use of bottled mineral

water to supplement the body need for minerals. But, in India ordinary bottled waters started flooding the markets bearing numerous trade names and labels like ozoned / sterilized / etc. water. Duplication (for quick money making) became rampant in India. The Indian public totally unaware of the quality status of such bottled waters, made buying such bottles at Railway / Bus Stands / etc. a status symbol. Many times, the quality of the Railway station tap waters may be better than the so called Indian bottled waters. The various Non Governmental Organizations (such as Delhi's Centre for Science & Environment) should come forward to analyze the said bottled waters and make the public aware of the dangers of consuming the Indian bottled waters.

Personal Lapses

The hygiene of storing and serving of water also poses dangers to human health. The following situation need consideration.

- The hygienic storing of drinking water is often neglected in India. The storing of water in copper, silver and gold vessels makes the water pathogens free and safe. Gold is best, silver next best and copper in that order. The present practice of storing cold water in plastic vessels (as has become fashionable and status symbolic in parties) is dangerous and may some times convert wholesome water in to unsafe water. Unfortunately, the Indian traditional practice of storing drinking waters (at home and in parties) in copper vessels has lately been abandoned. The author feels that the Indian educated need the most awareness.
- The water in unknown situations, jungles, picnic spots, etc. can be disinfected with chlorine/bromine tablets, but unfortunately in India., one has to beware of spurious tablets sold in Indian markets (irrespective of the shop's status). People should be made aware to buy only those tablets which are marketed by government owned organizations such as by the National Environmental Engineering Research Institute, Nagpur. The government should exercise a very strictly punitive legislation for health protecting products.
- The serving of water should be hygienic oriented, for example, the server should avoid his / her fingers dipping in the water meant for drinking.
- The conviction that certain water (also the server) is always safe or unsafe also plays a role in modifying the internal human system to cause the appropriate effect. This however, will need scientific studies.

CONCLUSION

The best thing would be to look at where the water comes from?, who gives it? and how is it given?

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OUR GUEST EDITOR



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EDITORIAL

Menorrhagia or heavy menstrual bleeding is a common gynecological condition affecting 20-30% of women. The problem of heavy menstrual bleeding has assumed greater importance in recent times, essentially because of two factors; one is that today's women experience 10 times more menstrual periods because of lesser number of pregnancies and resultant lesser periods of lactational amenorrhea. The other factor is that, they are more intolerant to inconvenience of menorrhagia as it affects the quality of life. The causes of menorrhagia vary from no demonstrable pathology (dysfunctional uterine bleeding) to malignancy. All cases of menorrhagia need to be evaluated to rule out or diagnose underlying pathology so that appropriate management can be instituted. The article on evaluation and work up of a woman with menorrhagia describes the practical approach to such a woman. In the younger age group anovulatory cycles result in heavy bleeding which usually resolves in 2-3 years with maturity of hypothalamic pituitary axis. Coagulation defects, thyroid disorders, infections and many other causes also contribute to menorrhagia in adolescents and are being dealt in a separate article along with the management guidelines. In the child bearing age, pregnancy complications and organic lesions are important causes and need to be ruled out in all cases of abnormal uterine bleeding. Malignancy and premalignant conditions should be ruled out in this as well as in elderly women. Pap smear and endometrial sampling are simple tests and must be done whenever indicated. Ultrasound, especially transvaginal ultrasound (TVS) and sonohysterography are useful modalities in evaluation of menorrhagia. Treatment is directed to the pathology identified. However, in 50 to 80 % of women no pathology, pelvic or systemic, is identified. The management options for these women include medical treatment, LNG intra uterine device, minimally invasive surgical techniques and as a last resort, hysterectomy. Very effective medical and minimally invasive treatments are available for menorrhagia and these can avoid hysterectomies in women with no underlying pathologies.

Recent advancements in the diagnostic and more importantly in the treatment modalities have made it possible to provide the women relief from this often incapacitating condition and significantly improve the quality of life. The current options available for management of menorrhagia with existing evidence are described in this symposium. Hope it will be useful and make an interesting reading

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EVALUATION & WORK UP OF A WOMAN WITH MENORRHAGIA

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Abstract : Menorrhagia is defined as heavy cyclical bleeding occurring at normal intervals with bleeding increased either in amount (> 80 ml) or duration (>7 days). A detailed history and examination can help the clinician make a fairly accurate probable diagnosis. Further investigations to confirm the diagnosis are guided by factors like age of the woman, presence or absence of high risk factors for endometrial carcinoma and by presence of indicators of any underlying abnormality. The first step is to rule out pregnancy and assess for severity and type of anemia by a detailed blood count and peripheral smear. Depending on the history, bleeding disorders and other medical disorders like hypothyroidism and PCOS should be investigated. As far as use of various diagnostic procedures for evaluation of endometrium is concerned, TVS appears to be a logical first choice as it is simple, non-invasive and cost-effective and helps in deciding the next step in work up of menorrhagia. If a focal lesion is suspected on TVS, SIS or hysteroscopy directed biopsy is indicated and if a diffuse lesion is suspected then an office endometrial biopsy may suffice.

INTRODUCTION

Normal menstruation refers to cyclical flow of blood lasting for 2-7 days at an interval of 28 ± 7 days. The average blood loss is 40 ± 20 ml. per cycle¹. Abnormal uterine bleeding (AUB) is defined as changes in frequency of menses, duration of flow or amount of blood loss. It encompasses both cyclical and non cyclical bleeding. The incidence varies from 10-30% of women in the reproductive age group and up to 50 % of peri-menopausal women².

Menorrhagia is defined as heavy cyclical bleeding occurring at normal intervals with bleeding increased either in amount (> 80 ml) or duration (>7 days). Even a single episode of prolonged bleeding lasting for more than 7 days can be classified as menorrhagia³. When the bleeding is prolonged as well as irregular it is known as menometrorrhagia. Population studies have shown that almost 9-14 % of women have blood loss averaging more than 80 ml per cycle⁵.

It has been shown that patients' perception of increased blood loss may not actually be true specially so in adolescents due to their limited knowledge of what is normal. The commonest subjective method to ascertain the amount of blood loss is a detailed menstrual history as regards the number and type of pads used by the woman and any history of passage of clots. Another method to ascertain whether the woman has excessive menstrual loss is to estimate the hemoglobin concentration. Women with menorrhagia are more likely to have hemoglobin less than 12 gm %. Estimation of serum Ferritin levels (normal 50 – 150 mgm/dl) is a better predictor. It has been shown to correctly predict 60 % of women with > 80 ml blood loss during their periods⁵.

An objective pictorial method for assessing blood loss was proposed by Higham (1990). The woman is asked to observe the degree of soakage of each pad she uses and mark it on a chart provided to her. Scores are assigned depending on the degree of soakage.

- Score 1 – lightly stained pad
- Score 5 – moderately soaked pad
- Score 20 – completely soaked pad
- Score 1 – passage of small clot
- Score 5 – passage of large clot

The total score per cycle is calculated and if it is more than 100 then it implies that the menstrual blood loss of the woman per cycle is > 80 ml.

At a cut off of 100, this method has a sensitivity of 86% and specificity

of 89 %⁶.

AETIOLOGY OF MENORRHAGIA

The aetiology of menorrhagia can be broadly classified into four categories (Table No 1) hormonal, haematological abnormalities, genital organ or genital tract related pathology and idiopathic (DUB)^{9, 10}. However the contribution of each of these four categories to menorrhagia varies according to the age of the woman. The commonest cause in adolescent girls is hormonal imbalance compared to genital tract related pathology in young adult women and

Table1: Etiology of Menorrhagia

Hormonal	Bleeding disorders	Genital tract and genital organ related pathology	Idiopathic
<ul style="list-style-type: none"> • Immature hypothalamus-pituitary-ovarian axis. • Hypothyroidism • Polycystic ovarian syndrome • Hyperprolactinemia 	<p>Congenital</p> <ul style="list-style-type: none"> • von Willibrand disease • Idiopathic thrombocytopenic purpura <p>Acquired</p> <p>Drug induced</p> <ul style="list-style-type: none"> • Anticoagulants as in case of heart disease • Antineoplastic drugs for malignancies <p>Malignancies</p> <ul style="list-style-type: none"> • Leukaemia 	<ul style="list-style-type: none"> • PID (Tubercular, Chlamydia) • Fibroid • Adenomyosis • Endometrial polyps • Endometrial cancer • Oestrogen producing ovarian tumours • Use of IUCD 	<ul style="list-style-type: none"> • DUB

pre-malignant and malignant lesions in peri and postmenopausal women.

WORK UP A WOMAN PRESENTING WITH MENORRHAGIA

Every woman presenting with menorrhagia needs to be systematically worked up. A detailed history is important as a good history can help the clinician to make a provisional diagnosis which can be further fine tuned by examination and finally confirmed by investigations.

History

History should broadly include a detailed menstrual history, sexual

history, medical history, history of drug intake and history of any bleeding disorders.

Menstrual history:

The menstrual history should include the age at menarche, duration of symptoms, and whether symptoms are progressive or not. Details of previous and present menstrual cycles as regards the frequency, duration and blood flow should be recorded. Any history of dysmenorrhoea should be elicited as it helps in making the differential diagnosis of menorrhagia. In case dysmenorrhoea is present, history related to the type of dysmenorrhoea needs to be asked. Dysmenorrhoea is congestive if the pain starts before the periods and gets relieved within a few hours of onset. This type of dysmenorrhoea is usually seen in women with P.I.D. or fibroids. It is as a result of pelvic congestion. Dysmenorrhoea which starts with the onset of periods is spasmodic and gets relieved in a day or so is spasmodic dysmenorrhoea. It is seen in women with fibroids, specially submucous or intramural wherein the uterus tries to expel the fibroid during periods resulting in spasmodic dysmenorrhoea. The patient typically describes the pain as that similar to labour pain. In adenomyosis the dysmenorrhoea starts before the periods, increases throughout the period and persists even after the periods. This type of secondary dysmenorrhoea in a perimenopausal woman is typical of adenomyosis. History of severe dysmenorrhoea with menorrhagia is strongly suggestive of adenomyosis or a submucous fibroid or fibroid polyp.

The date of the last menstrual period is important. It not only helps to rule out pregnancy but also helps in planning endometrial biopsy in the premenstrual phase. It is also important to know if the last period was normal in flow or not. This is because a woman may be pregnant and has implantation bleeding in the form of scanty periods but later presents with heavy bleeding with dysmenorrhoea which is actually inevitable or incomplete abortion. Sometimes women with anovulatory cycles may have very less bleeding in one cycle followed by very heavy flow in the next cycle.

Sexual history:

One should ask if the woman is sexually active and whether she has ever had any sexually transmitted disease.

Medical history:

Symptoms associated with medical conditions resulting in anovulation in self or her family members should be inquired. Table no. 2 gives the symptoms specific to the medical conditions.

Table 2: Clinical presentation - Etiology-wise

Symptoms	Associated medical condition
Acne , hirsutism, weight gain, infertility, acanthosis nigricans , type 2 diabetes mellitus	Polycystic ovarian syndrome (PCOS)
Any increase or decrease in weight, cold or heat intolerance	Thyroid disorder
Headache , blurring of vision, galactorrhoea	Pituitary tumours

History of drug intake:

History of use of anticoagulants like warfarin or aspirin, chemotherapeutic agents, illicit herbs ,dietary supplements, if present, could be a cause of menorrhagia. History of IUCD insertion is important as it is associated with menorrhagia in the initial 3-6 cycles.

Bleeding manifestations:

History of any cutaneous or mucosal bleeding, easy bruisability,

childhood epistaxis, excessive bleeding from superficial cuts and scratches, prolonged bleeding during dental extraction or history of postpartum haemorrhage could be due to an underlying bleeding disorder. In severe forms these disorders could also present with hemarthrosis and dissecting intramuscular haematomas. History of blood or blood component therapy should always be elicited.

Clinical examination:

This should include the following

(1) Pulse and blood pressure; (2) Pallor; (3) Icterus; (4) Palpable lymph nodes; (5) Sign of PCOS or androgen excess, thyroid nodule or enlargement, galactorrhea; (6) Bruising and petechiae; (7) Abdominal examination for any palpable lump, liver and spleen; (8) Per speculum and per vaginam examination to detect the possibility of pregnancy, foreign body or an anatomic source of bleeding. A bimanual examination may elicit tenderness suggestive of PID; an adnexal mass consistent with a functioning ovarian neoplasm, ectopic pregnancy, Tubo-ovarian mass or cyst; or uterine enlargement associated with pregnancy, fibroids, endometriosis or malignancy; (9) Pelvic examination is avoided in adolescents who are not sexually active. A per rectal examination may be carried out instead. Examination under anaesthesia can be done in those adolescents who do not respond to medical therapy.

Investigations:

A detailed clinical evaluation should be followed by investigations.

- 1) Urine *pregnancy test* to rule out pregnancy.
- 2) *Cervical cytology* in sexually active women if not done in the last three years.
- 3) Complete *blood count* with peripheral smear for degree of anaemia, type of anaemia and any evidence of thrombocytopenia
- 4) ESR
- 5) *Reticulocyte count* - if raised helps to confirm a history of excessive bleeding in patients who have a normal haemoglobin level
- 6) Serum *ferritin* levels
- 7) *Liver function tests*
- 8) *Chest X-ray*
- 9) In the presence of signs and symptoms of *endocrinal disease*, following tests should be carried out
 - *Thyroid disease*- Serum T3, T4, TSH
 - *Galactorrhea*- Serum Prolactin
 - *Hyperandrogenism*- S.Testosterone, S. Dehydroepiandrosterone sulfate, S.17 OH Progesterone
 - *PCOS*- Day2 FSH and LH, 2hr GTT and serum insulin and sex hormone binding globulin.
- 10) *Ultrasonography* – A transabdominal ultrasound examination followed by transvaginal ultrasonography is a simple, inexpensive and non invasive method for evaluation of the endometrium and adnexa in cases of menorrhagia. It can be used as an initial investigation to select cases which will require further evaluation by saline infusion sonohysterography (SIS), hysteroscopy or endometrial biopsy. The initial scan can rule out pregnancy and other anatomical abnormalities like polyps (sensitivity 65.2% – 72% , specificity 87.9% - 92 %) and fibroids (sensitivity 95% - 95.8 % , specificity 92% – 95.5%)^{11,12}. When done on day 4-6 of the menstrual cycle a cut off of 5 mm is used to rule out any significant endometrial pathology¹³⁻¹⁶. Women with

thicker endometrium can then be evaluated by saline infusion sonography. SIS involves ultrasound visualization of the endometrium after infusion of 5-10 ml of sterile saline and helps in distinguishing between globally thickened endometrium and focal abnormalities (sensitivity - 91%-94% , specificity 93% -98.7%)^{11,12} .Where the endometrium is globally thickened (> 3mm single layer) one can conduct a directed endometrial biopsy. Combining SIS with directed biopsy results in a sensitivity of 95%-97 % and specificity of 70%-98 % for endometrial pathology.^{17,18} . Presence of cystic ovaries support the diagnosis of DUB (anovulatory) or PCOS, whereas a unilateral adnexal mass may be suggestive of an ovarian tumour.

11) **Endometrial sampling-** It should be done in all women over 40 years and in younger women with high risk factors for endometrial cancer. It is also indicated in women who have no improvement in symptoms after 3 months of medical management. It is rarely indicated in adolescents. The sample should be sent for histopathological examination and AFB smear and culture. In perimenopausal women it should be coupled with endocervical sampling.

Risk factors for endometrial carcinoma

- Age > 40 years
- Weight > 90 kgs.
- History of anovulatory cycles
- Nulliparity with or without history of infertility
- History of use of tamoxifen
- Presence of diabetes / hypertension
- Family history of endometrial / colon cancer

Techniques of endometrial sampling

The various options available to a clinician for endometrial sampling are:

(i) **Office endometrial biopsy** – Office endometrial biopsy has a sensitivity of 67%-96%¹⁹⁻²¹ but may miss upto 18 % of focal lesions²² . It can be performed with the help of a Karman’s cannula no. 4 and a 20 cc syringe with which required negative pressure is created or a pipelle’s curette and does not require any cervical dilatation. As compared to dilatation and curettage it is a relatively safer technique with less chances of hemorrhage, infection and perforation.

(ii) **Dilatation and curettage** – Requires anaesthesia and has no major advantage over office biopsy. However in post menopausal women, Fractional curettage should be a preferred technique of endometrial sampling for ruling out endometrial carcinoma.

(iii) **Hysteroscopy directed biopsy** – Besides evaluation of the endometrium, hysteroscopy also has the advantage of diagnosing focal lesions like polyps, submucous fibroids and focal endometrial carcinoma.

8) Evaluation of haematological disorder: This is indicated in adolescent girls presenting with menorrhagia or when there is a clinical suspicion of a coagulopathy.

Routine use of screening tests like bleeding time, platelet count, PT, aPTTK is useful as it saves time and helps to direct the course of further investigations.

i) Bleeding time - It adds to the diagnosis if prolonged but otherwise may have little clinical use in diagnosis and

Table 3: Stepwise approach for evaluation of abnormal aPTTK and/or PT^{23,24}

Step I: Prolonged aPTTK and /or PT → Review history to rule out drug intake (heparin, warfarin), Liver disease etc

Step II: If negative history
Assess factor VIII levels → normal/reduced

Step III: (a) If factor VIII reduced → *Tests for confirming vWD

Abnormal (vWD) → Haemophilia A

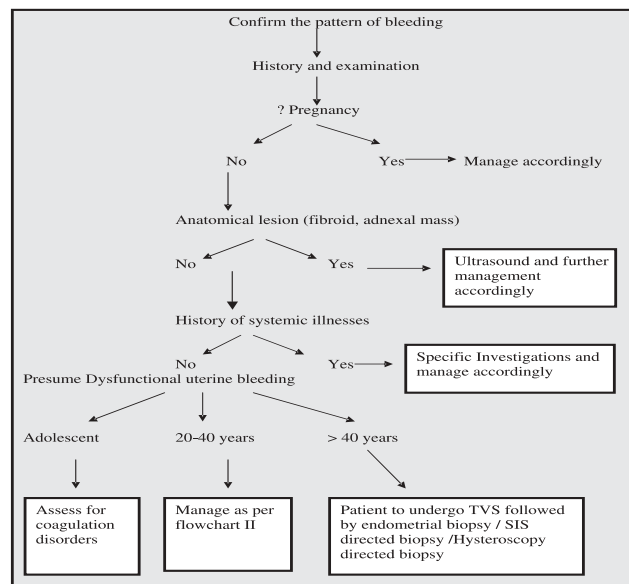
Normal → Haemophilia A

*von Willibrand disease^{23,24};

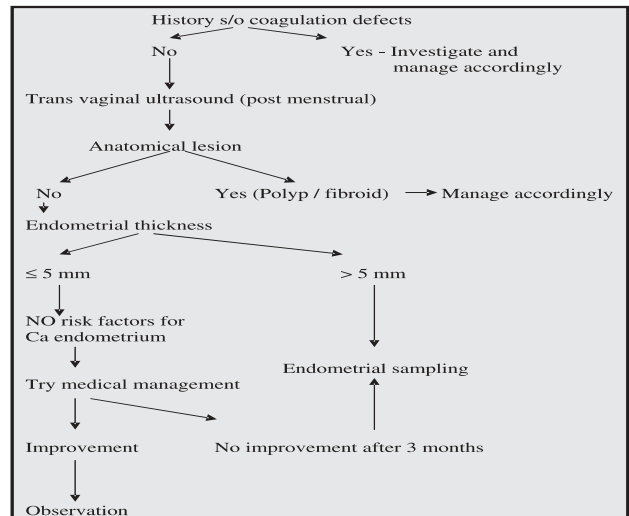
Tests include assays for von Willebrand factor activity (ristocetin cofactor), vWF antigen and a vWF multimer analysis and / or low-dose ristocetin aggregation assay if required.

(b) If factor VIII level normal → assess factor IX → decreased (Haemophilia B)

Flow Chart I: Algorithm of work up of a woman with menorrhagia



Flowchart II: Further work up in 20-40 years old women with menorrhagia



management. Normal bleeding time is 2 to 6 minutes.

- ii) Platelet count- It provide the most reliable and reproducible test of primary haemostasis. A low platelet count should be verified by a repeat platelet count and adequacy of platelets on peripheral smear.
- iii) Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTTK)

PT- It assesses the extrinsic and common pathway (factor VII, factor V, X, prothrombin, fibrinogen.)

aPTTK- It measures all the coagulation factors involved in the intrinsic and common pathways (factor VIII, IX, XII, factor V, X, prothrombin, fibrinogen). It has been accepted as the best single test for coagulation disorders. It reflects reduced levels of factor VIII and vWF.

The above tests provide a presumptive diagnosis, which can be further verified by the confirmatory methods.

An algorithm of work up of a woman with menorrhagia is shown in flowcharts I and II. The investigative work up of a patient of menorrhagia is essentially guided by the age of the woman, history, presence or absence of high risk factors for endometrial carcinoma and clinical examination. TVS appears to be a logical first choice as it is simple, non-invasive and cost-effective and it helps in deciding the next step in work up of menorrhagia. If a focal lesion is suspected on TVS, SIS or hysteroscopy directed biopsy is indicated and if a diffuse lesion is suspected then an office endometrial biopsy may suffice.

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MEDICAL MANAGEMENT OF MENORRHAGIA

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Abstract : One-third of all women experience heavy menstrual bleeding or menorrhagia at some point in their life and about fifty to eighty per cent of these women have no detectable pathology, genital or extragenital. The aim of therapy in these cases is to reduce blood loss, reduce the risk of anemia and improve quality of life. Medical treatment is the mainstay of treatment in the younger age group and is the initial choice in older women with no demonstrable pathology. Medical management involves non- hormonal and hormonal agents and include non-steroidal antiinflammatory drugs (NSAIDS), antifibrinolytics, progestins, estrogens, combined oral contraceptives, androgens and GnRH analogues. Non hormonal treatment, mefenamic acid and tranexamic acid is generally tried first and are effective in reducing blood loss by about 20 to 50% respectively. Progestational agents are indicated in anovulatory menorrhagia and endometrial hyperplasia. Oral contraceptives reduce the blood loss by 50% and regularize the cycles as well. GnRH analogues are very effective in controlling menorrhagia but are not the first line treatment because of the hypoestrogenic side effects. In order to make drug therapy successful, it is important to individualize the approach to management and involve the patient in this process. More than the measures of bleeding, that is, the duration, frequency, and volume, the degree of patient satisfaction may be influenced by factors such as cost, inconvenience, and treatment side effects. Effective medical treatments are available and have the potential to reduce the need for surgical interventions to a large extent.

INTRODUCTION

Menorrhagia, also known as heavy menstrual bleeding (HMB), is defined as a menstrual blood loss greater than 80 ml per cycle. One-third of all women experience heavy menstrual bleeding at some point in their life especially during adolescence and before menopause. About fifty to eighty per cent of women presenting with HMB have no demonstrable pathology, genital or extragenital. Acute menorrhagia may present as an emergency requiring prompt medical or surgical intervention. Chronic menorrhagia can lead to anemia and affects a woman's quality of life in her work, family, and social interactions. The aims of therapy are to reduce blood loss, reduce the risk of anaemia and improve quality of life. Four types of treatments are available for menorrhagia - medical therapy, levonorgestrel-releasing intrauterine system (LNG-IUS), endometrial resection or ablation and hysterectomy. In every age group, medical treatment is the initial choice and is especially indicated when there is no obvious pelvic abnormality. It is the mainstay of treatment in younger women. In elderly women, surgical treatment by endometrial destruction or hysterectomy is sometimes required. Medical management involves non-hormonal and hormonal agents. Non-hormonal treatment is given during menstruation itself and should be the first line in these women. Non hormonal options include nonsteroidal antiinflammatory drugs (NSAIDS) and antifibrinolytics. Hormonal agents include progestins, estrogens, combined oral contraceptives, androgens and GnRH analogues. General measures including reassurance and hematinics have to be initiated with any form of therapy. In order to make drug therapy successful, it is as important to individualize the approach to management and involve the patient in this process. However, there is considerable variation in practice and lack of consensus regarding the most effective therapy. Also poor compliance and unpleasant side effects have limited the satisfaction rates associated with medical therapy. Increased use of effective medical therapies has the potential to reduce the number of surgical procedures, such as endometrial ablation and hysterectomy. This

part of the review focuses on which drug to use and when and recent studies and developments regarding the drug treatment of heavy menstrual bleeding.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Nonsteroidal anti-inflammatory drugs or cyclooxygenase inhibitors are the most thoroughly investigated agents for medical treatment of abnormal uterine bleeding and bring about a reduction in mean menstrual blood loss of about 20%.¹ They also improve dysmenorrhea in up to 70 percent of patients.² Furthermore, these are also effective in women with a copper or non-hormonal intrauterine contraceptive device. NSAIDS act through the inhibition of endometrial prostaglandins.³ Women with ovulatory HMB, have relatively high levels of vasodilating prostaglandins such as PGE2 and PGI2 and therefore, experience therapeutic benefit secondary to reductions in the local levels of these compounds.⁴ The demonstrated involvement of prostaglandins in the genesis of menorrhagia points to cyclooxygenase inhibitors as a potentially effective treatment. Cyclooxygenase inhibitors, commonly referred to as non-steroidal anti-inflammatory drugs (NSAIDs), can be chemically classified into two main groups - COX-1 inhibitors which include aspirin, indomethacin, naproxen, ibuprofen, mefenamic acid, flufenamic acid, and meclofenamic acid. COX-2 inhibitors include celecoxib. Mefenamic acid is most commonly prescribed and is started on the first day of menses and continued for 5 days or until the cessation of menstruation. Usual dose is 500 mg, 2 to 4 times daily. Common side effects of NSAIDs are gastrointestinal irritation and inhibition of platelet aggregation. These agents are the first line treatment for most of the cases and are often preferred to estrogen-progesterone preparations.

ANTIFIBRINOLYTICS

The most commonly prescribed antifibrinolytic agent is the plasminogen activator inhibitor tranexamic acid. It is the mainstay

for the treatment of ovulatory HMB in most parts of the world. It is administered in a dose of 1 g every 6 hours for the first 4 or 5 days of the cycle and has been found to be associated with a reduction in bleeding volume from 40% to 60% in most women.⁵ Side effects include nausea and leg cramps. Most studies have demonstrated a favourable side-effect profile with no increased incidence of gastrointestinal effects or thrombogenic events.^{6,7} But there is a possibility of the potential to cause adverse effects on the cardiovascular system (myocardial infarction) which has been highlighted by a case report, especially when used along with combined oral contraceptive pill but it needs to be evaluated further.⁸

PROGESTINS

Oral progestogens have been the most commonly prescribed hormonal agents for menorrhagia. These are very effective in cases of anovulatory dysfunctional uterine bleeding. They halt the endometrial growth and allow for an organized sloughing of the endometrium. Progestins are able to induce a secretory transformation in otherwise estrogen-stimulated proliferative endometrium.⁹ They also increase the PGF₂-[alpha]/PGE ratio by stimulating arachidonic acid formation in the endometrium, which may also contribute to decreasing abnormal uterine bleeding.¹⁰ Progestagenic agents may be administered via a variety of routes and dose schedules, ranging from intermittent luteal phase or continuous oral administration, through intramuscular injection, or through continuous local administration via a levonorgestrel releasing intrauterine system¹¹.

These are specifically indicated in women with anovulatory bleeding.¹² and have been shown to reduce both the amount and duration of uterine bleeding.

For the **anovulatory type** of dysfunctional uterine bleeding presenting with acute haemorrhage high doses of progestogens are given. *Norethisterone acetate* which has a better hemostatic effect is administered in a dose of 10 mg two to three times per day depending upon the amount of bleeding and tapered down to 10 mg twice daily after about three days when the bleeding reduces and is continued in a dose of 10 mg daily for a total of 21 days. Withdrawal bleeding which is not excessive occurs after about 48 hours. Instead of norethisterone, *medroxyprogesterone acetate* (MPA) or *dydrogestrone* can be given in a similar fashion. For long term management in these women or for women presenting with not so severe bleeding, progestational agents mentioned above may be administered from 16th to 25th day of the cycle for 3 to 6 cycles. Withdrawal bleeding follows after cessation of treatment each month and approximately 50% of the women demonstrating improved cycle control.¹³

On the other hand for **ovulatory menorrhagia**, progestins given in the luteal phase of the menstrual cycle are not effective and need to be administered for 21 days from day 5 to day 25 for reducing menorrhagia in these women.¹⁴ Cyclic therapy is given for 3-6 cycles after which treatment is discontinued and the response is assessed.

In cases of menorrhagia progestins are administered continuously for about three to six cycles in women with endometrial hyperplasia on endometrial biopsy. A repeat biopsy is taken after completion of treatment to check for resolution of the pathology. Common *progestin side effects* include breast tenderness, weight gain, bloatedness and headaches.

The parenterally administered long-acting contraceptive agent depot medroxy progesterone acetate reduces menstrual blood loss. However, due to a high rate of adverse effects and concerns regarding the long-term effects on bone density¹⁵, they are a less favourable option for treatment of menorrhagia in women not requiring contraception.¹⁶

COMBINED ESTROGEN AND PROGESTERONE

Combined oral contraceptive pills (COC) can be used to reduce heavy menstrual bleeding in women with either anovulatory or ovulatory menorrhagia. COC's induce endometrial atrophy which results in reduction of blood loss.¹⁷ A randomized controlled trial of women taking an OC containing 30 µg ethinyl estradiol showed a 43 percent reduction in menstrual blood loss compared to baseline.¹⁸ Use of the COC pill has the additional advantage of reducing the symptoms of dysmenorrhea, providing contraception, cycle control with reduced withdrawal bleeding episodes, hormone replacement in the perimenopausal phase and protection from endometrial and ovarian cancer by about 50%.¹⁹ The presence of uterine myomas, which are estrogen-dependent, is not a contraindication for COC use.²⁰ Disadvantages of combination therapy include the need for strict daily use and systemic side effects.²¹ Combined oral contraceptives can be safely used in nonsmoking women over 35 who do not have risk factors for cardiovascular disease.²² Smoking, age above 35, a personal or family history of thromboembolic disease, and certain other medical conditions like uncontrolled diabetes and hypertension are contraindications to the use of oral contraceptives.

Use of high dose oral contraceptives may be considered in patients having heavy menstrual flow and becoming anemic. In these cases four pills containing 30-35 mcg ethinyl estradiol for 4 days are given followed by 3 pills for 3 days followed by 2 pills for 3 days and then one pill a day thereafter. effects This dose is then continued for 3 weeks which is followed by withdrawal bleeding on stoppage. At this point COC's may be stopped or continued for cycle control for 3 to 6 cycles

High dose OCPs give rise to nausea and vomiting and prior anti emetic reduces these unpleasant side effects.

ESTROGENS

High-dose estrogen therapy in the intravenous (IV) or oral form is useful in controlling acute bleeding episodes when the endometrium is thin, because it promotes rapid endometrial growth to cover denuded endometrial surfaces. Conjugated equine estrogen is used in the dose of 25 mg IV every 4 hours for up to 3 doses. Once bleeding has decreased it can be changed to oral estrogens 2.5 mg conjugated estrogen or 2 mg of micronized estadiol every 4 hours for 24 hours followed by a single dose daily for 14 to 21 days. In last 7 to 10 days medroxy progesterone acetate 10 mg once a day is added. Bleeding following withdrawal of estrogen and progesterone mimics normal menstruation.

ANDROGENS

Danazol is an isooxazole derivative of 17[alpha]-ethinyltestosterone. It suppresses ovulation and reduces ovarian production of 17-[beta]-estradiol. It also has direct effects on estrogen receptors in the endometrium and causes endometrial atrophy. Although in a Cochrane systematic review on the use

of danazol in the treatment of DUB, the authors concluded that danazol appears to be more effective than placebo, progestins, NSAIDs, and COCs in reducing heavy menstrual blood loss²³ it is generally not used because of its androgenic side effects. Reduction of menstrual blood loss by up to 80 percent^{24,24} Lamb MP. Danazol in menorrhagia: A double blind placebo controlled is reported. Following danazol therapy, 20 percent of patients reported amenorrhea and 70 percent reported oligomenorrhea. The recommended treatment is 100 to 200 mg daily for three months.²⁵ Danazol was also noted to have more adverse events like weight gain, oily skin, and acne compared to NSAIDs (odds ratio [OR] 7.0; 95% confidence interval [CI] 1.7-28.2) and progestins (OR 4.05; 95% CI 1.6-10.2); however, adherence to treatment was not affected. Thus danazol is effective for reducing heavy menstrual bleeding, but significant side effects limit its clinical use to short-term management of patient in whom estrogen progestin and anti-fibrinolytics are contraindicated or not effective.

GnRH AGONISTS

Gonadotropin-releasing hormone (GnRH) agonists are very effective in controlling menorrhagia but are not the first line treatment because of its hypoestrogenic side effects. It is specially useful in intractable menorrhagia and in severely anemic women as it gives time to build her up.

GnRH analogues are administered intramuscularly, subcutaneously, or by intranasal route. The common agents used include goserelin 3.6 mg subcutaneous every 28 days, leuprorelin acetate 3.75 mg every 28 days subcutaneous or intramuscular and triptorelin 3 mg every 28 days intramuscular. When administered continuously, GnRH agonists reversibly suppress pituitary secretion of gonadotropins and create a hypoestrogenic state leading to endometrial atrophy and amenorrhea. They may be helpful for short term use in inducing amenorrhea and allowing women to rebuild their red cell mass prior to surgery as bleeding recurs once treatment is stopped. These drugs have mainly been used in fibroid associated bleeding to bring about a reduction in the size of the fibroid. Their use has also been described for women with heavy menstrual bleeding, leading to a significant decrease in bleeding volume and length of menstruation.²⁶ However, there are some significant disadvantages to the use of GnRH analogs which include rapid bone demineralization associated with estrogen suppression, hot flashes and vaginal dryness after 6 months of use.²⁷ Add back therapy with conjugated estrogen 0.625 mg and medroxyprogesterone 2.5 mg daily is effective in preventing the hypoestrogenic symptoms. Thus though GnRH agonists are effective in reducing mean blood loss associated with DUB, it is limited to short-term use because of significant side effects and cost.

DESMOPRESSIN (DDAVP)

DDAVP is a vasopressin analogue and it has a role in the management of small subset of patients with type 1 von-Willebrand disease and hemophilia A presenting with menorrhagia. It is available as intravenous, subcutaneous injection and intranasal spray. It causes an increase in plasma concentration of factor VIII and von-Willebrand factor. Side effects include mild tachycardia, headache, flushing, hyponatremia and water intoxication. Patients need to be advised strict fluid restriction

and electrolyte monitoring for those who require several doses. It is usually given in the first 2 to 3 days of the periods but the dose and duration can be tailored according to the menstrual pattern of the patients. It can be used along with antifibrinolytics.

CONCLUSION

Effective medical treatment is available for the management of menorrhagia. Depending on the underlying abnormality and the needs of patient the most appropriate medical management can be chosen for the woman with reasonably good response

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HYSTERECTOMY FOR MENORRHAGIA: CURRENT TRENDS

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Abstract : Menorrhagia is defined as heavy cyclical bleeding occurring at normal intervals with bleeding increased either in amount (> 80 ml) or duration (>7 days). A detailed history and examination can help the clinician make a fairly accurate probable diagnosis. Further investigations to confirm the diagnosis are guided by factors like age of the woman, presence or absence of high risk factors for endometrial carcinoma and by presence of indicators of any underlying abnormality. The first step is to rule out pregnancy and assess for severity and type of anemia by a detailed blood count and peripheral smear. Depending on the history, bleeding disorders and other medical disorders like hypothyroidism and PCOS should be investigated. As far as use of various diagnostic procedures for evaluation of endometrium is concerned, TVS appears to be a logical first choice as it is simple, non-invasive and cost-effective and helps in deciding the next step in work up of menorrhagia. If a focal lesion is suspected on TVS, SIS or hysteroscopy directed biopsy is indicated and if a diffuse lesion is suspected then an office endometrial biopsy may suffice.

INTRODUCTION

Various treatment options are available for women suffering from menorrhagia namely medical management - hormonal and non-hormonal, minimally invasive endometrial ablative procedures and hysterectomy. Conventionally hysterectomy was the most accepted method for treatment of menorrhagia. However increased use of effective haemostatic agents like tranexamic acid, progesterone releasing intrauterine system (Mirena) and emergence of simple, safe and effective minimally invasive ablative procedures have given a new dimension to the management of menorrhagia. Currently medical management is preferred as the first line treatment for menorrhagia. Over the past decade, the rate of hysterectomy for menorrhagia has shown a significant decline. There has been a 36% reduction in the rate of hysterectomy in United Kingdom and all over the world¹. Similar trend has been reported from India².

Hysterectomy still remains the treatment of choice for women with menorrhagia due to fibroids, adenomyosis and endometrial hyperplasia with atypia. Many women with menorrhagia due to other causes also opt for hysterectomy due to the side effects, complications and limited efficacy of other alternative methods of treatment. Hysterectomy is not only associated with a higher long term satisfaction rate but also with a significantly higher morbidity and mortality³.

HYSTERECTOMY VERSUS OTHER ALTERNATIVE METHODS

Currently medical management is the first line therapy in the women with menorrhagia, a large number of women still opt for hysterectomy. In a review of eight trials by Marjori banks et al⁴. 58% of women randomized for medical treatment under went surgery with in two years due to lack of satisfaction with treatment. However LNG IUS is a highly effective treatment for menorrhagia and is a potential alternative to surgery. On comparing *hysterectomy* with *endometrial ablation*, randomized control trials have shown that hysterectomy is associated with greater cost, higher morbidity and longer recovery time but a significantly greater satisfaction rate^{5,6}.

Currently there are certain *hysterectomy related issues* that are being widely discussed and debated. These include the optimal route of hysterectomy, need for prophylactic oophorectomy and whether total or sub total hysterectomy should be performed for menorrhagia.

HYSTERECTOMY FOR MENORRHAGIA

Optimum route of hysterectomy

Hysterectomy can be performed by abdominal, vaginal or

laparoscopic route. The decision regarding the optimum route is influenced by multiple factors like indication of surgery, size of uterus, any associated pathology, need for concurrent removal of adnexa and expertise of the surgeon. Each approach has its own advantages and disadvantages. Abdominal hysterectomy is the most popular method. It has a distinct advantage of good exposure and easy access to ovaries, retroperitoneal space and upper abdomen but is associated with higher complication rates and longer hospital stay and recovery time. In the past vaginal hysterectomy was mainly done for uterovaginal prolapse. However recently there has been a considerable increase in the popularity of vaginal hysterectomy even in the absence of uterovaginal prolapse - non descent vaginal hysterectomy. It is associated with faster recovery, lesser post operative pain, lower complication rate and shorter hospital stay. It is not the method of choice in uteri more than 12 weeks in size, uterine malignancy and presence of dense adhesions and associated adnexal pathology.

Laparoscopic hysterectomy was initially introduced as a method of making a difficult vaginal hysterectomy easy by releasing adhesion and laparoscopic removal of adnexa etc. The patient recovery, post-operative pain and hospital stay are comparable to vaginal hysterectomy but the complication rate is significantly high. It has a longer learning curve and requires expensive equipment. LAVH is a good choice for women undergoing a difficult vaginal hysterectomy. Thus vaginal hysterectomy appears to be the best route for hysterectomy in the absence of significant pathology like adhesions, adnexal mass, malignancy etc. in which case either an abdominal or laparoscopic hysterectomy should be preferred. The final decision regarding the optimum route lies with the operating surgeon depending on his experience.

Prophylactic oophorectomy with hysterectomy for menorrhagia due to benign causes:

The rationale of concurrent removal of ovaries at the time of hysterectomy is primarily the risk and fear of ovarian cancer and future gynecological interventions. The percentage of women undergoing prophylactic oophorectomy in US is 38% in 18-44 yr age group and 78% in 45-64 yr age group⁷. Majority are performed in women at low risk of ovarian cancer. The overall lifetime risk of ovarian cancer is 1-1.5% and it increases to 5-7% in women with a positive family history of ovarian cancer. The reported risk of ovarian cancer in women with hysterectomy for benign disease is 0.45% as the ovaries that are left behind at the time of hysterectomy are essentially normal.

Although the removal of ovaries prevent ovarian cancer but it is

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also associated with a decline in hormones and its related problems. Sudden fall in the hormones following surgical oophorectomy result in vasomotor instability and subsequently genitourinary atrophy, decrease in libido, depression, dementia, and a 2 fold increase in the cardiovascular disease and osteoporosis. All these changes severely affect the quality of life of these women and contribute significantly to increase in morbidity and mortality due to coronary artery disease and fracture neck femur.

Ovarian hormones both estrogens and androgens play an important role in bone metabolism. They increase the bone formation and inhibit the bone resorption. Oophorectomy even after menopause is associated with a 50% increased risk of osteoporotic fractures as compared to women with intact ovaries⁸ and women older than 60yr have a 2 fold increase in mortality (OR 2.18, CI 2.03- 2.32) after low trauma hip fracture⁹. As regards coronary artery disease, hysterectomy with oophorectomy is an independent risk factor for myocardial infarction or coronary artery disease¹⁰. The number of years elapsed after menopause directly correlate with occurrence and severity of atherosclerosis¹¹. Oophorectomy even after 50 yrs of age increases the risk of MI by 40% (RR 1.4 CI 1.0-2.0) as compared to controls¹² and CAD is the most common cause of death amongst women.

In a recent review of 20 years of published data by Parker et al¹³ to study the relative risk of various oophorectomy related conditions has shown that ovarian conservation confers an overall survival advantage of 8.5% compared to a 0.47% mortality risk from ovarian cancer. This survival advantage is due to lesser women dying of CAD and fracture neck femur. Thus prophylactic oophorectomy is associated with a decrease in risk of ovarian cancer but an increase in risk of all cause mortality and fatal and non-fatal CAD.

This supports ovarian conservation at the time of hysterectomy for benign disease. In women with no high risk factors for ovarian cancer there seems to be a benefit of ovarian conservation at the time hysterectomy for benign disease with resultant decrease in risk of mortality due to CAD in women < 65 year of age and decrease in mortality due to fracture neck femur in those > 65 year¹⁴.

TOTAL VERSUS SUBTOTAL OR SUPRA CERVICAL HYSTERECTOMY

Total hysterectomy includes removal of both uterus and cervix where as subtotal or supracervical hysterectomy means removal of only body of the uterus leaving behind the cervix. Subtotal hysterectomy is usually performed in obstetrics for indications like PPH and rupture uterus in women with unstable general condition. The rationale for subtotal hysterectomy in these patients is to shorten the operation time. Most of the hysterectomies performed for gynecological indications are total except in rare circumstances where removal of cervix is likely to be associated with damage to surrounding organs. An increase in rate of subtotal hysterectomy for gynecological indications was observed in 1990's especially with increasing popularity of laparoscopic hysterectomy. The suggested factors in favor of subtotal hysterectomy were a decrease in damage to surrounding organs, complications, operative time and post operative problems like urinary symptoms, prolapse and sexual dysfunction. This was based on the understanding that the Frankenhauser nerve plexus was spared during subtotal hysterectomy. However recent studies have shown that there is no statistically significant difference in sexual and urinary problems following subtotal or total hysterectomy¹⁵. On the contrary subtotal hysterectomy is associated with cervical stump problems like persistent bleeding per vaginum¹⁶ and cervical stump carcinoma which may subsequently require

trachelectomy¹⁷. Moreover an increased tendency towards prolapse and urinary incontinence has been reported with subtotal hysterectomy possibly due to the absence of vault suspension in these cases¹⁵.

Total hysterectomy has the advantage of lesser women suffering from urinary incontinence prolapse and cervical stump related problems where as subtotal hysterectomy reduces operative time, blood loss during surgery and possibly complications like organ damage and infection. Thus total hysterectomy should be preferred over subtotal hysterectomy except in some patients where removal of cervix may be technically very difficult.

Thus hysterectomy has a definite place in the management of menorrhagia as it is the only definitive method of treatment. But unlike in the past it is not offered as the first line of treatment for menorrhagia except in women with menorrhagia due to fibroids, adenomyosis, DUB with histopathological diagnosis of endometrial hyperplasia with atypia or uterine malignancy. Vaginal hysterectomy should be the route of choice except if the uterine size is >12 weeks, there are extensive adhesions due to PID or endometriosis, associated adnexal pathology or suspected malignancy. Total hysterectomy should be done in all cases of menorrhagia unless removal of cervix is very difficult. The issue of ovarian conservation or removal should be discussed with all women undergoing hysterectomy for menorrhagia and an informed consent should be taken. All women who have not yet attained menopause should be encouraged to retain their ovaries if there is no family history of ovarian cancer. In those undergoing oophorectomy informed consent should include the increased risk of coronary artery disease and osteoporosis with removal of the ovaries.

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MINIMALLY ACCESS TECHNIQUES FOR MENORRHAGIA

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Abstract : Menorrhagia is a common complaint in gynaecological practice and has significant bearing on quality of life issues. Correct diagnoses of cause of menorrhagia is important and management should be directed to the specific cause. The treatment should be planned considering patient wishes, expected outcome, complications and cost effectiveness. The treatment options for women with menorrhagia with no demonstrable cause, that is, in women with dysfunctional uterine bleeding or DUB, are medical treatment, LNG IUS, endometrial ablation and hysterectomy. Most commonly medical management is followed by D&C and ultimately in hysterectomy in many cases. There is much interest globally in decreasing hysterectomy rates in women with DUB as they have anatomically normal uterus. Endometrial ablation techniques have been evolving since 1980's in response to need for safe and effective alternative to hysterectomy. Hysteroscopic ablation was the first to evolve among minimally access techniques for the treatment of DUB. Though there is no doubt about its efficacy, it is technically difficult, requires considerable skill and training and the learning curve is long. In 1990's many nonhysteroscopic techniques were developed. These methods are much simpler to perform with less risk than electrosurgical or laser endometrial ablation. Further, interventional radiological procedures like Uterine Artery Embolization have proven role in treating menorrhagia due to fibroid, adenomyosis and AV malformations, studies are needed before it can be used for treating menorrhagia due to DUB. Levonorgestrel intra uterine system has proved to be an effective alternative to not only the ablative techniques but also to hysterectomy. It is easy to introduce, safe and has minimal complications

INTRODUCTION

Menorrhagia affects 20-30% of women in the reproductive age group causing not only medical problems like anemia and fatigue but also restriction of physical activity, absence from work and discomfort. Traditionally medical therapy is used initially for these cases but it reduces blood loss by 30-50%. It is also associated with side effects, non compliance and return of symptoms on stopping the treatment. Despite these shortcomings medical therapy is the mainstay of treatment in young patients with menorrhagia. In elderly women with family completed, hysterectomy has been considered the definitive surgical management following medical therapy failure. Though it has high satisfaction rates it is a major surgical procedure with physical, social and emotional consequences besides the risk of minor and major operative complications. In a woman with no pathology in the uterus, hysterectomy for menorrhagia appears to be too radical a treatment.

Minimal access techniques, hysteroscopic and non-hysteroscopic, which target endometrium are therefore valid options. Levonorgestrel Intra uterine system (LNG IUS), originally designed for contraception, has emerged as an effective treatment for menorrhagia. Uterine artery embolization is another minimally invasive technique for treating menorrhagia associated with fibroid uterus.

DILATATION AND CURETTAGE

Dilatation and curettage as a diagnostic procedure, has largely been replaced by the other simpler techniques of endometrial sampling and in doubtful cases by hysteroscopy and directed biopsy. However when performed as a diagnostic procedure for menorrhagia in elderly women, it is sometimes curative in women approaching menopause. It is also effective in stopping an acute episode of bleeding as it removes the hyperplastic proliferative endometrium of that cycle while providing the endometrial specimen for histopathology. Except in these situations D&C has a limited role as a therapeutic procedure as the endometrium regenerates from the basal layer in the next cycle. Newer techniques of endometrial ablation, on the other hand, destroy the basal layer of endometrium and superficial layer of myometrium so that endometrium does not regenerate.

ENDOMETRIAL ABLATION

The concept of ablating the endometrium for treatment of menorrhagia

is not new. However, it came into actual clinical practice in 1981 when Goldrath presented his studies on hysteroscopic ablation of endometrium using Nd:YAG laser. For 15 years, hysteroscopic endometrial ablation was the principal method for destruction of endometrium. Although effective, it required considerable skill and training and there was a long learning curve, Number of complications, many of them very serious, were reported. In late 1990's a number of non-hysteroscopic techniques began to appear and soon became popular.

Selection Criteria for Endometrial Ablation:

Endometrial ablation (EA) is done only in women who have completed their family and do not desire future fertility. A thorough preoperative evaluation of endometrial cavity, myometrium, adnexa and the cervix is required before undertaking this procedure. Malignancy (focal/premalignancy) needs to be ruled out, thus endometrial sampling is mandatory preoperatively. Uterine size > 12cm is a contradiction. Uterovaginal prolapse, endometriosis and active PID preclude endometrial ablation.

The thickness of endometrium and access to entire endometrial surface is crucial to the successful outcome. Preoperative D&C, preoperative thinning of endometrium with Danazol or GnRH analogues can increase the success rate.

However, EA does not guarantee amenorrhoea and hence the importance of counseling. Endometrial ablation offers surgical alternative to hysterectomy to women with menorrhagia in terms of shorter hospital stay, absence of surgical incisions and rapid return to activity.

HYSTEROSCOPIC ENDOMETRIAL ABLATION (FIRST GENERATION ENDOMETRIAL ABLATION):

Endometrial ablation in these procedures is performed under direct vision using hysteroscope. Endometrium can be resected using a cutting loop (TCRE) or coagulated using a roller ball. A randomized study conducted at Lady Hardinge Medical College comparing TCRE and roller ball coagulation of endometrium showed both techniques to be safe with comparable success rates¹.

Transcervical Resection of Endometrium (TCRE):

This technique requires resectoscope / operating hysteroscope which consists of a telescope and a continuous flow sheath system (inner and

outer sheath) allowing for simultaneous in-and outflow of the distension liquid. Non electrolyte medium, usually 1.5% glycine solution is used to distend the uterine cavity using a continuous flow irrigation pump, thus maintaining a clear view. The resectoscope allows for two different techniques – resection and coagulation. Endometrial slices of 3-5 mm thickness can be resected with a U-shaped loop connected to a unipolar electrosurgical generator (50-100W) under direct endoscopic control. The main advantage is that it enables histopathological analysis of the material removed. Submucous myomas upto 3cm in size also can be resected. However, the technique requires skill and training to avoid penetrating too deep into the myometrium and causing perforation. A strict watch on fluid deficit has to be kept to avoid the serious complication of fluid overload.

Roller Ball coagulation:

It is performed with an endoscopic resectoscope but in this case the terminal loop is replaced with a roller ball. The roller ball electrode consists of a metal ball or bar connected to a unipolar electrosurgical generator and is used for systematic coagulation of the entire endometrium. Technically, this method is easier than TCRE since the endometrium is simply coagulated. However, the disadvantage is that it does not provide any specimen for histopathological examination.

Since myometrium is thinner and resection is a little difficult at the uterine cornua, coagulation is often performed at the cornua, followed by resection in the rest of the cavity. Any bleeding points at the end of the procedure can be coagulated with roller ball or bar.

Bipolar Coaxial System (Versapoint);

In this system bipolar cautery is used instead of unipolar and hence normal saline is the distension medium. Complications associated with glycine, that is hyponatremia, water intoxication etc, are therefore avoided

Nd:YAG Laser coagulation:

This technique is similar to electrosurgical coagulation but performed with a laser. The initial studies demonstrated high success rate of 94% and amenorrhea rates of 60-80%.^{2,3} However the use of laser for endometrial ablation is not popular because it is expensive and requires special training.

Success Rates

75-80% success rates are achieved with these procedures in terms of patient satisfaction and avoidance of hysterectomy.

Various factors affect the outcome of these procedures. A lot depend on the skill and expertise of the operating surgeon. The presence of adenomyosis is associated with increased failure rate and is found in 75% of post hysterectomy specimens.⁴ Also the failure rate is high in large uteri with large endometrial cavities.

Complications:

Complications with these techniques depend upon skill and training of the operating surgeon and include cervical and uterine perforation, hemorrhage and complications related to distension media.

NON RESECTOSCOPIC / NON HYSTEROSCOPIC ENDOMETRIAL ABLATION (NREA) OR SECOND GENERATION ABLATION TECHNIQUES

NREA refers to number of techniques where the destruction of endometrium is done with devices placed within the endometrial cavity without the use of uterine resectoscope or hysteroscope.

Advantages over Resectoscopic technique :

(1) Rapid to perform; (2) Require less skill and training; (3) No risk of systemic fluid absorption; (4) Results are comparable to resectoscopic techniques; (5) Potential for office use.

Patient selection:

Most of NREA devices require a relatively normal uterine cavity of length

<12 cm. Free fluid ablation (Hydrotherm Ablater) and MEA can be performed when the uterine cavity is irregular.

Anaesthesia :

All manufacturers state that their devices can be used in the outpatient setting without the need for general anaesthesia, however the evidence in the literature is variable. Various techniques have been reported under conscious sedation, local anaesthesia and no anaesthesia.

Techniques

Thermal Balloon Ablation

In this system, the endometrium is destroyed using thermal energy from the heated fluid in the balloon placed within the endometrial cavity. Different systems using this technique are described below:

Thermachoice :

In this system, a single use balloon catheter of outer diameter of 5.5 cm is inserted in the uterine cavity and balloon is filled with dextrose solution and heated to 87°C for 8 min at 160-180mmHg. The balloon catheter has a heating element which is connected through a cable to an electronic controlled device.

All published series except one have used this in uterine cavities of less than 10 cm and without polyps or submucous myomas.

A large multicentric study showed that thermachoice led to significant reduction in severity and duration of menstrual flow and dysmenorrhoea. 15% women were amenorrhoeic and 8% reverted to eumenorrhoea by 12 months.⁵

Another study showed comparable results of thermachoice with rollerball and TCRE as regards reduction in menstrual flow.⁶⁻⁸

Cavaterm

This system uses an oscillating pump in the central unit that vigorously circulate the fluid (glycine) in the balloon which is in intimate contact with the endometrial surface. Two versions of this device are available. The original device consist of a single use catheter having outer diameter of 8.5mm with a silicone balloon which can be adjusted according to the length of the endometrial cavity.

In this system the fluid in balloon is heated to 75°C for 15 min at a pressure of 200-220 mmHg.

Cavaterm Plus is the modified version of the original device wherein the fluid is heated to 78°C at pressure of 230-240mmHg, thereby decreasing the treatment time to 10 minutes.

This system can be used in cavities measuring 4-10 cm in length. Cervical canal length > 6 cm contraindicates its use. Various studies show no difference in amenorrhoea rate between Cavaterm and TCRE.⁹⁻¹² Two RCT's have been published wherein no difference in amenorrhoea rate between cavaterm and TCRE is found. They found a significantly shorter operating time and at 2 years a higher satisfaction and reoperation rates with cavaterm.¹³⁻¹⁴

Menotreat

This device has disposable catheters of 2 different sizes and the balloon is heated to 85°C at 200 mmHg for 11 min. In this device the fluid is heated within the controller, not the balloon catheter.

This device has limited availability. Only one published series has shown its effectiveness wherein 84.3% patients had 50% reduction in bleeding at 6 months following the procedure.¹⁵

Thermablate

This system comprises of a cartridge consisting of balloon, catheter and a reservoir attached to the control unit. The fluid is heated in the reservoir to 73°C before the treatment starts. When the fluid first enters the uterus, the temperature is 155°C and it decreases to 115°C by end of procedure ie in 128 sec at pressure of 180-200 mmHg. To achieve uniform temperature distribution, the pressure is pulsed periodically to mix the fluid in the balloon.

Many studies are not available on this device. Two studies show amenorrhoea rates of 25% and 90% satisfaction rate at 6 months and

no serious complications.¹⁶⁻¹⁷

Radiofrequency Electrosurgical Ablation:

Novasure

Novasure is currently in widespread use and this system consists of a controller unit and a 7.2 mm probe containing a bipolar radiofrequency electrode. After transcervical insertion of the probe, the surgeon measures the intercornual distance with the probe. This combined with the sounded uterine length allows the controller unit to calculate the amount of power required for the specific uterus. The sheath is pulled back after which the gold mesh electrode expands and conforms to the shape of uterine cavity. The radiofrequency energy then ablates the endometrial surface for around 90 seconds.

The probe has many features. In addition to the radiofrequency electrode, it contains channel for CO₂ that tests uterine integrity after probe placement. It also has provision of suction which gets activated during the process of endometrial vaporization and desiccation thus maintaining effective surface contact of the electrode with the endometrial surface.

The sounded uterine cavity length should be under 10 cm and the cavity must be symmetrical. No endometrial preparation is necessary.

A number of studies have compared this device with REA and other NREA techniques and the results are promising.¹⁸⁻²⁰

Cryotherapy

This technique uses cold temperature to freeze and destroy the endometrium. Liquid Nitrogen or compressed gases are used to achieve temperature around -90°C. In this technique 5.5mm cryoprobe is inserted transcervically and the tip of the probe is placed in one cornu of the uterus then moved to other cornu and the remainder of the uterine cavity. Ultrasound is used to monitor the depth of tissue freezing. Usually 2-3 freeze thaw cycles are required to ablate the entire endometrial cavity taking around 10-20 min.

Advantages of Cryotherapy are it is easy to use, is safe as it is done under ultrasound to monitor ablation depth can be outpatient setting and requires less anaesthetic due to analgesic effect of cold temperatures.

In the immediate post operative period minor side effects include pain and persistent discharge in some cases.

Late side effects are abdominal and vaginal pains, prolonged tiredness and perimenopausal symptoms.

Free Fluid Endometrial Ablation

In this method endometrial ablation is done using hot water directly into the endometrial cavity, thus overcoming the possibility of missing some areas which are not in contact with the balloon. Two systems using this technique are available- the HydroThermablator and the Enabl system.

Hydro thermablator

This system is based on circulating hot saline at 90°C into the uterine cavity under direct hysteroscopic guidance for 10 min to ablate the endometrium. The device consist of disposable sheath that fits over 3mm hysteroscope which is connected to a controller unit. After transcervical insertion of device into the endometrial cavity, diagnostic hysteroscopy can first be performed and then the unit is started. The process takes approximately 3 min to heat the saline to 90°C, 10 min to ablate the endometrium and 1 min to cool down after which the device is withdrawn. For safety concerns, the unit is electronically monitored closed system which automatically alarms and shuts down when the fluid escapes via cervix or fallopian tubes thereby reducing the intracavitary pressure. This technique has the potential to be used in patients with abnormal endometrial cavities including intracavitary polyps and myomas.

Two retrospective studies have proven the efficacy of this procedure in patients with abnormal endometrial cavities, however more studies are needed to confirm this.²¹⁻²²

Enabl System

This system does not require the use of hysteroscope. Here a flexible probe which is attached to a controller unit maintains a tight seal at the internal os and circulates fluid in the uterine cavity at 85°C for 15 min. More studies are needed to prove its efficacy for future use.

Microwave EA

In this method, microwave energy is used to ablate the endometrial cavity. The device consists of multiuse 8 mm probe which is connected to a microwave generator. The generator generates microwaves of 9.2GHz which heats the local tissue to 90°C upto depth of 6 mm. After insertion of probe into the uterus the intracavitary position of the device is confirmed and the machine is activated. Sweeping movements are used from fundus downwards to ablate the entire endometrium. The procedure takes about 2-4 minutes.

Diode Laser (ELITT - Endometrial Laser Intrauterine Thermotherapy)

In this technique diode laser is used to destroy the endometrium. The units are used at 30 W for 5 min creating a zone of tissue necrosis of 6 mm. Preliminary clinical studies are promising however large RCT's are needed.^{23,24}

Photodynamic Therapy

This therapy is used upon destroyed endometrium by causing local cytotoxic effect. The endometrium is pretreated by agents which get activated by monochromatic light. They react with tissue oxygen producing singlet oxygen that is cytotoxic and causes tissue necrosis. Larger studies are needed to prove its efficacy in clinical practice.

Chemoablation of the Endometrium

In this technique chemical agents are used to ablate the endometrium. Only one study has so far been published using this technique. They used 95% trichloroacetic acid which was instilled in the uterine cavity via a 3 Fr catheter. Pretreatment with GnRH agonist was done in half the patients.²⁵ The results of the technique are comparable to other NREA techniques but more studies are needed to confirm its efficacy.

Complications of NREA techniques:

Minor immediate complications include nausea, vomiting, pelvic pains, endometritis, urinary tract infection, haematometric and pelvic infection.

Reported serious complications include sepsis, adnexae/ uterine necrosis, lower genital tract, thermal injury.

UTERINE ARTERY EMBOLIZATION (UAE):

Uterine artery embolization has proven efficacy in abnormal uterine bleeding due to fibroids (success rate of 80-95%) and adenomyosis (success rate of 56-92%)^{26,27} Bleeding due to AV malfunction has also been treated using UAE. A small 5 Fr catheter is threaded through a femoral artery under angiographic imaging and guided into the uterine arteries Polyvinyl alcohol particles or triocetyl gelation microspheres are released to block the blood vessels that feed the fibroid or adenomyosis causing them to shrink.

The main advantages of this technique are it is less invasive requires less recovery time and can be performed under local anaesthesia or intra venous sedation However, side effects include bleeding, hematomas at puncture site, allergic reactions to contrast dye, miss embolization of non-target organs and severe post-procedural pain.

LEVONORGESTREL RELEASING INTRAUTERINE SYSTEM (MIRENA)

Levonorgestrel containing intrauterine device was initially designed for contraceptive purposes. Subsequently, its effect on decreasing the

menstrual blood flow was noted and it became a highly effective tool in treating menorrhagia.

This device consists of a T-shaped frame (32 mm by 32 mm) made of polyethylene surrounded by elastomer sleeve in vertical part which contains 52 mg of Levonorgestrel. It releases 20 microgram of Levonorgestrel daily at constant rate over 5 years.

Mechanism of action: LNG causes decidualization of the endometrial stroma, atrophy of the endometrial glands and strong inflammatory infiltrate. Estrogen receptors are downregulated in the glands and stroma thereby inhibiting stimulation by estrogens and causing endometrial atrophy. These changes appear as early as one month after LNG-IUS insertion and are independent of phase of menstrual cycle.

LNG-IUS has been shown to decrease menstrual blood loss by 74-97% and increase hemoglobin levels thereby treating anemia.²⁸⁻³⁵

Currently, LNG-IUS is considered the most effective first line medical therapy for reduction of menstrual blood loss and the overall management of dysfunctional uterine bleeding (DUB). It also serves as a contraceptive method in addition to treating heavy menstrual bleeding.

It is an effective modality of treatment in women with menorrhagia who want future child bearing. Fertility returns rapidly after removal of LNG-IUS and the course of future pregnancies is unaffected.

Various studies³⁵⁻³⁹ comparing LNG-IUS with endometrial ablation techniques have found comparable results as regard reduction in menstrual flow and patient satisfaction. LNG-IUS insertion requires minimal skill and can be used effectively to treat DUB in low resource settings and at lower cost.

Studies comparing LNG with hysterectomy regarding patient preference of treatment and cost analysis indicated that maximum number of patients (68%) preferred LNG-IUS as treatment modality and it was more cost effective than hysterectomy.^{40,41}

Cervical dilatation is required before its insertion into the uterine cavity in nulliparous women. Adequate analgesic can be achieved by administration of NSAID given 1 hour prior to insertion or by use of paracervical block with 1% lignocaine.

Complications are rare with LNG-IUS and include perforation, embolism, expulsion and infection.

Benefits of LNG-IUS far outweigh its risks and its effectiveness in treating DUB and menorrhagia associated with fibroid, endometriosis and endometrial hyperplasia can make it the treatment of choice especially in women desiring contraception as well.

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MANAGEMENT OF MENORRHAGIA IN ADOLESCENTS

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Abstract : Menorrhagia is common in adolescents and young women. In most cases, it is consequent to anovulation due to immaturity of the hypothalamic-pituitary-ovarian feedback mechanism, but in many cases it may be the presenting sign of an underlying illness requiring further evaluation and long term treatment and follow up. The second most common cause of menorrhagia in adolescents and young women is bleeding disorders the main etiology being idiopathic thrombocytopenic purpura and von Willibrand disease. However it is essential to rule out pregnancy in all adolescents who present with unexplained heavy bleeding especially in those who previously had regular cycles. Management of menorrhagia in adolescents is a challenging condition. Management depends on its cause and severity. The primary treatment even in severe cases of bleeding is medical and surgical intervention is rarely warranted. The various principles of management of menorrhagia in adolescents are: control of acute episode, maintenance of normal flow during subsequent cycles, treatment of underlying cause, treatment and prevention of anaemia and allay anxiety.

INTRODUCTION

Menorrhagia is common in adolescents and young women. In most cases, it is consequent to anovulation due to immaturity of the hypothalamic-pituitary-ovarian feedback mechanism, but in many cases it may be the presenting sign of an underlying illness requiring further evaluation and long term treatment and follow up. Besides interfering with daily activities of adolescents and young women, it is associated with the problem of delayed diagnosis and management due to hesitancy on the part of them to seek help.

ETIOLOGY

The aetiology of menorrhagia can be broadly classified into four categories- hormonal, haematological abnormalities, pregnancy related complications and genital organ or genital tract related pathology. However, the contribution of each of these four etiological factors in causing menorrhagia varies with the age of patient. The commonest cause in an adolescent girl is hormonal imbalance compared to pregnancy related complications in young adult women and premalignant and malignant lesions in premenopausal and postmenopausal women respectively.

Focussing on aetiology of menorrhagia in adolescents and young women it was observed in a study that 74% were secondary to hormonal imbalance, 19% due to haemostatic disorders, and remaining 7% were due to pregnancy related complication and local pathology¹. In another study on 106 teenagers presenting with heavy period to a paediatric hospital 85% were found to have evidence of anovulation while 23% had a bleeding disorder².

D) Hormonal

The basic problem is anovulation which may be secondary to immature hypothalamic-pituitary-ovarian axis, hypo or hyperthyroidism, adrenal disease, polycystic ovarian syndrome, pituitary tumours, drug abuse, eating disorders and significant level of sporting activities³. As anovulatory bleeding is unrelated to anatomic lesions of the uterus, some authors refer to this as dysfunctional uterine bleeding (DUB)⁴. It can be irregular, excessive or prolonged bleeding from uterine endometrium. Adolescents presenting with menorrhagia often represent a subset of these anovulatory patients. In majority, etiologic factor centres around slow

maturations of the hypothalamic-pituitary-ovarian axis in female adolescents, leading to unopposed secretion of estrogen resulting in an unstable endometrium. The establishment of orderly ovulatory bleeding may take up to 5 years, however it usually establishes within fifteen months after menarche⁵. This is the most common cause of adolescent menorrhagia and contributes to about 74% to 85% of all cases^{1,2}.

II) Haematological disorder

The second most common cause of menorrhagia in adolescents and young women is bleeding disorders. It can be congenital or acquired. The prevalence as reported in literature ranges from 8.2% to 48%^{2,6}. Claesens and Cowell found bleeding diathesis to be the cause of menorrhagia in 19% of their cases over a period of 9 years in a paediatric clinic¹, the main etiology being idiopathic thrombocytopenic purpura and von Willibrand disease^{1,2,3,7}.

*Idiopathic Thrombocytopenic Purpura (ITP)*⁸

ITP is defined as isolated thrombocytopenia with normal bone marrow and the absence of other causes of thrombocytopenia. It is primarily a disease of increased peripheral platelet destruction, with approximately 60% of patients having antibodies to specific platelet membrane glycoprotein. It is also known as immune thrombocytopenic purpura. The diagnosis of ITP is one of exclusion. Despite the destruction of platelets by splenic macrophages, the spleen is normally not enlarged. In fact, in the presence of enlarged spleen, investigations to rule out other possible causes of thrombocytopenia are indicated.

Von Willibrand disease

With the initiation of menstruation following sloughing of the endometrial lining, the primary stage of haemostasis takes part in controlling the amount of blood loss during menses. vWF mediates platelet adhesion to damaged subendothelium, which leads to platelet activation, secretion of granule contents and aggregation to form the platelet plug. Qualitative and quantitative defects in either vWF or platelets lead to defective haemostasis and thus, patients with these defects are more likely to experience menorrhagia. vWF is required for normal platelet adhesion and also acts as a carrier of factor VIII in the plasma. When vWF is deficient or aberrant, factor VIII

deficiency and abnormalities in the early steps of primary haemostasis result. Majority (95%) of young women who have von Willibrand disease experience menorrhagia. Classically, menorrhagia may be the presenting symptom of von Willibrand disease, with a history of heavy bleeding from the very first menstrual cycle. Typically a family history of menorrhagia can be elicited. vWF levels are under the influence of hormones, which complicate the disease expression, and diagnosis of vWF deficiency. The level of vWF is lowest in early follicular phase rising to as much as 20% by midcycle. The level increases with age approximately 15% for each decade of life⁹. In the classic case, the results of screening tests reveal a normal platelet count and a prolonged aPTTK. In many cases, the aPTTK may be normal. Criteria for the laboratory diagnosis of vWD are imperfect and no test by itself is sensitive and specific enough to diagnose all patients. The vWF and factor VIII are acute phase reactants. Their levels increase with stress, trauma, estrogen therapy and pregnancy. Thus fluctuating level of vWF from time to time make the diagnosis of vW disease difficult. A battery of tests should be considered to conclusively evaluate a patient.

III) OTHER CAUSES OF MENORRHAGIA

It is essential to rule out pregnancy in all adolescents who present with unexplained heavy bleeding especially in those who previously had regular cycles. Also pelvic inflammatory disease particularly chlamydia endometritis and tubercular endometritis should be excluded. Tumours and polyps as causative factors are very rare but are usually detected on ultrasonography and/or pelvic examination. These diagnoses need to be kept in mind especially in patients where management is proving difficult.

MANAGEMENT

Management of menorrhagia in adolescents is a challenging condition. Management depends on its cause and severity. The primary treatment even in severe cases of bleeding is medical and surgical intervention is rarely warranted. There are no studies available to support any specific treatment plan or any particular hormone regime for the management of menorrhagia in adolescents; choice is based on clinical experience¹⁰.

Principles of management:

- 1) Control of acute episode
- 2) Maintenance of normal flow during subsequent cycles
- 3) Treatment of underlying cause
- 4) Treatment and prevention of anaemia
- 5) Allay anxiety.

Management of acute episode of bleeding and maintenance of normal flow during subsequent cycle

All patients with acute episode of severe bleeding need hospitalisation. Arrest of acute episode of bleeding can be achieved in most patients with high dose oral contraceptives pills (OCP) or progestin alone preparations. Progestin alone preparations (medroxyprogesterone acetate or 19 nortestosterone derivatives) are administered in the dose of 15 – 30 mg daily in 3 - 4 divided doses till 1 -2 days after the bleeding stops and then gradually tapered to 5 mg once or twice a day for a total of 21 days from the initiation of therapy. This is followed by withdrawal bleeding and maintenance therapy in the dose of 5 -10 mg daily from 5th to 25th day of the menstrual cycle for 3 -6 cycles. Nortestosterone derivatives have a better haemostatic effect than medroxyprogesterone derivatives. As regards combined oral contraceptive pills one tablet is given every 4 hours till 1-2 days after the bleeding stops and then gradually tapered to 1-2 tablets daily for a total of 21 days from the start of therapy.

This is followed by withdrawal bleeding and 3-6 cycles of combined pills starting from day 2 of the menstrual cycle. Antiemetics have to be given to reduce the nausea and vomiting associated with intake of oral pills. In severely anemic girls the withdrawal bleeding can be postponed by continuously administering the hormonal pills for 2-3 months to gain time to build them up. It is essential to counsel the patient to maintain a regular interval between pills e.g. if a pill has to be administered 8 hourly, she should be advised to take it at 6am, 2pm and 10pm.

Occasionally conjugated equine estrogens (Premarin) 25mg 6 hourly intravenously for a maximum of 6 doses is used to arrest severe acute haemorrhage. It is to be followed by combined oral contraceptive pills 6 to 8 hourly for 3 to 4 days and tapered slowly to once daily for a total of 21 days from initiation of therapy.

Acute episode of bleeding in adolescents and young girls with history of haemostatic disorders

Adolescents and young girls with vWD¹¹:

In patients with von Willibrand disease, acute bleeding episode can be controlled by either increasing endogenous vWF levels with desmopressin (DDAVP) or replacing vWF using an intermediate-purity Factor VIII product or cryoprecipitate, which contains vWF.

i) Desmopressin (DDAVP)

The dose is 0.3 to 0.4 µg/kg body weight intravenously. It avoids the need to use plasma products. The dose can be repeated every 24 hours, but the effect is reduced after some days of treatment.

ii) Factor VIII products

Reserved for patients unresponsive to desmopressin, it is essential to use a virally inactivated product that contains vWF. These products are called intermediate purity Factor VIII concentrates. Recommended dose schedule for Factor VIII is 14-20 iu/kg body weight. It is available as Factor VIII concentrate (500 iu/bottle).

iii) Cryoprecipitate

It is effective, but is not available in virally inactivated form in most countries. Cryoprecipitate containing 80-100 iu of Factor VIII is usually obtained from 250 ml of fresh frozen plasma and is administered in the dose of 1 pack/ 4 kg body weight.

Adolescents and young girls with idiopathic thrombocytopenic purpura¹²:

Platelet infusion is required in the presence of excessive bleeding. Dosage required is 6 to 8 unit of platelet concentrate or 1unit/10kg body weight. One unit of platelet concentrate increases the platelet count by 5,000 to 10,000/cu mm. It is obtained from a single donor unit of blood. Platelets are also available as platelet concentrate, which is collected by plateletpheresis from a single donor and is equivalent to 3-10 units of platelet concentrates. Acute bleeding can be controlled with glucocorticoids and intravenous immunoglobulins. Emergency splenectomy may be indicated in cases not responding to medical measures.

Some other occasionally utilized techniques for control of acute haemorrhage are the use of an inflated balloon of a Foley's catheter as a tamponade to control uterine bleeding and rarely the use of uterine artery embolization has been reported for life threatening bleeding at menarche¹³.

Need for blood transfusion is individualized on the basis of amount of bleeding and general condition of patient. It is indicated in the presence of rapid blood loss of >15% of total blood volume

manifested by orthostatic symptoms, irrespective of level of haemoglobin or hematocrit.

Alternative modalities available for managing subsequent cycles These are extended OCP regime, long acting depo-medroxyprogesterone acetate (DMPA), Levonorgestral releasing IUD, non steroidal anti-inflammatory drugs, antifibrinolytic agents, danazol and GnRH analogues.

OCPs have been reported to reduce menstrual loss by 43%¹³. Over the last few years, use of extended regime is becoming more common. Numerous clinical trials on women with menorrhagia have shown that extended regimen without hormone free interval, is a safe and effective method to relieve these symptoms and ultimately induce amenorrhoea in 80% to 100% of women by 10 to 12 months use till such time their haemoglobin is restored to normal¹⁴.

Intramuscular injection of a long acting progestational agent such as depo- medroxyprogesterone acetate (DMPA) has been used over the last decade to achieve therapeutic amenorrhea in the management of menorrhagia. However, some patients experience breakthrough and irregular bleeding. Such irregular bleeding pattern may further complicate the tendency for uncontrolled bleeding in patients with haematological abnormalities.

Non steroidal anti-inflammatory drugs like mefenamic acid (500mg 8 hourly) and antifibrinolytic drug like tranaxaemic acid (1gm 6-8 hourly) are indicated as an alternative to OCPs during menstruation in those patients who are hemodynamically stable and have moderate to heavy flow. NSAIDS and antifibrinolytic drugs reduce menstrual loss by an average of 30% and 50% respectively.^{15,16}

Danazol¹⁷ is an isoxazol derivative of 17 α ethinyl- testosterone and has a pure progestogenic action. It inhibit release of pituitary gonadotropin thereby suppresses the endometrium. However, its use is limited due to its cost and side effects like androgenic features, weight gain, muscle cramps, skin rashes etc.

GnRH agonists¹⁸ causes pituitary down regulation and subsequent inhibition of cyclical ovarian activity. It is effective in reducing mean blood loss (MBL), however its use is limited to short term because of its cost and significant side effect like osteoporosis etc.

TREATMENT AND PREVENTION OF ANAEMIA

All adolescents with anaemia (haemoglobin less than 12 gm%) are treated with 180-200mg of elemental iron in divided doses whereas those with haemoglobin more than 12gm% should be prescribed prophylactic dose of 100 mg of elemental iron daily.

REASSURANCE

Reassurance is needed for all adolescents with menorrhagia to allay anxiety both related to disease and treatment. Parents and guardians are often reluctant for use of hormonal therapy in the form OCP etc. for their children. Proper counselling needs to be done.

PROGNOSIS AND FOLLOW UP^{19, 20}

Adolescents with menorrhagia constitute a high risk group as there is an increased incidence of anaemia, need for transfusion, subsequent infertility, spontaneous abortion, and impaired reproductive potential. Chronic anovulation in PCOS also predisposes patients to endometrial hyperplasia and frank carcinoma in later life.

The importance of continued follow up in these girls is reinforced by the results of a 25 year prospective evaluation of adolescents' menstrual abnormalities. In 291 patients, 2 years after onset of the presenting episode, bleeding problem continued in 60% at 4 years, in 50% at 10 years and in 30 to 40% after more than 10 years. The worst prognosis was found in those with menorrhagia at the time of menarche.

The girls with underlying coagulation disorder remain a therapeutic challenge, best managed by the combined effort of both a haematologist and gynaecologist.

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INTERNATIONAL MEDICAL SCIENCES ACADEMY

IMSACON 2010

10th/11th September 2010, Royal Society of Medicine, London W1

The Old School House, Otterden, Kent ME13 0BX

raghugaind@aol.com

January 2010

Dear Delegates,

Happy New Year to All of You!

At a meeting on 12th January 2010 at the Royal Society of Medicine (RSM) the date and venue for this year's IMSA CON was finalised. You will please note the date is Friday 10th and Saturday 11th September 2010 and will be held at RSM.

RSM provides excellent facilities and can accommodate in comfort up to 300 participants and, if need be, there is an overflow room which could accommodate an extra 150 delegates with a video link to the main auditorium.

At a meeting last month, in Delhi, with the officers of IMSA, it was agreed that the registration fee per delegate would be £200 (sterling). Registration for accompanying partners/spouse would be £115 (sterling). This includes room hire of the auditorium complex plus separate catering/exhibition space, all standard audio/visual equipment with an AV technician throughout the event, a purpose built registration desk for our exclusive use, 3 coffee breaks throughout the day, with Danish, Croissant, etc with the first break and a hot or cold fork buffet including 2-courses, tea and coffee.

With the next Newsletter I will be sending you a registration form, but in the meantime, it would be helpful if those of you who are intending to join us in September could let me know the following details:-

Name, e-mail address, name of accompanying persons, travel requirements, accommodation required (specifying at this stage the dates and any excursions within the United Kingdom or Europe.) Our travel agents will endeavour to offer you the cheapest and most comfortable mode of travel and stay during the period of the conference and otherwise. They will also help you with your visa requirements.

We have appointed Cambridge Healthcare Solutions as our organising events company for the IMSA 2010 Conference. I would, however, like you in the first instance to direct your enquiries and requirements to the office of the Organising Chairman, Raghu Gaind (RG). It would be most helpful and efficient in time and response if the communication were via e-mail and the subject is clearly declared as IMSA CON 2010.

Dr Dan Danapal (DD) of Harley Street Healthcare Clinic, W1 is the Organising Secretary and Dr Mak Khan (MK) is associated with Cambridge Healthcare Solutions.

The Gala Dinner for the Conference would most likely be at BMA House (British Medical Association). There are likely to be other receptions which I will announce later.

The Scientific Sub Committee is formulating the academic programme for the Conference which has identified the following as the issues of contemporary concern:-

1. Community Care
2. Terminal Care
3. Rehabilitation of Patients with Chronic/Long Term Disabilities
4. Nano Technology in Medical Investigations and Therapeutics.

Any other suggestions would be most welcome.

The Academic Sessions would be from 9.30am sharp to 1.00pm with a break for coffee and from 2.30pm to 5.30pm with a break for tea on both days. Evening receptions would be from 7.30pm onwards.

Pre and Post Conference excursions, to suit your requirements, would be tailor made and through Cambridge Healthcare Solutions. They will offer daily sight seeing tours in London and surrounds. Three to five days tours of Scotland, Lake District, Wales, France and Benelux countries and five to seven days excursions to tour Europe, to include Germany, Switzerland, and Austria. If you require a more extensive tour, this can be arranged. It is the intention of the tour organiser to tailor make the trip in accordance with your wishes.

Accommodation in London has to be booked well in advance and will depend upon, again, your requirements and your budget. We have a whole spectrum of facilities available to us. Their firm rates will become known after the Easter holidays and will be circulated in the April Newsletter. We have agreed a substantial discount from the RSM who provide excellent accommodation. My own Club (Oriental) offers very comfortable accommodation and is around the corner from RSM.

At this stage I request that those who intend to participate in the meeting should identify the numbers in their party and their requirements as indicated above.

With every good wish to you and for a successful Conference.

Raghu Gaind
Organising Chairman

Dan Danapal
Organising Secretary

Mak Khan
Cambridge
Healthcare Solutions