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Modern Hippocratic Oath - Let's Learn

Greetings dear readers. How many times we enter the gate of the College and pass the board displaying the Hippocratic oath without really reading it in detail. After reading this, I started trying to find whether some newer versions have come up because the original oath is invoking God that we, Indians are not even familiar with. This is one modification which I found is very relevant to today's world and I want to share this with all of you.

**Modern Hippocratic Oath**

I swear to fulfill to the best of my ability and judgement this covenant:

I will respect the hard won scientific gains of those physicians in whose steps I walk and gladly share such knowledge as is mine with those who are to follow.

I will apply for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science and that warmth, sympathy and understanding may outweigh the surgeon's knife or chemist's drug.

I will not be ashamed to say 'I know not' nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.

I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problem, if I am to care adequately to the sick.

I will prevent disease whenever I can for prevention is preferable to cure. I will remember that I remain a member of Society with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.

If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter.

May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

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Anju Huria
Editor, JMCC
Clinical and microbiological profile of patients with diabetic foot ulcer – an observational study

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ABSTRACT

Objective: Diabetic foot ulcer is a major healthcare problem that is a significant cause of morbidity, mortality and financial burden. This study was conducted to determine the clinical and microbiological profile of patients with diabetic foot ulcer.

Materials and Methods: A total of 60 patients of diabetic foot ulcer presenting to the diabetic foot clinic in Government Medical College and Hospital, sector 32, Chandigarh were enrolled in an observational study. Age, sex, BMI, duration of diabetes, blood sugar and HbA1C levels, treatment being given for diabetes, neurological status of affected foot and wound culture were observed.

Results: Diabetic foot ulcers were common in age> 50 years (68.3%). Patients presenting with diabetic foot ulcer were more frequently men (88.3%) with BMI 18-25 (73.3%) and had diabetes for a longer duration>10years (55%). Their fasting plasma glucose was mostly between 126-200mg/dl (91.7%), postprandial glucose between 200-250mg/dl (40%) and HbA1C>9.5 (65%). Majority of the patients were on oral hypoglycemic agents (83.3%). 93.3% patients had sensory neuropathy for hot sensations and 53.3% and 55% had loss of vibration and cold sensation. Gram negative aerobes (85.4%) were the most common organism isolated from wound culture.

Conclusions: Most of our patients were male. Majority of patients also had coexistent neuropathy and most had abnormally elevated glycosylated hemoglobin levels. Gram-negative microorganisms were commonly isolated from our patients. Most common isolates were from Enterobacteriaceae family.

Keywords: Diabetic foot ulcer, infections, micro-organisms

INTRODUCTION

During the last 20 years, the world has witnessed an unparalleled increase in the incidence of diabetes mellitus, to the extent, that today; diabetes is considered a global epidemic. Of the overall disease spectrum, diabetic complications account for the greater part of diabetes-related morbidity and healthcare costs. It is well known that diabetic patients have a high risk of developing complications including retinopathy, nephropathy, cardiovascular diseases, neuropathy and diabetic foot ulcer. The most constant ailments a diabetic patient suffers, is the diabetic foot, which is defined as any infection, ulceration, and/or necrosis of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease of the lower limbs. Approximately 10-15% of diabetic patients run the risk of developing ulcers. Ramsey et al reported a cumulative 3-year incidence of 5.8% in diabetic patients in the USA.¹

Indeed, the diabetic foot is now well established as the leading cause of nontraumatic lower extremity amputations the world over, frequently contributing to the mortality of diabetes. The International Working Group on the Diabetic Foot estimated the loss of a foot or leg attributable to diabetes occurring every 30 seconds in the world. In addition, foot complications in diabetic patients inflict an enormous financial burden on the society, since amputations are associated with substantial direct (i.e. hospitalization and medication) as well as indirect (i.e. loss of working days) costs.²
This prospective study was conducted to assess the clinical and microbiological profile of diabetic patients with foot ulcer presenting to Government Medical College and Hospital, Chandigarh that would aid in better assessment and management of such patients.

MATERIAL AND METHODS

The study was carried out prospectively on 60 patients of diabetic foot ulcer presenting to the diabetic foot clinic in Government Medical College and Hospital, Sector 32, Chandigarh.

Study design- Prospective observational study.

After written informed consent, patients who were known diabetic with ulcer limited to the foot with ABI > 0.7 and normal arterial Doppler study were included. Patients suffering from other associated conditions like carcinoma, venous ulcers, burns, vasculitis, buerger's disease, drug therapy for example corticosteroids, chemotherapy or radiotherapy that may interfere with wound healing were excluded from the study. A detailed proforma was filled noting down patient particulars, relevant history, medical examination and diabetic status of patient. A complete hemogram, renal function tests, blood sugars, HbA1c levels and X-ray foot were performed in all patients. Neurological examination was performed using 128 Hz tuning fork for large fibre functions. Small fibre function was assessed using hot and cold objects. Wound cultures were taken at the time of presentation.

Various parameters such as age, sex, BMI, duration of diabetes, blood sugar and HbA1C levels, treatment being given for diabetes, neurological status of affected foot and wound culture were observed.

Statistical analysis: The statistical analysis was carried out using statistical package for social sciences (SPSS Inc., Chicago, IL, version 17.0 for Windows). All the data was recorded on a specially prepared proforma. The categorical variables were presented as number & percentages. Data were presented by using percentages and proportions.

Ethical justification: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

OBSERVATIONS AND RESULTS

A total of 60 patients with diabetic foot ulcer were included in the study and observed for their clinical and microbiological profile. Table 1 shows the patient characteristics and clinical history.

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In this study, 68.3% patients were more than 50 years of age, 30% were between age group of 30-50 years and less than 30 years of age accounted for only 1.7%. Of all the patients studied, male to female ratio was 7.6:1.

Of the 60 patients, 73.3% had normal BMI and 26.7% were in the overweight category.

55% patients had diabetes for more than 10 years duration, 26.7% had diabetes for 5-10 years duration, 10% had diabetes for less than 5 years and only 8.3% who developed diabetic foot ulcer were recently diagnosed.

Table 2 provides laboratory data on diabetic control status including fasting blood glucose levels, postprandial and HbA1c.

5% of patients had FBS <126 mg/dl, 91.7% had FBS between 126-200 mg/dl, and 3.3% had more than 200 mg/dl. Postprandial was <200 mg/dl in 33.3%, 200-250 mg/dl in 40% and >250 mg/dl in 26.7%. HbA1c was >9.5 in 65% of the patients, between 7.5-9.5 in 26.7% and <7.5 in 8.3%.
The treatment that the patient was taking and associated neuropathies are described in Table 3.

83.3% of diabetic foot ulcer patients coming to OPD were on treatment with oral hypoglycemic agents and 16.7% were on insulin therapy. 93.3% had neuropathy for hot sensation, 55% had neuropathy for cold sensation and 53.3% had loss for vibration sense.

Microbiological profile of the patients is given in Table 4.

The treatment in decreasing order were Klebsiella (33.7%), Proteus (23.3%), Pseudomonas (16.7%), Staphylococcus (13.3%), E.coli (8.3%), Acinetobacter (1.7%), E.coli/ACI (1.7%) and Streptococcus (1.7%).

DISCUSSION

Diabetic foot ulcers result from multiple etiological factors. Aging and diabetes duration are two known risk factors in the development of diabetic foot ulcers, apparently mutually related, as the group of greater age reflected a greater duration of diabetes. In our study, 68.3% patients were more than 50 years of age, 30% were between age group of 30-50 years and less than 30 years of age accounted for only 1.7%. Tentolouris N et al studied 379 subjects with diabetes and found foot ulceration mostly in men and those with longer diabetes duration. Of all the patients in our study, 88.3% were males and 11.7% were females.

In a study of 219 diabetic patients by Armstrong DG subjects with neuropathic ulceration had a significantly longer duration of diabetes than controls i.e. subjects who have never had foot ulceration. Similarly in our study, 55% patients had diabetes for more than 10 years duration, 26.7% had diabetes for 5-10 years duration, 10% had diabetes for less than 5 years and only 8.3% who developed diabetic foot ulcer were recently diagnosed.

In a study by Sohn MW et al a significant association was noted between body weight and foot ulceration. The
lowest risk was found for overweight or Class I obese individuals (BMI 25–34.9) and the risk increased as BMI increased. Those with BMI 40–44.9 had 40% higher risk and those with BMI ≥ 45 had 2.1 times higher risk within 6 years. They also found an elevated risk associated with normal weight as compared with overweight and Class I obese individuals. They demonstrated a J-shaped association between body weight and foot ulcer risk. In concordance with their study, 73.3% of our diabetic foot ulcer patients had normal BMI and 26.7% were in the overweight category.

As per Rozsos I et al, poorly controlled blood sugar level is responsible for majority of diabetic foot problems. Kabak S et al have reported higher incidence of gangrenous lesions in patients with poorly controlled blood sugar levels. Similar trends were observed in our study wherein 95% of patients had FBS >126 mg/dl and 66.7% had postprandial sugar levels >200mg/dl. In a study by Sruissadaporn S the mean FBS and HbA1C levels of the ulcer group were significantly higher than those of the control group, suggesting that the diabetic patients with foot ulcers had poorer glycaemic control than those without foot ulcer. Our observations showed similar results with HbA1c >7.5 in 91.7% of the patients.

In all studies where an association was reported, treatment with insulin was associated with an increased risk of diabetic foot ulcers. On the contrary in our study, most of patients with diabetic foot ulcers were on OHA. The reason for this could be that majority of patients coming to GMCH belong to lower socioeconomic status and were convinced to continue with OHA therapy.

Persons of type 2 diabetes are at increased risk of developing peripheral and autonomic neuropathies. Peripheral polyneuropathy is associated with sensory symptoms such as numbness, pain and hyperaesthesia. In the present study, 93.3% patients having sensory neuropathy for hot sensations and 53.3% and 55% had sensory loss for vibration and cold sensations respectively. Our results are consistent with case control studies that have shown neuropathy to be a pivotal risk factors for both ulceration and amputation in persons with diabetes mellitus.13,14

Study conducted by Greene et al showed that distal mixed sensory motor autonomic neuropathy was most common. There was predominance of sensory neuropathy over motor neuropathy. Levin ME stated that most important neuropathic factor in ulcer formation was loss of pain and temperature sensation. They defined two symptom complexes one consisting of pain and paraesthesia and the other of decreased or absent sensation of pain and temperature. Boulton AJM stated that plantar ulceration was significantly associated with decreased vibratory sensations. Mayne N stated that with time the sensory neuropathy tends to deteriorate with loss of vibration and position sense. He also noted that the hyperaesthesia and hyperalgesia usually improved with treatment.

In our study Klebsiella (33.7%) was the most common organism isolated from wound culture followed by Proteus (23.3%), Pseudomonas (16.7%), Staphylococcus (13.3%), E.coli (8.3%), Acinobacter (1.7%), E.coli/ACI (1.7%) and Streptococcus (1.7%). Gram-negative aerobes were most frequently isolated (51.4%), followed by gram-positive aerobes and anaerobes (33.3 and 15.3%, respectively) in a study by Gadeppalli R et al. Various other studies have demonstrated gram negative bacteria as the predominant pathogens.

CONCLUSIONS

Most often, patient with diabetic foot ulcer are more than 50 years and males. Mostly were more than 10 years duration and very less were overweight. With high glycosylated Hb more than 7.5 neuropathy was common.

Gram-negative microorganisms were commonly isolated from our patients. Most common isolates were from Enterobacteriaceae family. The most common microorganism isolated was Klebsiella (33.7%). The most common Gram-positive isolate was Staphylococcus aureus (13.3%).

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

Manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

REFERENCES


Recent advances in drug therapy of hyperlipoproteinemias

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INTRODUCTION

Hypercholesterolemia is a major risk factor for atherosclerosis, which leads to development of coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease. It increases the incidence of myocardial infarction and death. Management of hyperlipidemia involves use of lipid lowering drugs as adjunct to dietary and lifestyle changes which includes exercise and smoking cessation. The various lipid lowering agents available currently include statins, fibrates, niacin, bile acid sequestrants, ezetimibe and few other agents of lesser clinical use. Statins (3-hydroxy-3-methylglutaryl Co-enzyme- A reductase inhibitors, HMG-CoA reductase inhibitors) are currently the most prescribed lipid lowering drugs. Statins have been recommended as first line treatment for hypercholesterolemia by both the European Atherosclerosis Society and the American Heart Association. Members of this class of drugs including simvastatin, atorvastatin, pravastatin, lovastatin, fluvastatin and rosuvastatin have different extent of lipid-lowering effects and drug interaction profile. It has been proven beyond doubt that lowering of low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular morbidity and mortality and their role in secondary prevention of CAD is undisputed. Lowering of LDL-C to target levels recommended by National Cholesterol Education Programme guidelines (NCEP, ATP III) is a cornerstone to management of hyperlipidemia in current medical practice.

Statins exert their major effect—reduction of LDL levels—by inhibiting hepatic cholesterol synthesis through specific and competitive inhibition of HMG-CoA reductase. This leads to depletion of critical intracellular pools of cholesterol, which in turn increases the transcription and expression of LDL receptors on hepatocytes. The greater number of LDL receptors on the surface of hepatocytes results in increased removal of LDL from blood, thereby lowering LDL-C levels. Degradation of LDL receptors is also reduced by statins. However, it has been observed in various studies that many individuals treated with statins do not achieve target levels of LDL-C which leads to persistence of LDL-associated risk.

Familial Hypercholesteremiases

Primary hyperlipoproteinemias are a group of genetic disorders of lipoprotein metabolism. They include six different types of clinical entities depending upon the primary lipoprotein fraction which is raised. Patients with homozygous familial hypercholesterolemia (HoFH) represent the most severe patients within the spectrum of dyslipidemias. Untreated Low-Density Lipoprotein Cholesterol (LDL-C) levels in these patients are usually in the range 500 to 1200 mg/dL. These patients exhibit limited responsiveness to most lipid lowering drugs. Patients with heterozygous familial hypercholesterolemia (HetFH) tend to have untreated LDL-C levels of 250-500 mg/dL. Many of these patients are responsive to statins and/or other specific drugs. Despite the reduction of LDL-C by 50-65% by these drug combinations a significant number of these patients (5-10%) have a severe and/or refractory form of HetFH. They are unable to achieve the treatment goals (NCEP, ATP III guidelines) after maximal oral therapy. The only current therapy option for these patients is Low Density Lipoprotein-apheresis (LDL_a). Hence, newer LDL-C-lowering agents that act via mechanisms distinct from HMG-CoA reductase inhibition are under investigation.

Newer lipid lowering agents

Three new classes of drugs have shown promising results in clinical trials for treatment of highly elevated LDL-C levels in patients suffering from primary familial hyperlipidemias. The first two have recently been approved by the US FDA while the third has shown promising results in clinical trials.
Lomitapide
It is the first new LLD to be approved by FDA in 2012 for treatment of homozygous familial hypercholesterolemia (HoFH). It is an inhibitor of microsomal triglyceride transport protein (MTP) and also decreases LDL-C. MTP is involved in transfer of triglycerides to apolipoprotein B in liver cells and secretion of VLDL. Lomitapide was evaluated in 35 patients of HoFH who were already on statins where it lead to reductions in LDL-C by 40-50%. This orphan drug is approved for use orally once a day in the after evening meals in conjunction with diet and other LLDs. The most important adverse effect of lomitapide is hepatic steatosis, seen in about 8% and raised liver enzymes in 30% patients. Other less serious side effects are diarrhoea, nausea, abdominal pain and vomiting. To ensure safe use it has been approved with a Risk assessment and management strategy (REMS).

Mipomersen
It is the other newly approved agent for treatment of homozygous familial hypercholesterolemia by the US FDA in 2013. Mipomersen is a short, single-stranded antisense oligonucleotide which binds to a specific 20-base sequence on m-RNA coding for apolipoprotein B-100. This leads to reduced synthesis of apolipoprotein B-100 thereby decreasing VLDL secretion into systemic circulation. It is administered as a single weekly injection in conjunction with diet and statins. Mipomersen has been evaluated in three phase 3 clinical trials in patients of familial hyperlipidemias. There was a mean reduction of 25-35% in LDL-C with lowering of triglycerides and lipoprotein (a). Side effects seen commonly included injection site reactions, flu-like symptoms, headache and hepatitis with increased liver transaminases. It has been approved with a Risk assessment and management strategy (REMS).

Agents that inhibit proprotein convertase subtilisin/ kexin type 9 (PCSK9 inhibitors)
Though not yet approved by the FDA, these agents are in late stage of development and appear to be the most promising drugs in the pipeline, acting through a novel target. PCSK9 is the latest member of the proprotein convertase family, which currently consists of 9 members. PCSK9 is an important mediator in lipid haemostasis. The major part of circulating LDL-C is removed from the plasma by hepatic uptake. This process is mediated via transmembrane LDL-Receptor (LDLR) that internalizes bound LDL particles by endocytosis. After intracellular dissociation, the LDLR recycles to the cell surface for reuse. Low intracellular cholesterol levels activate the sterol regulatory element binding protein-2 (SREBP-2), leading to increased LDLR gene expression, which enhances LDL-C clearance from the circulation. Importantly, SREBP-2 also induces expression of PCSK9, leading to enhanced LDLR degradation. This mechanism is thought to be important for regulating cholesterol haemostasis. This effect may negate the effect of statins, which act mainly by increasing expression of LDLR on hepatocytes. Statins also increase the expression of PCSK9 in normolipidemic and dyslipidemic individuals. This may help explain the rationale of use of PCSK9 inhibitors in familial hypercholesterolemia. Clinical trials of monoclonal antibodies targeting PCSK9 have shown large reductions in LDL-C while given along with statins or as monotherapy. Currently three monoclonal antibodies targeting PCSK9 are in phase 3 trials. These include alaricumab, evolocumab and bococizumab. The adverse effect profile of these agents is still unclear but there are concerns relating to cognitive function and increased atherosclerosis by mechanisms other than hepatic LDLR reported in experimental studies. It remains to be seen how these promising agents actually fare in the war against the 'bad cholesterol' once they gain formal approval and are used in clinical practice.

CONCLUSION
The new drugs may be an advancement over the oral therapy for familial hyperlipidemias. However, long term studies are required to ensure the safety of these newer agents. Another important point regarding these drugs is the high cost of these drugs which are monoclonal antibodies or antisense oligonucleotides.

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Osteoporosis – “An emerging epidemic”
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ABSTRACT
Osteoporosis is highly prevalent condition characterized by decrease in bone mass associated with micro-architectural changes in bone structure. Fragility fractures especially of hip & vertebrae are most cumbersome complications of this disease and are associated with marked morbidity & increased risk of mortality. Dual energy X-ray absorptiometry (DEXA) is the main tool to measure bone mineral density which helps in diagnosis of Osteoporosis. Decision to treat should be based on comprehensive fracture risk assessment. Anti-osteoporotic drugs should be used along with non-pharmacologic approaches & particular drug should be selected on the basis of its efficacy & safety considerations. This review article gives a synopsis of pathogenesis, diagnosis & current evidence in management of osteoporosis.

Keywords: fragility fracture, bone mineral density, bisphosphonate, osteoporosis

INTRODUCTION
It is a disease characterized by low bone mass & micro architectural deterioration of bone tissue leading to increased bone fragility & further increased fracture risk. BMD ± 1 SD of young adult is considered as normal. The WHO definition of Osteoporosis is bone density that falls 2.5 standard deviation below the mean for young healthy adults of same sex – also referred as T-score of – 2.5. BMD > 1 SD or < 2.5 SD lower than young adult mean is considered as low bone mass (Osteopenia). Post-menopausal women who are in lower end of the young normal age (T-score < 1.0) are considered as having low bone density & have an increased risk of osteoporosis. BMD > 2.5 SD lower than young adult mean in presence of 1 or more fragility fractures is considered Severe Osteoporosis.

Epidemiology
Osteoporosis occurs more frequently with increasing age as there is loss of bone tissue leading to increase in fracture risk. Loss of ovarian function & also estrogen at menopause precipitates rapid bone loss in women making them prone to develop osteoporosis.

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Major risk factors for Primary Osteoporosis

Non-modifiable -

i) Personal history of fracture during adulthood
ii) History of fracture in first degree relative.
iii) Advanced age
iv) Female sex
v) Dementia

Potentially Modifiable –

i) Current cigarette smoking
ii) Low calcium intake
iii) Excessive alcohol intake
iv) Low body weight (< 58 Kg)
v) Inadequate physical activity
vi) Recurrent falls
vii) Estrogen deficiency

PATHOPHYSIOLOGY

Bone remodeling

Osteoporosis results from age related changes in bone remodeling. There are a number of extrinsic & intrinsic factors that exaggerate this process. Enhanced bone remodeling may be superimposed on low peak bone mass. It has been seen that a genetic locus on chromosome 11 is associated with high bone mass. In adults bone remodeling is principal metabolic skeletal process to maintain skeletal strength & supply calcium from skeleton to maintain serum calcium as well. Bone remodeling is regulated by several circulating hormones like estrogens, androgens, vitamin D, PTH & locally produced growth factors. These factors primarily are responsible for the rate at which new remodeling sites are activated. This process results initially in bone resorption by osteoclasts followed by repair in which new bone tissue is synthesized by osteoblasts. Cytokine responsible for communication between osteoblasts, other marrow cells & osteoclasts has been identified as RANK Ligand (RANKL) [receptor activator of nuclear factor kB]. RANKL is secreted by osteoblasts & osteoclast receptor for this protein is known as RANK. Activation of RANK by RANKL results in osteoclast development & activation. Osteoprotoegerin, another protein, is also secreted by osteoblasts. Modulation of osteoclast recruitment & their activity appears to be related to these three factors. Physical activity as well as nutrition also plays an important role in osteoclast activation.

In young adults bone tissue that is resorbed is replaced by equal amount of newly formed bone tissue. So there is no change in overall skeletal mass after peak bone mass is achieved in adulthood. After age 30-45 there is alteration in balance between formation & resorption & resorption supersedes formation. This imbalance is even more exaggerated in women after menopause. Any amount of increased remodeling produces reversible reduction in bone tissue & also leads to permanent loss of bone tissue & disrupted skeletal architecture. Decreased apposition of new bone on periosteal surface along with bone resorption decreases its strength & further increases risk of osteoporosis-related fractures.

Calcium

Insufficient calcium intake may impair peak bone mass during growth leading to increased risk of osteoporosis in older age. During adult life, insufficient calcium intake during adult life can lead to relative secondary hyperparathyroidism which increases rate of bone remodeling to maintain serum calcium. Long term effects of these compensatory mechanisms are detrimental to skeleton as increased remodeling & ongoing imbalance between resorption & formation lead to rapid loss of bone tissue.

Vitamin D

Optimal targets for Vitamin D are > 30ng/ml & to achieve this level most adults require intake of 800-1000 units/day, particularly those who are not exposed to sunlight. Vitamin D insufficiency also leads to compensatory secondary hyperparathyroidism which is an important risk factor for osteoporosis & fractures. Vitamin D deficiency also leads to increased PTH levels & alkaline phosphatase & reduced levels of ionized calcium.

Estrogen status

Estrogen deficiency causes bone loss by activation of new bone remodeling sites & increased imbalance between bone formation & bone resorption. Menopause is the most common estrogen deficient state. Loss of estrogen increases production of RANKL & may reduce osteoprotoegerin levels causing activation of osteoclasts. Estrogen may also have a role in determining life span of osteoblasts by controlling their rate of apoptosis. Life span of osteoblasts may decrease whereas that of osteoclasts may increase in estrogen deficient states. Vertebral fractures are most common early consequence of estrogen deficiency.
Physical activity

Prolonged inactivity results in significant bone loss & vice versa. These changes are most marked when activity is more during childhood which is growth period & before the onset of puberty. When exercise is initiated during adult life, the effects of exercise on skeleton are modest.

Drugs

Several drugs can produce osteoporosis. Heparin stimulates bone resorption & inhibits bone formation leading to osteoporosis. Anticonvulsants like phenytoin, barbiturates & carbamazepine can result in low bone mass. SSRIs inhibit osteoblast replication & bone formation thus leading to increased risk of fractures. Immunosuppressive agents like cyclosporine & Tacrolimus are associated with bone loss. GnRH analogues & Aromatase inhibitors which block conversion of androgens to estrogen can also lead to osteoporosis. Long term use of PPIs is also associated with bone loss & increased risk of fractures. Thiazolidinedione use is also associated with bone loss as activation of PPARɣ inhibits osteoblast formation.

Cigarette consumption

Prolonged cigarette smoking has detrimental effects on skeletal tissue by its direct toxic effects on osteoblasts & indirectly by modifying estrogen metabolism. Cigarette smoking can also cause intercurrent respiratory illnesses, frailty, decreased exercise, poor nutrition & need for other medications like glucocorticoid which have a negative effect on bone mass.

CLINICAL FEATURES

Vertebral crush fractures (VCFs) – VCFs which occur spontaneously or with minimal trauma are most common clinical presentation of osteoporosis. Term postmenopausal osteoporosis or Type 1 osteoporosis is applied to VCFs at younger age which occur mainly in women whereas senile osteoporosis or Type 2 osteoporosis applies to hip fractures in men & older women.¹

Clinical profile of VCFs varies a lot as some patients may have compression of only one vertebra while others may have involvement of multiple vertebrae which can collapse. Most common site for VCFs is thoracic vertebra below T₆ & in lumbar vertebra. Most common clinical presentation of patients with VCFs is back pain. Height loss is also a sensitive indicator of compression. Many patients are completely asymptomatic. Multiple VCFs cause severe impairment of function. Kyphosis & loss of lumbar lordosis can exacerbate back pain & decreased chest wall expansion may reduce vital capacity. Compression of abdominal contents can cause quiet discomfort. Pain can also be caused by impingement of ribs on the iliac crest.

Hip fracture

Fractures of proximal femur are a major cause of morbidity & mortality in elderly. These fractures are in femoral neck or at base of greater trochanter & are in most cases are due to minimal trauma. Increased frequency of falls & continued bone loss in older people leads to more prevalence of hip & femoral fractures. Many elderly patients can't regain previous level of activity after hip fracture & require prolonged nursing care. It is important to perform complete diagnostic evaluation in such patients & a prevention & treatment plan should be there because another hip fracture or another fragility fracture at other site may occur.³

Colles' fracture

Fracture of distal radius is caused by falling on outstretched hand. There is increased incidence among women after age of 40 years & may be due to pre & peri-menopausal bone loss.¹ Incidence of Colles' fracture in men does not rise with age. Proper evaluation for osteoporosis should be done in patients with Colles' fracture.

Osteoporosis can result in fractures at any site with exception of face. Measurements of bone mineral density & further diagnostic work up should be done for all fractures that occur with minimal trauma.

Secondary osteoporosis

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<th>Causes of Secondary osteoporosis</th>
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<td>I) Endocrine disorders</td>
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<td>Cushing's syndrome</td>
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<td>Adrenal insufficiency</td>
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<td>Type I Diabetes Mellitus</td>
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<td>Hyperparathyroidism</td>
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<td>II) Hypogonadal states</td>
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Various genetic & acquired diseases are associated with increased bone loss leading to osteoporosis termed Secondary osteoporosis. Factors that contribute to bone loss are unique for each disease & include nutritional status, reduced physical activity & factors that affect bone remodeling. In most of the circumstances, the primary diagnosis is made before osteoporosis presents clinically.

**CLINICAL EVALUATION OF METABOLIC BONE DISEASE**

**Bone densitometry**

The gold standard investigation for measuring bone mass is Dual-energy X-ray absorptiometry (DEXA). DEXA can provide accurate & reproducible values for bone mineral density (BMD). BMD is usually measured in lumbar spine, hip & distal radius. DEXA has many advantages like radiation exposure is minimal & scanning time is short (5 - 20 mins). Its disadvantages are that changes with disease progression or therapy are small & it is moderately expensive too. In younger individuals such as perimenopausal or early post-menopausal women, spine measurements of BMD in spine may be most sensitive indicator of bone loss. Due to aortic calcification & osteoarthritic spurs, anteroposterior measurements of BMD in lumbar spine in older patients are subject to error therefore it is better to perform lateral densitometry but this measurement is less precise. Standard practice is to relate the results to normal values by using “T” score which compares individual results to those in young population that is matched for race & sex.

Z-scores compare individual results to those of an age matched population that also is matched for race & sex. A T-score below -2.5 in the lumbar spine, femoral neck or total hip is considered diagnostic of osteoporosis.

**Quantitative computed tomography (QCT)**

CT is used to measure bone density of the spine & the hip & peripheral CT is used to measure bone density in forearm or tibia. Results obtained from CT vary from all others modalities as it is three-dimensional & provides a true density. Trabecular bone & cortical bone content can be measured specifically by this modality. But QCT is more expensive, involves more radiation exposure

**Ultrasound**

It measures bone mass by calculating the attenuation of the signal as it passes through bone or speed with which it traverses the bone. Because of its relatively low cost & mobility, it can be commonly used as screening procedure. Hip is preferred site of measurement bone mass as since it predicts the risk of hip fracture, most important consequence of osteoporosis.

**Indication for BMD tests**

Bone mineral density should be measured in postmenopausal women assuming that they may have one or more risk factors for osteoporosis in addition to age, sex & estrogen deficiency. Bone mineral density measurements should also be considered in all women by age 65. Following are the indications for measuring BMD :-

1) Post-menopausal women at risk of osteoporosis.
2) Vertebral abnormalities on X-ray suggestive of osteoporosis
3) Glucocorticoid treatment for > 3 months & dose equivalent to ≥ 7.5 mg of prednisolone.

4) Primary hyperparathyroidism

5) Monitoring response to treatment for osteoporosis

**When to treat**

The treatment for osteoporosis should be considered when BMD is > 2.5 SD below mean value for young adults (T-score ≤ -2.5) consistent with diagnosis of osteoporosis.

Treatment should also be considered in postmenopausal women with risk factors for fracture even if BMD is not in osteoporotic range.

Possible risk factors for fracture are: age, prior fracture, cigarette smoking & excessive alcohol use, family history of hip fracture, low body weight, glucocorticoid use & rheumatoid arthritis.

**Biochemical markers**

Biochemical markers assess rate of bone formation & bone resorption. Increased turnover i.e. high rates of resorption & formation correlates inversely with bone mass & may predict a high rate of bone loss & increased risk of fracture. Most common clinical use of biochemical markers is rapid assessment of response to antiresorptive agents. Decrease in resorption markers can be seen at 3-6 months as a result of treatment which is evident even before changes in BMD are measurable by DEXA. Biochemical marker response to treatment is particularly helpful in asymptomatic patients & may also help ensure long-term adherence to treatment. Following markers of bone metabolism are in clinical use commonly. Serum bone-specific alkaline phosphatase, Serum osteocalcin & Serum propeptide of type I procollagen are markers of bone formation while Urine & serum cross-linked N-telopeptide & Urine & serum cross-linked C-telopeptide are markers for resorption.

**Diagnosis**

Osteoporosis can be detected before fracture occurs by measuring BMD. The goal of diagnosis in patients with no history of fractures is to predict future fracture risk & plan prevention. As such BMD alone is insufficient for fracture risk assessment, age & other risk factors can be added & fracture risk can be assessed based on WHO fracture risk assessment test FRAX 

which provides estimate of 10-year probability of a fragility fracture.

Universal screening of Women should be screened universally after 65 years of age for osteoporosis. Women who have multiple risk factors e.g. low body weight or a personal or family history of fragility fracture are recommended screening in early age also. Bone density should also be measured in men & premenopausal women with fragility fracture. BMD measurements can quantitate severity of bone tissue loss which helps in predicting future fracture risk & may be used to monitor therapeutic response.

History should include details about calcium intake & nutrition, any change in height or weight, physical activity & lifestyle, menstrual history & reproductive history, history of smoking/ alcohol intake or personal / family history of fragility fractures & history of other metabolic or endocrine disorders. Physical examination should include a careful height measurement, assessment of spine & evaluation for thyroid & adrenal disease.

Radiologic assessment of spine fractures should be done. If there are neurologic abnormalities or if fracture is associated with normal bone density which raises suspicion of malignancy, MRI or CT may be done. Laboratory workup should include serum calcium & urinary 24-hour calcium & 25-hydroxyvitamin D should also be measured. Serum alkaline phosphatase & phosphorus are checked to rule out hyperparathyroidism & osteomalacia. Complete blood count, ESR & Serum electrophoresis can help to rule out myeloma. Thyroid function tests should be done if suggestive clinical features are present. In younger patients with osteoporosis, gonadal & pituitary hormones can be measured. Celiac disease should be ruled out in patients with features of malabsorption syndrome.

**TREATMENT**

**Risk factor reduction**

Patients should be thoroughly counseled to decrease impact of modifiable risk factors associated with bone loss & falling. Smokers should be advised to quit smoking. If patient is taking glucocorticoids, their necessity as well as dose should be checked. TFTs should be done to check if excessive dose of thyroxine is not prescribed as thyrotoxicosis can enhance bone loss. Risk factors for falling can be taken care by review of medications that might be associated with orthostatic
hypotension / sedation & alcohol abuse treatment. Avoiding slippery rugs, checking carpet conditions especially on stairs & providing good light on way to washroom are important preventive measures for fall & subsequent fractures in fracture prone individuals. Treatment for visual defects is strongly recommended. Elderly patients with neurologic ailments e.g. stroke, Parkinson's disease & Alzheimer's disease are more prone to falls & require specialized care & supervision.

**Nutritional recommendations**

**Calcium** – Optimal calcium intake reduces bone loss & suppresses bone turnover. Dairy products are rich source of calcium but some patients still require calcium supplementation. If a calcium supplement is required, it should be taken in doses ≤ 600 mg at one time as higher doses lead to decreased calcium absorption. Calcium supplementation should be calculated on basis of elemental calcium content of the supplement. Carbonate containing Calcium supplements should be taken with food since they require acid for solubility while calcium citrate supplements can be taken any time irrespective of food timings. BMD response to antiresorptive therapy is adequate when a patient is taking optimum calcium. Recommended calcium intake ranges from 1 – 2 g/day for prevention & treatment of osteoporosis.

**Vitamin D** – Vitamin D is synthesized in skin under influence of ultraviolet rays in sunlight. Majority of population is Vitamin D deficient due to limited sun exposure & less intake & they don't maintain optimal levels [> 75 µmol/L (30ng/ml)] . Vitamin D helps in intestinal absorption of calcium through formation of 1,25 dihydroxy Cholecalciferol. Daily recommended intake of Vitamin D is - 200 IU for adults < 50 yrs of age, 400 IU for 50-70 years & 600 IU for > 70. Calcium & Vitamin D in tandem increase bone mass, decrease bone loss & can decrease incidence of fractures. Vitamin K is required for optimal carboxylation of osteocalcin. Long term anticoagulant use has been associated with reduced bone mass.

**Exercise**

In young individuals, exercise increases the likelihood that they will attain maximal genetically determined peak bone mass. Weight bearing exercises prevent bone loss in postmenopausal women but beneficial effects disappear on discontinuation of exercise. Exercise also has beneficial effect on neuromuscular function & it improves coordination as well as balance thereby reducing risk of falling.

**PHARMACOLOGIC THERAPIES**

**Estrogens** – Various types of estrogens reduce bone turnover, prevent bone loss & increase total body bone mass. Their mechanism of action is by inhibiting osteoclasts directly as well as indirectly through cytokine production. Estrogens are quite effective in women with menopause & in post-menopausal women with or without established osteoporosis. Estrogen replacement can lead to reduction in osteoporotic fractures including. Beneficial effects are seen in those women who start treatment early & continue with the treatment. The benefit declines after discontinuation of treatment & there is no residual protective effect against fractures by 10 years after discontinuation of therapy. Therefore patients who discontinue estrogens need to be carefully monitored & alternative therapy should be considered in such individuals. Combined estrogen-progestin treatment (HRT) increases risk of fatal as well as nonfatal myocardial infarction (~29%), stroke (~40%) & venous thromboembolism (~100%) There is rise in incidence of breast cancer (~ 26%) but also a ~ 37% risk in reduction in risk of colon cancer. Therefore estrogens are no longer considered primary treatment option for osteoporosis.

**Selective estrogen response modulators (SERMs)**

Two selective estrogen response modulators (SERMs) are currently in use – Tamoxifen & Raloxifene, later is mainly used for treatment and prevention of osteoporosis. Raloxifene reduces bone turnover & bone loss in post menopausal women. It reduces occurrence of VCFs but its effect on reducing risk of non vertebral fractures is not known. It also causes reduction in incidence of invasive breast cancer and is not associated with increased risk of uterine cancer in contrast to Tamoxifen. Raloxifene reduces LDL levels but does not increase HDL. It is associated with increased risk of thromboembolism & may produce hot flashes.

**Bisphosphonates**

They are approved for the treatment & prevention of post- menopausal osteoporosis. Risedronate & Alendronate are approved for steroid induced osteoporosis & osteoporosis in men also. These drugs considerably reduce the risk of vertebral & hip fracture. Because of their gastrointestinal side effects particularly esophageal irritation; once weekly therapy is preferred over daily therapy with bisphosphonates. They are poorly absorbed orally & must be taken empty stomach.
with a glass of water & patient must remain upright for at least 30min to prevent esophageal irritation. This problem can be circumvented by using parental bisphosphonates.

Zoledronic acid is approved for intravenous use once yearly in osteoporosis with reduction in risk of VCFs & hip fracture. Treatment with Zoledronic acid can lead to increased incidence of atrial fibrillation (~2%) & Arthralgia & Fever (~15%) Ibandronate, another bisphosphonate which is shown to reduce VCF & risk of nonvertebral fractures can be given orally 150 mg per month.

Bisphosphonates are structurally related to pyrophosphates which are incorporated in bone matrix. They specifically inhibit osteoclast function & reduce osteoclast number by inducing apoptosis. Nitrogen containing bisphosphonates block enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway & inhibit protein prenylation. Due to this, intracellular protein trafficking is disturbed which may lead to apoptosis. Some bisphosphonates are retained in skeleton for quite longer periods but its consequences, if any, are unknown.

ADVERSE EFFECTS

Osteonecrosis of Jaw (ONJ) – Exposed necrotic bone in maxillo-facial region, not healing even after 6-8 weeks in patients with no history of craniofacial radiation. ONJ often occurs after some invasive procedure like dental extraction or occurs in patients with ill-fitting dentures or periodontal disease mainly due to increased bone turnover at these sites. Patients should be informed about risk of this complication, even if minimal & also importance of regular dental checkups & oral hygiene. Invasive dental procedures should be done first & healing should be complete before starting bisphosphonate therapy. Over 90% of reported cases of ONJ have been seen in cancer patients.

Atypical femur fractures (AFF) – An association is observed between bisphosphonate use & occurrence of atypical femur fractures. 30% of these fractures are bilateral & are located in subtrochanteric region of femoral shaft. Bone biopsies in such patients show markedly reduced bone turnover.

Drug holiday

Bisphosphonates are unique in that drug accumulates in bone & their residual benefit in terms of fracture reduction persists for sometime after a 3-5 year course of bisphosphonate treatment. As a result “Drug Holiday” concept has emerged as a break in bisphosphonate therapy resets the clock for ONJ & AFF. Although there are no guidelines on “drug holiday”, following protocol can be followed:

1. Bisphosphonate treatment is given for 3-5 years if fracture risk is considered mild & then discontinued. The “drug holiday” can then be continued until there is a fracture or noticeable fall of BMD whichever comes first.
2. Bisphosphonate treatment is given for 5 years if fracture risk is considered moderate, then “drug holiday” can be observed for 3-5 years or until there is a fracture or noticeable fall of BMD whichever comes first.
3. In case of high fracture fracture risk, bisphosphonate treatment is given for 6-10 years, then “drug holiday” of 1-2 years can be taken or until there is significant decrease in BMD or the patient has a fracture, whichever comes first.

Increase in bone turnover markers or fall in BMD should be considered as indicators to decide when to end a drug holiday.

Calcitonin

It inhibits function of osteoclasts & bone resorption & can enhance bone mass but effects are not long lasting, so its efficacy is doubtful. Due to its analgesic properties, it may be used in patients with recent painful VCFs. It is available as subcutaneous injections & nasal spray. Subcutaneous injections often produce GI side effects. Calcitonin is not helpful in prevention of osteoporosis & is not sufficiently effective to prevent bone loss in early menopause.

Denosumab

This monoclonal antibody increases bone mass in post-menopausal women with osteoporosis & those with breast cancer treated with hormonal agents. It is indicated as anti-osteoporotic agent in postmenopausal women who have high risk of fractures including those with a history of fracture & those who have failed or intolerant to other osteoporotic therapies. It is fully human monoclonal antibody to RANKL. It exerts its action by binding to RANKL & inhibits its ability to initiate formation of mature osteoclasts & initiate bone resorption. It also reduces survival of osteoclast so it induces potent antiresorptive action & may contribute to
occurrence of ONJ. It is given twice yearly by subcutaneous injection & increases BMD in spine, hip & forearm & reduces vertebral, hip & nonvertebral fractures in postmenopausal women. Its serious adverse effects include hypocalcemia, dermatitis, rashes, eczema & infections.

Parathyroid hormone (synthetic PTH)

This synthetic hormone also produces substantial increase in bone mass & has reduced incidence of fractures in men & women with osteoporosis⁹. It is most likely to be effective in those individuals who continue to lose bone or who develop fractures on antiresorptive therapy. It may be particularly useful in glucocorticoid-induced osteoporosis. It has direct positive effect on osteoblasts & results in early bone formation before activation of bone resorption. It stimulates osteoblast replication, enhances their recruitment & inhibits osteoblast apoptosis thereby causing true increase in bone mass & an apparent restoration of bone microarchitecture.

It must be given by once daily subcutaneous injection (20 µg) maximum for a period of 2 years. Patients receiving synthetic PTH (Teriparatide) must be carefully monitored for hypercalcemia & hypercalciuria. Anabolic response to PTH may be delayed as a result of prior or concomitant therapy with bisphosphonates. Treatment with bisphosphonates after a course of PTH helps in maintaining benefits of PTH therapy. Adverse effects are relatively mild & include muscle pain, headache, nausea weakness &dizziness.

Strontium Ranelate

It drug is anabolic as well as antiresorptive. It increases bone mass throughout the skeleton & reduces risk of vertebral & nonvertebral fractures. Its mechanism of action is that it gets incorporated into hydroxyapatite, replacing calcium that might explain some of its fracture benefits. Although side effects are minimal but severe but rare allergic reactions have been reported. There may be slight increase in risk of venous thrombosis, seizures & abnormal cognition.

Cathepsin K inhibitor

Odanacatib, a Cathepsin K inhibitor, is mainly used for treatment of post-menopausal osteoporosis¹⁹. This agent is mainly a bone-resorption inhibitor but it preserves bone formation to some extent also. Cathepsin K, a lysosomal cysteine proteinase, is an enzyme which is expressed by osteoclasts for degradation of bone matrix. Because of its high collagenase activity, it can dissolve bone calcium hydroxypatite.

A Cathepsin K inhibitor should be selective over other Cathepsins B, L & S which degrade collagen in other tissues such as skin & lung to avoid adverse effects such as morphea-like skin reaction & respiratory abnormalities. It does not cause increased risk of ONJ but risk of atypical fracture femur looks similar to that observed with bisphosphonates.

Because of its long half-life, it can be used once-weekly. It also results in sustained suppression of bone resorption bio-markers. Odanacatib continuously increases BMD at hip & lumbar spine over 5 years. Complete regression of this effect is observed after stopping the treatment with declining BMD & there is increased bone turnover also It reduces the incidence of fragility fractures at spine & non-vertebral sites including hip. It is generally well tolerated but can cause diarrhea & pain in extremities in women. It appears a useful new option in treatment of post-menopausal osteoporosis.

Other potent anabolic agents

Growth hormone alone or in combination with other agents has not shown consistent positive effects on bone mass. Anabolic steroids, derived from testosterone, have primarily antiresorptive function causing decrease in bone turnover but may also stimulate osteoblastic activity. Their effects on bone mass appear weak & their use is limited by masculinizing side effects. Statins may also cause increased bone mass & reduced fractures but results from clinical trials are mixed.

Management of Fractures

Osteoporotic fractures of hip & femur are usually treated surgically. An intensive rehabilitation program is critical in fractures of hip & spine. VCFs require short periods of bed rest. Pain relief in VCFs can usually be achieved with analgesics & local physical therapy. In patients with severe pain due to VCFs, Calcitonin can also be used. Surgical treatment of individual VCFs can be done by injection of bone cement (Methacrylate) into vertebral body (Vertebraloplasty or Kyphoplasty). Back strengthening exercises & heat treatments may help in chronic pain. Multiple VCFs are often associated with psychological symptoms which can be alleviated by family support &/or psychotherapy. Medications are required in case of more prominent symptoms.
Treatment monitoring

Presently we don't have exact tools for monitoring treatment of osteoporosis. BMD remains an established monitoring tool & changes must exceed ~ 4% in spine & ~ 6% in hip to be considered significant. Due to its larger surface area & greater reproducibility, hip is considered the preferred site for BMD monitoring. BMD should be repeated at intervals > 2 years & a change in treatment regimen is recommended only if there are momentous reductions in BMD.

For monitoring of treatment, Biochemical markers of bone turnover can also be helpful. If these markers are to be used used, they should be measured before the start of therapy & repeated ≥ 4 months after therapy is initiated. A positive change in biochemical markers & an increase in BMD can be useful as it prompts patients adhere to treatment regimens.

Glucocorticoid-induced osteoporosis

It is the most common form of secondary osteoporosis especially that induced by exogenous glucocorticoids. Cushing’s syndrome caused by an excess of endogenous glucocorticoids may also present as osteoporosis but it is not so common. Patients with certain diseases like rheumatoid arthritis, chronic obstructive pulmonary disease & inflammatory bowel disease take exogenous glucocorticoids. Such patients are at an additional risk because disease-associated inflammation, poor nutrition & immobilization can add to bone loss. It is more prevalent in post-menopausal women as they also have primary osteoporosis as well as in elderly people. However, fragility fractures can occur in any patient, even in young growing individuals who are on chronic glucocorticoid treatment. Increased fracture risk occurs within a few months of initiating therapy & once treatment is stopped, this risk rapidly declines. Increased bone loss can occur with any route of drug administration including high-dose inhaled glucocorticoids & intra-articular injections also & even alternate-day dosing does not ameliorate the skeletal effects of glucocorticoids.

Glucocorticoid-induced osteoporosis results due to enhanced bone turnover leading to increased bone resorption & decreased bone formation. Increased resorption can occur due to induction of RANKL by bone marrow stromal cells & osteoblasts. Glucocorticoids also play a role in decreasing intestinal absorption of calcium & increase urinary calcium & phosphate excretion also. Decreased bone formation is the result of inhibition of osteoblast replication, differentiation as well as suppression of their function. Fracture risk is much more in glucocorticoid induced osteoporosis than post-menopausal osteoporosis at comparable levels of BMD. Rib fractures & aseptic necrosis of femoral or humeral head is also commoner in glucocorticoid-induced osteoporosis.

All patients on long-term (> 3 months) glucocorticoids should have regular assessment of bone mass at both hip & spine using DEXA. Bone loss caused by glucocorticoids can be prevented & fracture risk can be significantly reduced by using lower doses of steroids & use of topical & inhaled steroids is preferred. Smoking cessation, limitation of alcohol intake & participation in weight bearing exercise is also important. All patients who are taking glucocorticoids should receive adequate calcium & vitamin D supplementation. Bisphosphonates can be used in patients being treated with glucocorticoids to cut down fracture risk. Calcitonin has also been shown to have protective effect in spine. In women with glucocorticoid-induced osteoporosis, Synthetic PTH (Teriparatide) can also increase bone mass substantially.

CONCLUSION

Ever-increasing prevalence of osteoporosis & its catastrophic consequences has led us to the conclusion that osteoporosis is not merely a “natural byproduct” of aging. Efforts should be made for better screening, early diagnosis & proper institution of anti-osteoporotic therapy. Search should also be made for secondary causes of osteoporosis. Patient should also be educated about non-pharmacological means of treatment & risk factor reduction. Therapy should be based not only on BMD assessment but on comprehensive risk factor assessment. Bisphosphonates are cornerstone of osteoporosis therapy but now many novel agents have come up which bolster our armamentarium to counteract rapidly emerging “osteoporosis epidemic.”

REFERENCES


Current trend in the management of high-grade (4 and 5) renal injury and future directions

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ABSTRACT

In the management of high-grade (4 and 5) renal injuries, the surgical exploration usually leads to unwarranted nephrectomy in almost all cases. Now, inevitable nephrectomy is being avoided in few specialised trauma centres. With current management options, majority of hemodynamically stable patients can be successfully managed nonoperatively. Improvements in the radiographic technology and development of a validated renal injury scoring system has led to improved staging of renal injury severity which is relatively easy to monitor. This article is an overview of multidisciplinary approach involved to facilitate the care of high-grade renal injury patients.

Keywords: High-grade, blunt-trauma, nephrectomy, conservative, embolization.

Renal injury occurs in about 1-5% of all traumas cases and can be classified according to mechanisms of injury.¹² Blunt renal injury is leading mechanism accounting for 81-95% of cases.³⁵ In the one study from Australia, 89 grade ≥ 2 renal injuries were recorded with blunt-trauma accounting for 94.4%; 57.3% were grade 2 injuries, 12.4% grade 3, 25.8% grade 4 and 4.5% grade 5. Road traffic accident was most common cause of injury, accounting for 48.3% of all renal injuries.⁶ Majority of blunt renal injury cases are associated with the injuries to other abdominal organs but usually low-grade injuries are managed conservatively.⁷

In the management of renal injury patients, surgical exploration usually leads to nephrectomy in all except few specialised trauma centre. Given the success of conservative management in other solid organ injuries of abdomen, this approach is being increasingly applied to renal trauma patients.

Improvements in radiographic techniques and development of a validated renal injury scoring system have led to the improved staging of renal injury severity which is relatively easy to monitor. In addition, improved hemodynamic management of patients in specialized trauma units have led to improved outcome with nonoperative management. Further, the selective treatments with advanced radiological interventional procedures have decreased the need for surgical intervention. Now, the successful haemostasis can be achieved for patients with blunt and penetrating renal injuries using selective renal angioembolization.²⁸⁹

Current Understanding of Renal Injury Grading

The American Association for the Surgery of Trauma (ASST) organ injury severity scale is the 'gold standard' for assessment of traumatic renal injuries since its inception.¹⁰ Prognostic value this injury severity scale has been proved repeatedly and beyond doubt by several studies. Unfortunately, the ASST grading system for renal injury is very broad, often leading to a significant discrepancy in the grading between grade 4 and 5 injury in the literature. ASST defined the 'shattered kidney' as grade 5 injury, subsequently many severe grade 4 injuries were misclassified as grade 5 renal injury because of this designation of the 'shattered kidney'. However, to overcome this discrepancy between renal injuries grading, Buckley and Mc Aninch¹¹ modified the ASST grade 5 renal injuries which now includes only those injury that involve main renal artery or vein causing total devascularisation of kidney in most cases either by renal hilar avulsion or by the obstructive intimal renal arterial flap (Fig-1). This modified ASST
organ injury scale of grade 4 and 5 renal injury has been referred as Renal Injury Staging Classification (RISC) (Fig-2). Although, changes encompassed in RISC have added to uniformity within the literature but this does not accurately predict as what renal injuries will be failing with the conservative management. Reckoning, the wide spectrum of haemorrhage risk within grade 4 injuries as expanded by the revised RISC, it highlights the importance of developing a predictive model in high-grade renal injury with greater contemporary role of the conservative management.

**Radiological Imaging**

In the suspected patients of blunt renal injury, the indications for imaging are gross haematuria, microscopic haematuria with systolic blood pressure <90 mm Hg, the presence of other major associated injuries or when there is a high index of suspicion based on the mechanism of injuries. It is pertinent to note that the absence of haematuria does not exclude renal injury. In the trauma patients, a bedside abdominal ultrasound is routinely performed as a part of focussed assessment to identify the hemoperitoneum. But, it has a relatively low sensitivity for identification of free-fluid in the retroperitoneum.

Undoubtedly, computed tomography (CT) is the 'gold standard' for the visceral imaging following blunt trauma to abdomen. Arteriovenous phase identifies active extravasation, whereas delayed phase imaging assesses renal collecting system, ureteric continuity and haematoma.

If a suspected renal injury patient progress to operative room for an emergency laparotomy without undergoing the CT scan, then one-shot intravenous urography (IVU) should be performed at the time of surgery using 2ml/kg intravenous contrast in the operative room. IVU is helpful in assessing the degree of renal injury and also to confirm the presence of contralateral functioning kidney.

In the modern era of helical CT, the renal angiography has become an adjunctive diagnostic imaging in renal injuries. Definite indications for angiography include a suspected renal artery thrombosis or segmental renal artery injury (laceration or pseudoaneurysm) for which renal artery stenting or embolisation may be considered. The absence of renal parenchymal enhancement on CT scan suggests a main renal artery thrombosis and it does not require further confirmation by angiography in the majority of cases. The renal vein opacification in the non-enhancing kidney is an indirect sign of renal artery occlusion.

Without any question, the MRI provides excellent renal anatomical details but offer no clear advantage over the CT scan. Unfortunately, the MRI is time consuming, require sequestration of patients into MRI machine with less ability to detect urine extravasation and its rapid availability always remain doubtful.

**Predictors of Renal Haemorrhage**

In the study by Dugi et al reported from Parkland Hospital in year 2010, three significant risk factors were identified on initial computed tomography (CT) which include intravascular contrast extravasation, complex renal laceration (combined medial and lateral laceration in the affected kidney) and a perirenal haematoma.
distance ≥ 3.5 cm from the renal capsule. These were found to be independently associated with the need of intervention in high-grade (4 and 5) renal injury.19,20 The authors assigned 1-point to each of these risk factors to calculate a 'renal trauma risk score' with a total score of 0 to 3 points. Patients with renal trauma risk score (RTRS) of 0-1 point which had about 7% risk of intervention for renal haemorrhage were classified as ASST-grade 4a renal injury and those with 2 or 3 points which had 67% risk of intervention as ASST-grade 4b injury. Clinical parameters which have been used successfully as independent predictors to define the risk of intervention including renal exploration for haemorrhage includes an elderly patients (less hemodynamic reserve compared to young), shock, comorbid states, solitary functioning kidney (SFK) and the requirement for ≥2 units of packed red blood cells to resuscitate the patients of renal injury.21

Conservative Management of High-grade Renal Injuries

Majority of the hemodynamically stable patients with high-grade renal injuries can be managed nonoperatively.22,23 Management of high-grade renal injuries with superselective renal angioembolization has shown to decrease nephrectomy rate by avoiding iatrogenic or unnecessary nephrectomy which has resulted into an increased renal salvage rate.6 Overall, the success rate for angioembolization of an isolated renal artery branch is about 70-80%.5 Surgical gelatine, steel coils, polyvinyl alcohol or autologous clot has been employed to occlude the bleeding renal artery branches. The arterial branches as small as third or fourth order of division can be successfully embolized using above agents and the procedure can be repeated if necessary to obviate the surgical intervention and possible nephrectomy (Fig-3). Postembolization syndrome is seen in around 10% of the cases. In future, interventional vascular stenting and endovascular technique may have more definite role to play in the patients of renal artery thrombosis.5 Despite, the encouraging reports, time constraint of ischemia and associated other organ injuries may limit the success of these less-invasive techniques.24,25 Currently, at most specialised trauma centres units, the nephrectomy is rare event for high-grade renal injury but being reserved only for some cases of renovascular injuries.26 Absolute indications for renal exploration includes a life threatening haemorrhage from renovascular injury, ureteropelvic junction (UPJ) avulsion and urinoma formation which is unresponsive to minimal invasive procedures like ureteral DJ or drainage. Relative indications for exploration are the laparotomy being done for other associated abdominal visceral injuries, concomitant pancreatic or bowel injury and a large devascularized renal segment.

In the specialised trauma centres, where a nonoperative management was rigorously adopted, nephrectomy rate in high-grade injuries dropped with a proportionally increase in renal salvage rate.10,31 Having said this, the most common management of the high-grade renal injury remains a nephrectomy which is an accepted treatment in the centres lacking facility for renal angioembolization and ICU facilities.32

Subsequent Management

Conservative management of renal injury involves a close clinical reassessment of the patients and observations with serial estimations of hematocrit, initially twice daily. The patient must be kept to strict bed-rest until the haematuria is resolved. Although, the role of antibiotics not clear but intravenous (IV) broad spectrum antibiotics should be used if there is suspicion of pelvic collecting system (PCS) damage and urine leakage.

Fig-3: Postembolization angiography of grade 4 injury (Note: Vasospasm of proximal segment of renal artery).
A repeat abdominal CT imaging with delayed phase is recommended for the high-grade renal injuries between 36 and 72 hours. After this duration, the further repeat radiological imaging adds very little provided patient remains stable. Therefore, it seems reasonable to repeat imaging only when there is a change in the patient's condition. For the minor grades of renal injury, a repeat imaging is not necessary and it is waste of available resources.

**COMPLICATIONS**

*Extravasation of urine*

Urinoma formation (Fig- 4) is the most common complication occurring in about 1-7% of renal trauma patients. Development of a vague flank discomfort, palpable mass, adynamic ileus, low-grade fever or declining renal function raises suspicion of urinoma formation which may be confirmed by CT scan.

It resolves almost spontaneously in about 76-80% of cases. Intervention is required, if there remains a persistent urine leak or collection. Typically, the insertions of a retrograde stent or percutaneous nephrostomy greatly aids the resolution. Although, the percutaneous drainage of urinoma is uncommonly required.

*Infection*

Perinephric abscesses or infected urinoma may develop secondary to bacterial seeding or concomitant enteric or pancreatic injuries. Management with percutaneous drainage is often successful, although an open drainage of multiloculated collections is sometimes required.

*Delayed Haemorrhage*

It is a common complication, especially with the deep lacerations of renal cortex and medulla. Clinically, the patient present with haematuria, falling hematocrit or hemodynamic instability. It is often associated with pseudoaneurysm (Fig- 5) or arteriovenous fistula formation. Delayed haemorrhage is seen in about 13-25% of grade 3 and 4 renal injuries patients that can be managed expectantly. However, in most cases it can be successfully treated with renal angioembolization.

*Nonviable Renal-Segments*

Injuries with devitalised renal segments can be managed conservatively. But, these injuries are associated with a higher complication rate and need for delayed intervention, thus requiring close monitoring of the patient.

*Renal Hypertension*

Patients treated expectantly for renal injuries may develop posttraumatic hypertension in 42% of cases.
The renal artery injury or compression from hematoma/fibrosis (Page's kidney) may lead to development of renovascular hypertension which mediated by increased renin secretion in response to renal ischemia. As the incidence relates to the severity of renal injury, thus patients with grade 4 and 5 injuries should have the periodic monitoring of their blood pressure for prolonged period. Occasionally, a nephrectomy may be required to control renovascular hypertension which is refractory to usual medical treatment. Successful treatment with the repair of arterial stenosis or partial nephrectomy has been reported by many.5

**Renal Insufficiency**

Risk of renal impairment depends on the pre-existing renal diseases, age, presence of solitary kidney and concomitant multiorgan failure. In one study, the large review of all grades of renal trauma revealed that the risk of requiring dialysis is about 0.46%.37 Needs of dialysis was associated with higher grades of AAST and age older than 40 years. In high-grade renal injuries, the risk can be as high as up to 6%.38

**Follow up**

General recommendations include a 3 monthly follow up that comprise of the physical examination, urinalysis, blood pressure measurement and renal function assessment.7 A limited published data is available regarding role of follow up imaging in high-grade renal injuries. Some specialised trauma centres advocate even a renography for the quantitative assessment of renal function following grade 4 and 5 injuries.5 Long term monitoring for renovascular hypertension is required in all high-grade renal injuries. Patients with concomitant injuries, such as colonic or pancreatic needs individualized imaging to monitor and prevent related complications.

**CONCLUSION**

High-grade renal injuries may be a life-threatening condition but if handled correctly, these can be safely managed without the need for nephrectomy. Blunt trauma accounts for the vast majority of renal injuries with a greater proportion of less severe injury grades. Majority of hemodynamically stable patients can be managed conservatively. Angioembolization is an alternative treatment option to control haemorrhage, especially in patients who do not require intervention for concomitant injuries. A multidisciplinary team approach coordinated by trauma specialist facilitates the care of these renal injury patients.

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Acute respiratory distress syndrome: New strategies in management

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ABSTRACT
Acute respiratory distress syndrome is a complication comprising of acute inflammatory lung injury with high mortality and morbidity and leads to long term consequences among the survivors. Many strategies have been formulated and tried but the treatment remains still a dilemma. Here, we present various strategies for combating this life threatening complications.

Keyword : ARDS, Management

INTRODUCTION
Management of ARDS is a unique challenge in terms of its varied causes, fulminant presentations and significant associated morbidity and mortality. Various treatment strategies studied / elaborated so far and the evidences for current treatment options are highlighted here.

Acute respiratory distress syndrome (ARDS) is a potentially catastrophic form of acute inflammatory lung injury with a significant mortality rate and long-term consequences among survivors.¹ ² Large scale clinical trials of multiple therapeutic strategies, including nitric oxide,³ ⁴ anti-oxidants,⁵ ⁷ surfactants,⁸ corticosteroids⁹ and immunomodulating agents such as IL-10¹⁰ and granulocyte-macrophage colony-stimulating factor¹¹ have all failed. Supportive care with mechanical ventilation remains the cornerstone with the only definitive evidence being restricted to low volume ventilation thereby minimising the risk of ventilator induced lung injury. Here, we discuss the current evidence base for ventilatory support and adjunctive therapies in patients with ARDS.

VENTILATORY MANAGEMENT

Invasive ventilation
Significant mortality with NIV have been observed in patients with P/F ratio less than 150mm Hg in presence of hemodynamic instability or altered sensorium, so early intubation in these patients is beneficial.

Low tidal volume Vs High Tidal volume
Traditional concept of high tidal volume strategy to reduce atelectasis resulted in an increased incidence of ventilator induced lung injury VILI (volutrauma, atelectrauma, oxygen toxicity, and Biotauma) which further exacerbated the lung inflammation and contributed to multiple organ dysfunction.¹³ ¹⁴

Efforts to minimize VILI led to the introduction of low volume strategy¹² that is supported by various studies. The response to low-tidal-volume (4-6 ml/kg predicted body weight) ventilation should be assessed initially on the basis of Pplat. The goal should be to maintain a plateau airway pressure (i.e., the pressure during an end-inspiratory pause) of 30 cm of water or less; if this target is exceeded, the tidal volume should be further reduced to a minimum of 4 ml per kg of predicted body weight.

Choice of ventilator mode
Pressure control may be theoretically advantageous than volume control mode, but current recommendation is to use the ventilation mode that allows us to reach the objectives individually adapted to the clinical condition of the patient and to the existing lung mechanics in the most effective way possible.¹⁵-¹⁷

Recruitment manoeuvres
Various recruitment strategies¹⁸-²² have been shown to improve oxygenation but none has been shown to provide mortality benefit.²³-²⁴ The best method to measure optimal peep is²⁵-²⁸ as debatable as is to predict what level of peep would cause overdistension rather than recruitment in a given patient.

Prone positioning
Proning has previously been shown to improve oxygenation in patients with ARDS but there was no
evidence that it also reduces mortality. In 2 meta-analyses of prone position trials, patients with the most severe ARDS had decreased mortality with prone positioning. This finding led to a clinical trial of studying effects of prone positioning for 16 hours per day in patients with moderate-to-severe ARDS (PaO2/FiO2 <150 with FiO2 of at least 0.6 and PEEP of at least 5 cm H2O). This randomised clinical trial of 466 patients showed significant reduction in 28-day mortality in the prone group. The only catch is that given the potential complications of proning including facial oedema, pressure sores, catheters and tubes dislodgment, prone positioning should only be considered as a rescue therapy for refractory hypoxemia in centres with experienced staff.

**Extracorporeal membrane oxygenation**

Extracorporeal membrane oxygenation (ECMO) is another rescue strategy used in patients with refractory hypoxemia. This strategy has really gaining ground after the past H1N1 influenza pandemic in adults. In a randomised controlled trial, transfer of patients with severe ARDS to a tertiary centre capable of providing ECMO on expert basis led to improved outcomes, although there was criticism that not all transferred patients received ECMO.

**High frequency oscillatory ventilation**

HFOV use in adults with ARDS with refractory hypoxemia has been reported earlier but has been in news due to the recent H1N1 influenza pandemic. But the reported results in moderate to severe ARDS have not been encouraging with at least one trial showing potential harm. But with known oxygenation benefits due to higher mean airway distending pressures, HFOV may still have a role as a rescue therapy for patients with severe ARDS and refractory hypoxemia.

**PHARMACOLOGICAL ADJUNCTS**

**Pulmonary vasodilators**

Inhaled nitric oxide is a short-acting pulmonary vasodilator that selectively improves perfusion to well-ventilated alveoli thereby reducing intrapulmonary shunt and improving oxygenation. But, the use of inhaled nitric oxide is not associated with any mortality benefit, is expensive, and requires a specialist delivery system. Generally, a starting dose of 5 ppm to a maximum of 20 ppm is used.

Inhaled NO has also been reported to have numerous potential harms.

- Use may produce toxic radicals but it is debatable what is more harmful - the toxic radicals or the ongoing exposure to high fractions of inspired oxygen.
- Potential rise in Methemoglobin and NO2 concentrations and the implications of need to monitor such levels.
- Inhaled NO may be renal dysfunction.
- Theoretical immunosuppressant effects of Inhaled NO - the risk of nosocomial infection.
- NO may be potentially mutagenic.

**Inhaled prostacyclin** - It has been less extensively studied but has similar theoretical benefits to nitric oxide in terms of selective pulmonary vasodilatation. Advantages are that Prostacyclin is considerably less expensive than NO and more so, it does not require the same commercial delivery system as nitric oxide. The potential harms – theoretical side effects such as systemic vasodilatation and platelet dysfunction, the nebuliser requires continual observation during prostacyclin delivery and also the fact that the technique still remains an unproven rescue therapy for life-threatening hypoxaemia.

**Prostaglandin E1** - Prostaglandin E1 (PGE1) is a potent, endogenous antiinflammatory mediator and vasodilator. Under proper conditions, it can suppress a variety of neutrophil functions, such as oxygen radical production, phagocytosis, and chemotaxis. Some suggest that PGE1 (eg, alprostadil, epoprostenol) can enhance oxygen delivery by increasing cardiac output. PGE1 has been associated with several side effects, including hypotension, fever, diarrhea, thrombocytopenia, dysrhythmias, and worsening oxygenation, presumably due to poor V/Q matching. Hemodynamic intolerance frequently limits the dose of PGE1 that can be given.

A formulation of PGE1 packaged in a liposome bilayer was developed to improve delivery of PGE1 to the lung while decreasing its systemic side effects. In a phase II trial involving 25 patients, use of the drug resulted in a significantly greater extubation rate at 8 days. Oxygenation was improved among persons receiving liposomal PGE1 in a large, Phase III clinical trial, but no reduction in the duration of mechanical ventilation or
improvement in survival was noted. There is no role for intravenous PGE1 at this time.

Aerosolized PGE1 produces similar effects as inhaled NO or inhaled prostacyclin, with rapid reductions noted in pulmonary vascular resistance and improvements observed in PaO2. Clinical experience is more limited with inhaled PGE1 than these other inhaled vasodilators, and none of these agents has been demonstrated to positively influence clinical outcomes.

**Neutrophil elastase inhibitors** - Neutrophil elastase is the target of inhibition for alpha-1 antitrypsin, and its unopposed release produces tissue injury at sites of inflammation. Neutrophil elastase is believed to play a role in the endothelial injury and increased vascular permeability associated with acute lung injury.

Sivelestat (ONO 5046) is a reversible competitive inhibitor of neutrophil elastase, and early animal and human studies suggested this agent improved outcomes following acute lung injury. However, a multicenter randomized controlled trial of 492 mechanically ventilated patients with acute lung injury treated with sivelestat or placebo found no difference between groups in 28-day all cause mortality, ventilator requirement, or respiratory mechanics.

**Arachidonic acid inhibitors** - Lipid mediators, such as thromboxanes, leukotrienes, platelet activating factor (PAF), and various prostaglandins, may contribute to the pathogenesis of ARDS. It is this thought that has led to trials with several drugs for use in ARDS but with no significant positive results.

**Ketoconazole** - Ketoconazole, an antifungal drug and thromboxane A2 inhibitor, can inhibit expression of several of the above mediators, including thromboxane B2 and leukotriene B4. Several studies have suggested that prophylactic ketoconazole may decrease the incidence of ARDS. As an example, one double blind, randomized, placebo-controlled trial of 71 critically ill surgical patients found that ketoconazole decreased the incidence of ARDS from 31 to 6 percent. Another randomized, double blind, placebo-controlled study of 54 septic patients found that ketoconazole significantly reduced the frequency of ARDS from 64 to 15 percent while decreasing mortality from 39 percent to 15 percent. Evidence for this protective effect was strengthened by a study in which the implementation of a ketoconazole ARDS prophylaxis guideline was associated with a decreased incidence of ARDS.

In contrast, a subsequent multicenter trial involving 234 patients randomized to begin ketoconazole or placebo within 36 hours of the recognition of acute lung injury did not support a role for the drug as a treatment for early ARDS. No differences between treatment groups were found in mortality, ventilator-free days, or physiologic endpoints.

**Ibuprofen** - Ibuprofen was shown to decrease pulmonary edema formation and improved hemodynamic parameters and oxygenation in a septic porcine model. But, a randomized, double blind, placebo controlled trial in 455 patients with sepsis found that ibuprofen did not decrease the incidence or duration of ARDS. In view of the unpromising results, there is no promising role for further study of ibuprofen or similar agents for the prevention or treatment of ARDS.

**Antioxidants** - Reactive oxygen species, such as the superoxide anion, hydroxyl radical, hydrogen peroxide, and hypochlorous acid are believed to play an important role in the establishment and propagation of ARDS. Toxic oxidants are produced by activated neutrophils, macrophages etc and these may be exacerbated by high levels of supplemental oxygen. The intracellular glutathione levels have been shown to be depleted in ARDS in at least one study.

**Glutathione** - Depletion of antioxidants increases the lung's vulnerability to oxidative injury, and restoration of antioxidant defenses therefore may be an option. Two agents capable of repleting glutathione, N-acetylcysteine (NAC) and L-2-oxothiazolidine-4-carboxylate (Procysteine) have received the most extensive study.

One double blind, randomized, placebo-controlled trial of 66 ARDS patients compared NAC to placebo and found no improvement in oxygenation or survival. A subsequent study showed that NAC restored granulocyte glutathione stores but did not decrease the cell's spontaneous production of reactive oxygen species. Finally, a prospective, randomized, double blind, placebo-controlled trial compared procysteine to NAC and placebo in 46 patients. Both procysteine and NAC effectively restored glutathione stores and appeared to decrease the duration of lung injury. There was no survival benefit in this study. There is little ongoing interest in further study of these agents for the treatment of ARDS.
Lisophylline - The level of circulating free fatty acids (FFAs) increases several-fold in ARDS. Some FFAs can be oxidized in the setting of systemic inflammation to act as pro-inflammatory mediators. Lisophylline (1-[5R-hydroxyhexyl]-3,7-dimethylxanthine) has been shown to decrease levels of circulating free fatty acids in both healthy volunteers and animal models of ARDS and sepsis. In addition, lisophylline decreases the release of the proinflammatory cytokines tumor necrosis factor-alpha, interleukin (IL)-1-beta, and IL-6 from activated monocytes. A randomized controlled trial in adults with ALI or ARDS was stopped after the enrollment of 235 patients when interim analysis showed no difference in survival or other clinical end points between the two groups.

Fluid balance
An association between positive fluid balance and worse outcome in patients with ARDS has been demonstrated in a number of studies. Data from the ARDS Network Fluids and Catheter Therapy Trial convincingly support the use of a conservative fluid management strategy in ARDS, with the use of diuretics in haemodynamically stable patients to achieve an even fluid balance associated with improved oxygenation and faster liberation from mechanical ventilation. However, these findings need caution in interpretation in light of a recent report showing potential for worse long-term cognitive function in a subset of the trial survivors. In consensus, using small-volume fluid boluses titrated to resolution of hypoperfusion states should be the norm and diuretics or ultrafiltration should be employed to restore euvolaemia in haemodynamically stable patients. It is also worthy to note that hypovolaemia may exacerbate hypoxaemia by virtue of increased intrapulmonary shunt and in some cases, clinical benefit may only be derived from administration of fluid boluses.

Neuromuscular blockade
Neuromuscular blockers are reported to improve patient-ventilator synchrony, to improve chest wall compliance and to reduce oxygen consumption by respiratory (and other skeletal) muscles thereby resulting in an improved mixed venous saturation. In a large RCT, cisatracurium infusion for a 48-hour period early in the course of moderate-severe ARDS (PaO2/FiO2 ratio <150 mmHg) resulted in a reduction in the duration of mechanical ventilation and mortality. Concerns regarding the use of neuromuscular blockers relate primarily to the risk of critical illness myopathy and reportedly, Aminosteroid muscle relaxants such as rocuronium may present a higher risk than benzylquinolinium compounds such as cisatracurium in this regard. It is judicious thinking to use an appropriate neuromuscular monitoring technique (eg: train of four) for any patient on relaxant infusions.

OTHER PHARMACOLOGICAL ADJUNCTS
Albumin along with furosemide: Hypoproteinaemia may be a risk factor for ARDS and thus, the use of albumin along with furosemide was studied in two small phase II trials. In both the trials, Albumin use was associated with improved oxygenation, diuresis and haemodynamics, and represents an approach in need of further evaluation.

Corticosteroids: High-dose steroids used in the early stages of ARDS have no benefit and rather lead to some increased infectious complications. One small randomised study suggested a survival benefit in the late (fibroproliferative) phase of ARDS, but a larger study failed to replicate this benefit despite showing improvements in physiological parameters. It is only the use of low-dose steroids in early ARDS that has shown improvements in gas exchange without improvements in clinically significant endpoints. Overall, steroids have yet to establish their role in the definitive management of ARDS.

Beta agonists - There was initial enthusiasm on using beta agonists to treat ALI or ARDS based on evidence that Terbutaline increases the clearance of alveolar edema in lung explants, reduction of high-altitude pulmonary edema by Inhaled salmeterol and possible decreased alveolar-capillary permeability in patients with ARDS possibly by simulating alveolar wound repair.

In a double-blind, controlled trial, 40 patients with ALI or ARDS were randomised to receive intravenous albuterol (15 mcg/kg per hour) or placebo for seven days. Intravenous albuterol was associated with less lung water (9 versus 13 mL/kg) and lower plateau airway pressure (24 versus 30 cm H2O). Patients in the albuterol group had a higher incidence of supraventricular arrhythmias (26 versus 10 percent) that was not statistically significant.

Surfactant - Endogenous surfactant modulates alveolar surface tension and prevents atelectasis. Surfactant also promotes mucous clearance, scavenges oxygen radicals, and suppresses inflammation.
Alveolar collapse has a major role in the shunt physiology of ARDS. Abnormal surfactant function may lead to collapse of lung areas leading to regional imbalances in lung ventilation with consequent overdistension / cyclic atelectasis / shear injury in different lung areas. Exogenous surfactant was therefore expected to ameliorate many of these problems.

Numerous randomized trials have found no clinical benefit from recombinant surfactant protein C, synthetic surfactant, or freeze dried natural animal surfactant in patients with ARDS, despite benefit in animal models. An illustrative report described two multicenter, randomized, double blind trials that enrolled a total of 448 patients with ARDS and compared standard therapy to recombinant surfactant protein C based surfactant plus standard therapy. Patients were treated within a period of 24 hours with up to four intra tracheal doses of study drug. Surfactant group encouragingly had greater improvement in oxygenation during the first 24 hours of treatment but with no significant differences in mortality or need for mechanical ventilation.

A subsequent meta-analysis of five studies demonstrated that exogenous surfactant administration was associated with improved oxygenation compared to controls, although the difference was not statistically significant (mean +13.18 mmHg, 95% CI, -2.95 - +29.32 mmHg). In addition, exogenous surfactant did not alter mortality (odds ratio 0.97, 95% CI 0.73-1.30).

The variable results may reflect important differences in the methods of drug delivery, in concurrently employed ventilation strategies, or in the different forms or dosages of surfactant (ie, different types and amounts of protein and phospholipid). Most recently, 'nail in the coffin' has been the expected publication of the CARDS Trial showing administration of Calf lung surfactant (calfactant) was not associated with improved oxygenation or longer-term benefits relative to placebo.

**Gene therapy for ALI/ARDS**

Transfer of α2 subunit or β1 subunit of Na+/K+ ATPase has been demonstrated to increase the expression of Na+/K+ ATPase on alveolar epithelial cells and to improve alveolar fluid clearance. Anti-inflammatory effects have been found with the delivery of genes encoding anti-inflammatory cytokines such as interferon protein 10 (IP-10), IL 12 and transforming growth factor beta-1 (TGF-β1). Heme oxygenases (HO) are essential enzymes, which degrade heme into carbon monoxide (CO), biliverdin and free iron. Due to its anti-inflammatory, anti-apoptotic and probable anti-viral properties the inducible HO isoform HO-1 is an important molecule which has been used in different genetic approaches to mitigate acute lung injury. Gene transfer of HO-1 provided lung protection against hyperoxia, influenza virus pneumonia and endotoxin mediated lung injury.

Mesenchymal stem cells (MSC) are multipotent stromal cells that can differentiate into a variety of cells types including osteoblasts, chondrocytes, adipocytes etc. These cells can be isolated from bone marrow, fat, umbilical cord blood, placental tissue, skeletal muscle. MSCs differentiating into several cell types have been sown to have regenerative properties. They can release many molecules with immune modulatory and anti-inflammatory effect. Moreover, MSCs lacking the HLA II molecules may escape the immune response after allogenic or xenogenic transplantation and may be used as carriers for gene therapy.

**CONCLUSION**

It is clear that our knowledge with respect to pathophysiology of ARDS is still limited and therefore the treatment options are so much limited. The only definitive evidence based recommendation is to use lung protective low volume ventilation in patients with ARDS so as to avoid generating shear forces which may otherwise incite a pro inflammatory cascade resulting in multi organ dysfunction syndrome. The only saving grace being the recent reported mortality benefits of prone position ventilation in patients with severe ARDS. Whether gene therapy promises something definitive is a question for the future but as of now lets propose to follow LOVLOW - low volume, low water strategy at least in hemodynamic stable patients.

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Acute Respiratory Distress Syndrome


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Current trend in medical expulsive therapy (MET) for the treatment of ureteral stones

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ABSTRACT

Medical expulsive therapy (MET) has been described as an effective conservative treatment option for small ureteral stones. The agents that have been investigated include NASAIDs, corticosteroids, calcium channel blockers, α-1 adrenergic blockers and most recently PDE inhibitors. NASAIDs have no role in medical expulsion of ureteral stone. Despite, the fact that corticosteroid and nifedipine have received great attention as potential useful adjunctive but they are not recommended as monotherapy. To date, only α-1 adrenergic blockers are recommended as monotherapy for MET in distal ureteral stones. The new drug called silodosin has shown much better result in some recent study. Although, PDE inhibitors are novel alternative treatment option but require further investigation. This review provides an overview of recent MET best practice guidelines and various agents in current use.

Keywords: Ureteral stone, medical expulsion, NASAIDs, alpha-blocker, steroid, PDE- Inhibitors

INTRODUCTION

Symptomatic ureteral stones represent the most common emergency condition treated by Urologists.¹ Management is usually conservative in the first instance because of high spontaneous passage rate. Invasive treatment is recommended when ureteral stones are not expected to pass, do not pass spontaneously or become problematic. The American Urological Association (AUA) and European Association of Urology (EUA) guidelines for the treatment of ureteral stones recommended appropriate evidence based use of shock wave lithotripsy (SWL), percutaneous nephrolithotomy, or ureteroscopy depending on stone size and its location within the ureter.² However, these minimally invasive procedures are not risk-free and need some experience resulting in higher cost of treatment.³,⁴

It is also well perceived that if these stones could be expelled out using pharmacological agents, then these procedures and associated cost can be avoided. Additionally, if the efficacy of these procedures can be improved by use of pharmacological agents, then the cost of auxiliary procedures can be reduced. Moreover, the accurate prediction of stone expulsion may prevent unwanted procedures and its complications. In uncomplicated patient, the probability of spontaneous passage is based on a number of factors including stone size, its position, degree of impaction and obstruction. A meta-analysis by AUA Guideline Panel determined that ureteral stone size < 5 mm will spontaneously pass in upto 98% of cases.¹ For the stone size >7mm, the chance of spontaneous passage are low. Overall stone passage rate for proximal, middle and distal ureteric stones was 25%, 45% and 75%, respectively.⁵,⁷

Time to spontaneous passage also depend on size. Ureteral stones upto 2 mm may take 8 days and 4-6 mm size takes 22 days to pass.³ Most authors recommend that the stone passage time should not exceed 4-6 weeks due to risk of renal damage.²,⁶ Conservative management is not appropriate in patients with prolonged partial obstruction (>4-6 weeks), persisting pain and infection (UTI).

Primary agents that have been evaluated for MET are nonsteroidal anti-inflammatory drugs (NASIADs), corticosteroids, calcium channel blocker and α-1 adrenergic blocker. More recently, even phosphodiesterase inhibitors (PDE) are being investigated as potential agent. We performed a systemic
review of the various pharmacological agents being used in the patients of ureteral stone for medical expulsion.

**DATASOURCES**

A literature search was conducted using the key terms ureteral stones, medical expulsive therapy, α-blockers, calcium channel blockers, corticosteroid and NSAIDs. All the studies published in the English language and from peer reviewed journals were taken. The studies evaluating the available pharmacologic agents for expulsion of ureteral stones were analysed.

**MEDICAL EXPULSIVE THERAPY**

1. **NSAIDs**

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are first choice for ureteral colic because of their efficacy. They exert only peripheral action, hence no narcotic effect, do not depress respiration and cause no constipation. Analgesia is achieved through reduction in anti-inflammatory response, local edema and renal blood flow (RBF) but this also reduces the glomerular filtration rate (GFR) up to 35%. Even ureteral peristalsis is reduced through direct ureteral muscle relaxation and decrease in intraureteral pressure following fall in the GFR. The action is caused mainly by the inhibition of cyclo-oxygenase enzyme (COX) activity which regulates the synthesis of prostaglandins and autacoids such as thromboxane.

Benefits of NSAIDs in ureteral stone is due to reduction in the RBF that decreases renal collective system pressure, ureteral smooth muscle relaxation and decrease in stone induced ureteral edema. The latter two effects have been hypothesized to facilitate stone passage as well.

There are three classes of NSAIDs, according to their inhibition of cyclo-oxygenase enzyme (COX): (a) nonselective COX inhibitors such as Acetyl-Salicylic Acid, Indomethacin and Diclofenac; (b) selective COX-1 inhibitors, e.g. Ketoprofen and Flurbiprofen; (c) selective COX-2 inhibitors, i.e. Meloxicam, Celecoxib and Rofecoxib.

Two randomized controlled study assessed the ability of NSAIDs to facilitate stone expulsion. In first study by Kapoor et al, it was demonstrated that patients receiving Indomethacin suppository did not experience either an increased stone expulsion rate or decreased time to expulsion compared to placebo. Significantly, the patients receiving indomethacin needed a statistically significant less amount of narcotic analgesic. In another study by Laerum et al, it was shown that although oral Diclofenac, a nonselective COX inhibitor, did not increase stone expulsion rate compared to placebo but a significantly decreased in pain and hospital admission was noted. Aforementioned studies suggest that nonselective COX inhibitors are not effective in facilitation of ureteral stone expulsion. In the study by Nakad et al, it was shown that COX-2 protein and its mRNA are significantly expressed in the obstructed human ureter and selective COX-2 inhibitors might be useful. Despite selective COX-2 inhibitors having fewer gastrointestinal side effects, they are contraindicated in patients with renal impairment because they drastically decrease glomerular filtration. Thus, the role of COX-2 inhibitors needs to be further investigated.

2. **Corticosteroids**

The stone level edema is an important, arresting ureteral stone passage and explains why even a 2 mm stone size can cause obstruction. In a prospective study by Porpiglia et al, they examined the effects of corticosteroid alone and in conjunction with alpha-blocker in the expulsion of distal ureteral stones. This was the first study to effectively assess the efficacy of corticosteroids as a monotherapy in ureteral stone expulsion. A total of 111 patients were examined, all were enrolled in 4 groups, the 1st group received Tamsulosin 0.4 mg daily, 2nd group Deflazacort 30 mg daily, 3rd group received both Tamsulosin 0.4 mg & Deflazacort 30 mg daily and control 4th group received only analgesic. The stone expulsion rates of 4 groups were 60%, 37.5%, 84.8%, and 33.3%, respectively. A significant difference was observed between 3rd group and other groups (p value < 0.001) and mean stone size ranged from 5.71 to 5.96 mm. Only side effects noted in Tamsulosin alone group were 2 episodes of hypotension. In another study, they demonstrated that the use of corticosteroids (Deflazacort) proves efficient only when administered together with Tamsulosin. Thus, the role of corticosteroids in medical expulsive therapy needs further clarification in the future.

In the study by Saita et al and Borghi et al, they examined the role of corticosteroid in combination with calcium channel blockers. Both study demonstrated a significant increase in expulsion rate of distal ureteral stones in patients who received combined Methylprednisolone and Nifedipine therapy. No significant side effects were described in either study.
Recently, Hwang et al, reassessed the role of corticosteroid as adjunct to α-blocker in the expulsion of distal ureteral stones of <1 cm size. Patients were divided into 2 groups: control (analgesia only) and treatment group (Alfluzosin 10 mg and Methylprednisolone 8 mg). Although, the stone expulsion rate was significantly increased in the treatment group but dizziness and headache was reported in 8.5% of the patients with no steroid-related side effects.\(^19\)

These studies reviewed only short term courses of corticosteroid, prescribed to avoid adverse effects associated with their prolonged use. Therapy should be avoided in patients with diabetes, gastric ulcers and steroid intolerance. Although, the corticosteroids have been found as an effective adjunctive to α1-blockers and calcium channel blockers but evidence remain insufficient to recommend these drugs as monotherapy.

3. Calcium-Channel Blockers

Ureteral smooth muscle contraction is dependent on transcellular, intracellular calcium and calcium fluxes. Stones may induce ureteral spasm, inhibiting its passage. Calcium channel blockers, which inhibit the influx of extracellular calcium, have been prescribed to facilitate ureteral stone passage. Hertle and Nawrath demonstrated that Nifedipine and Verapamil suppresses fast phasic contraction without affecting slow tonic contraction suggesting that ureteral spasm may be inhibited without affecting peristaltic contraction.\(^20,21\)

Calcium channel blockers and their role in MET continued to be explored. Nifedipine is the only calcium channel blocker that has shown some benefit in stone expulsion.\(^22-24\) Studies have indicated that nifedipine is effective in reducing renal colic but improvement in stone expulsion rate is minimal. Alpha-blockers are significantly better than Nifedipine, facilitating ureteral stone expulsion and relieving renal colic.\(^18,24,25\) Therefore, the recent EAU guidelines do not recommend calcium channel blocker as monotherapy for MET (28). However, they may be safely used in conjunction with α1-blockers in appropriate selected patients.\(^23,25,26\)

The systematic review by Seitz et al assessed the effectiveness of calcium channel blocker in stone expulsion. Nine studies were reviewed which included a total of 6896 patients. Pooled data demonstrated a higher stone expulsion rate among patients treated with calcium channel blockers alone compared to control group. A relative risk of 1.49 (CI 1.33-1.66) and absolute risk reduction of 0.26 was observed. No significant side effects were noted.\(^27\)

Although, calcium channel blocker has shown promising results in distal ureteral stone expulsion but α1-blockers are more efficacious. The systematic review by Cao et al examined the studies directly comparing α1-blockers to calcium channel blocker in the management of lower ureteral calculi.\(^28\) A total of seven studies (3897 patients), published between 2004 and 2013 were reviewed, with mean stone size measuring 4.7 to 8.5 mm. Pooled estimates were statistically significant between α1-blockers (Tamsulosin) and Nifedipine groups with a relative risk of 0.81 (CI: 0.75-0.88, p value <0.00001), indicating that Tamsulosin is associated with distinctly better expulsion rates than nifedipine.

4. α1-Adrenergic Blockers

α1- Adrenergic blockers (alpha-blocker) inhibits contraction of ureteral musculature, reduce basal tone, decreased peristaltic frequency and colicky pain, facilitating ureteral stone expulsion. Three different subtypes of adrenergic receptors identified includes: α-1a, α-1b, and α-1d.\(^7\) Sigala et al demonstrated that α1-d receptors are expressed in all parts of ureter especially in the distal part and in significantly greater amount than α-1a & α-1b subtypes.\(^20,30\) They also found that distal ureter has highest density of α-1a receptors.

Tamsulosin, a selective alpha blocker with both α-1a and α-1d antagonist, has been studied by various authors. Initially, Cervenacov et al evaluated the efficacy of tamsulosin in expulsion of distal ureteral stones.\(^22\) In this study, all patient received Tramadol 50 mg and Diazepam 5 mg once as well as Escin 40 mg and Diclofenac 50 mg 3 times a day. Stone passage rate was higher in the treatment group than in control group and statistical analysis was not performed. Although, use of Escin rather than corticosteroid make these results difficult to compare with those of other studies. These findings prompted other investigators to evaluate Tamsulosin efficacy in longer trials.

Terazosin, another selective α1-adrenergic antagonist, has recently shown to facilitate stone passage. Tekin et al in their prospective randomized trial in 75 patients with distal ureteral stones ≤ 15 mm in diameter found that patients with 5 mg Terazosin daily for 4 weeks had a more statistically significant increase in stone expulsion rate than those receiving no treatment (77% vs 46%).\(^31\) This treatment was particularly effective for stones < 8 mm, observed for subgroup (95% vs 56%). Drug related side effects were minimal and no patient dropped out from the study.
Yilmaz et al in their controlled trial evaluated the comparative efficacy of alpha blocker Tamsulosin, Terazosin, and Doxazosin.33 The control group had a significantly lower stone expulsion rate (53.57%) and longer stone expulsion time compared to treatment groups. In this study, no patient received corticosteroids or antispasmodic which permitted accurate assessment of the absolute efficacy of these agents. The author demonstrated that tamsulosin, terazosin and doxazosin were equally effective in distal stone expulsion in comparison to control group and further that corticosteroid therapy may not be necessary. These finding indicated a possible class-effect. However, larger studies are required to further validate this small-scale study.

Dellabella et al, further tested the theory that corticosteroid are not necessary for expulsion of ureteral stones and compared Tamsulosin plus Deflazacort with Tamsulosin monotherapy.34 At the end of study, while the stone expulsion rates were similarly high between two groups, the median time to stone expulsion was shorter in group receiving both Tamsulosin and Deflazacort (3 vs 5 days). The rate of emergency department visits, hospitalization and work days lost were similar between 2 groups. The author concluded that although the addition of Deflazacort resulted in similar expulsion rate but time to stone expulsion was less.

A large meta-analysis by Hollingsworth et al clearly outlined the benefit of alpha-blockers in MET.35 Patients treated with alpha-blockers had 65% greater chance of spontaneous stone expulsion with pooled risk ratio of 1.54 (confidence interval [CI] 1.29-1.85) compared to control (p value <0.0001). The mean stone size ranged from 3.9 to 7.8 mm. The most common side effect reported was transient hypotension in 3.3% to 4.2% patients.

Silodosin, a new substitute of tamsulosin has received greater attention of urologists. Alpha1-adrenoreceptors are principal contributor in phenylephrine induced ureteral contraction in isolated human ureter. Dell’Atti, compared the efficacy of Silodosin and Tamsulosin in the expulsion of distal ureteral stones size 4 to 10 mm.36 A total of 136 patients were enrolled in and equally divided between 2 groups. One group received Tamsulosin 0.4 mg daily and other group Silodosin 8 mg daily. A significantly increased expulsion rate was seen in patients treated with Silodosin compared to Tamsulosin (80.30% vs 61.2%) (p value < 0.003). No severe side effects were observed. However, retrograde ejaculation was more often reported in Silodosin group.

Belief, that Silodosin is superior to Tamsulosin in distal ureteral stone expulsion was further tested by Gupta et al.37 A total of 100 patients with distal ureteral stones ≤ 1 cm were enrolled, group-1 received Tamsulosin 0.4 mg daily whereas group-2, Silodosin 8 mg daily. Stone expulsion rate in group-1 and 2 was 58% and 82% respectively (p value < 0.008). Mean time to stone expulsion was 19.5 days in group-1 and 12.5 days in group-2 (p value < 0.01). Also, the retrograde ejaculation was more in patient receiving Silodosin.

5. Phosphodiesterase Inhibitors

Recently, the phosphodiesterase inhibitors (PDE) are being evaluated by some authors for their new role in ureteral stone. They act by inhibiting nitric oxide/cyclic guanosine monophosphate (cGMP) signalling pathways, which results in increased level of cGMP, leading to smooth muscle relaxation in ureter and stone expulsion.38 Taher et al identified that Isoenzyme-IV is dominant over other PDEs in regulation of ureteral smooth muscle. Rolipram, a selective PDE-IV inhibitor has been shown to facilitate ureteral relaxation.39 (41). Most recently, Romics et al in a randomized double blinded controlled trial showed that Drotaverine, a selective PDE-IV inhibitor significantly reduce acute renal colic in comparison to placebo.38

A relaxing effect on ureteral muscle has also been observed in patients receiving Vardenafil, Tadalafil, much longer in Vardenafil.46

Kumar et al examined the role of Tadalafil in conjunction with tamsulosin and corticosteroid therapy.39 The study was based on the assumption that combining various drugs acting through different mechanisms can achieve a increased ureteral relaxation and reduction in intramural pressure. Patients were divided in 2 groups. One group was given Tamsulosin 0.4 mg daily and other was treated with Tamsulosin 0.4 mg combined with Tadalafil 10 mg daily. Both groups received Prednisolone 5 mg daily for 1 week. Mean stone size in group-1 & 2 were 7.05 mm and 6.67 mm, respectively. In group-2, an increased stone expulsion rate as well as decreased time to expulsion was observed. Results were not clinically significant and side effects including headache, dizziness, orthostatic hypotension and backache occurred more frequently in group-2. Improved erectile function was seen in 12.9% patients receiving Tadalafil.
Further study is required to comment on their exact role of PDE in the stone expulsion.

DISCUSSION
At present, NSAIDs despite being first choice for ureteral colic are not useful in expulsion of ureteral stones.

Corticosteroids alone have very low rate of stone expulsion (37.5%) but when combined with Tamsulosin, the stone expulsion rate improved to 84.8%. Thus, use of corticosteroids (Deflazacort) proves efficient only when administered together with alpha-blockers. Further, steroids should be avoided in the patients with diabetes, gastric ulcers, or steroid intolerance. Their long-term use should also be avoided due their adverse effect. At present these are not recommended as monotherapy for MET.

Nifedipine is the only calcium channel blocker that has been shown to be of some benefits in ureteral stone expulsion. Multiple studies have shown that when combined with alpha-blockers (Tamsulosin), then time to stone expulsion is significantly decreased from 5-9.3 to 2.7-7.9 days. However, alpha-blockers have been found to be significantly better than Nifedipine in facilitating stone passage and relieving renal colic. The same study also demonstrated lower rates of hospitalization, ureteroscopy and fewer work days lost with Tamsulosin than Nifedipine. Presently, even the calcium channel blocker can not be recommended as monotherapy for MET.

Multiple trials have proved that alpha-blockers (Tamsulosin) are most important in MET. Moreover, when they are combined with corticosteroids (Deflazacort), although expulsion rate remained almost unchanged but mean time taken to expulsion decreased significantly from 5 to 3 days. Tamsulosin, Terazosin, and Doxazosin are equally effective in distal ureteral stone expulsion.

New uroselective alpha-blocker Silodosin has proved to be even better. Two studies have shown significant increase in the stone expulsion rate in patients treated with Silodosin (80.30%) in comparison to Tamsulosin (61.2%).

Use of phosphodiesterase inhibitor (PDE), Tadalafil has further increased stone passage rate with decreased in expulsion time and it is very efficient due to its fast action.

A number of trials have evaluated benefits of MET on endpoints such as ureteroscopy and hospitalization rates and work days lost. Hospitalization rate is significantly reduced from 9-34% for control to 0-9% for Tamsulosin and 20% with Nifedipine. Ureteroscopy rate was similarly reduced from 30-31% in controls to 0-1.4% with Tamsulosin therapy and 20% with Nifedipine. Work days lost was decrease from 5 to 2 days for Tamsulosin and by 1.76-3 days for Nifedipine. Although no formal cost benefit analysis has been done for MET in ureteral stones but a significant cost saving could arise from this therapy. Cost of SWL and ureteroscopy is about Rs.25, 000 and Rs.60, 000 respectively in India. The total costs of therapy for a typical 28 day course of alpha-blocker range from Rs.300 to Rs.600 in India. An adjunctive role of these with alpha-blocker may allow for avoidance of repeat SWL procedures and significantly cost savings.

Selection criteria for MET in ureteral stones are derived from the entry criteria of the available studies. MET should be avoided in patients with hydronephrosis, UTI, solitary kidney, or diabetes mellitus.

In the described studies, most ureteral stones were located in the distal ureter with no greater than 15 mm size.

CONCLUSION
During ureteral stone treatment, the decision must be made whether to manage stone medically or to intervene surgically. Exclude the patients with coexisting infection, severe obstruction, intractable pain, renal insufficiency and solitary kidney in which a prompt surgical intervention is mandatory. Patients have a choice in the management of their stones. Selection of the most appropriate treatment should consider several important factors including stone size and its location, available technique, surgeon's skills, patient's choice and treatment cost. Recently, a cost effectiveness model revealed that a conservative approach to ureteral stones is associated with lower cost than invasive procedures, provided it results into stone expulsion.

Addition of corticosteroids, calcium channel blockers, alpha-blockers or both will improve spontaneous stone passage rate. These may also decrease time to stone expulsion as well analgesia needed. Multiple clinical trials have proved that adjuvant drugs are clinically safe, efficacious, well-tolerated and inexpensive. MET decreases the cost of treatment by decreasing hospital admission rate and thus overall cost of treatment.
role of PDE inhibitors in MET need to be further proved by more number of studies. We recommend concomitant administration of Nifedipine or Deflazacort with α-blocker to facilitate ureteral stone expulsion and to decrease stone expulsion time, whenever there is no contraindication. However, till date, α 1A-D specific adrenoreceptor antagonist, Tamsulosin, remains the first choice in MET for the treatment of ureteral stones.

REFERENCES


Local anesthetic toxicity: etiology, prevention and management

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ABSTRACT

Local anesthetics are the most commonly used drugs in medical and dental setting. In this article we have discussed extensively the etiology of LA toxicity ranging from dose, anesthetic agent, age of patient, possible drug interactions and so forth. Methods to prevent neurological and cardiovascular toxic effects, its diagnostic symptoms, and effective management.

Keywords: LA toxicity, LA Dental, Neurotoxicity, Cardiovascular toxicity

INTRODUCTION

In routine clinical dental and medical practice intraoperative pain control local anesthesia. The most feared complication of regional anesthesia is systemic or local anesthetic toxicity. Complications involving the central nervous system and cardiovascular system can be alarming. The adverse outcomes are often severe and have been well documented in the literature.¹ In 2001, the American Society of Regional Anesthesia and Pain Medicine published a series of related articles that included a review of resuscitation strategies for local anesthetic cardiac toxicity.²

The history of local anesthetics goes back in 1852 when Charles Gabriel Pravaz of Lyon invented a silver hollow needle, which he combined with a miniaturized glass syringe of approximately 1.5ml to use for intradermal injection. Alexander Woods³ of Scotland refined this in 1853 and developed the metallic hollow needle. In 1859, alkaloid responsible for the stimulating effect of the coca plant was isolated by german chemists, Albert Niemann and Wilhelm Lossen, and called it cocaine.⁴ The Austrian pharmacologist Karl Damian Ritter von Schorff was the first to postulate of cocaine as a narcotic. He explained CNS effect as the mechanism behind skin insensibility. Later in 1884, Sigmund Freud proposed to his friend Carl Koller⁵, the use of cocaine as local anesthetic, who demonstrated the analgesic properties of cocaine in the eye. In dental profession, William Halsted⁶, an American surgeon, used a syringe to inject cocaine in order to relieve pain by anaesthetizing the branches of the mandibular nerve. Following the discovery of cocaine, Alfred Einhorn⁷ manufactured procaine in 1905 and Nils Lofgren⁸ subsequently introduced lignocaine in 1943.

Eventually, in less than a year's time, toxicity to cocaine was reported. Thus, the medical and pharmaceutical industry set in search for new, less toxic drugs.⁹ Manipulations were done in existing molecular structures, however, the invent of the ester group did not return optimum results. The main drawback with ester group was their shorter duration of action. Prototype of this group was procaine and a popular example is topical anesthetic benzocaine. Therefore, in quest of increasing the duration of action, the drugs were prepared in an oily formulation, which in turn proved to be neurotoxic locally or by enhancing the lipophilicity of the molecule that made it more central nervous system and cardiotoxic. The first amide local anesthetic drug was Lignocaine that was made available for clinical use. Although, the block was acceptable, but unfortunately the duration of action was short acting⁹. Many attempts were made to increase its duration of action that included adding vasoconstrictors, continuous administration via indwelling catheters, encapsulation in biodegradable polymers and binding to cyclodextrins. Among these, the most popular method that continues to be used in clinical setting is the addition of vasoconstrictors. Other drugs that belong to the amide group are articaine, bupivacaine, lidocaine, mepivacaine and prilocaine.

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Review Article
ETIOLOGY OF LOCAL ANESTHETIC TOXICITY

The concentration of LA reaches toxic plasma levels following either direct intravascular injection or absorption from the site of injection that is associated with neurological or cardiovascular symptoms. These plasma level values, though have been determined for an “average” patient, however, they need to be customized for patients with comorbidities or extremes of age.

Physicochemical properties

Lipid soluble longer acting agents generally have slower systemic absorption. This feature is significant during continuous administration techniques. It has been concluded that, longer acting drugs have high incidence of local toxicity due to accumulation while shorter acting drugs depict high rates of systemic toxicity.\(^\text{19}\)

Intrinsic vasoactive properties

Few drugs such as Ropivacaine and levobupivacaine have longer duration of action, associated with slower systemic absorption owing to their intrinsic vasoconstrictor properties. These are considered to be safer than bupivacaine that exhibits intrinsic vasodilator properties.\(^\text{18}\)

Dose (concentration and volume) of LA

It has been expressed that increasing the local anesthetic concentration can prolong its duration of action. However, beyond a certain limit there is an unreasonable increase in systemic absorption. This can be attributed to satiety of local binding sites and the superlative vasodilator effects of more concentrated solutions. Thus, dose calculations must be done accordingly and increasing the amount of LA in attempt to increase the duration of action should not be practised.\(^\text{17}\)

Addition of vasoconstrictors

Addition of vasoconstrictor agents to the local anesthetic solution, such as epinephrine lends various advantages such as slow systemic absorption, provides bloodless field, and prolongs the intensity and duration of action of the nerve block. These effects are more conspicuous with the short acting amides that bear to have greater systemic absorption. Addition of epinephrine is also modified by the presence of intrinsic vasoactivity of the local anesthetic such as ropivacaine, where its effects are concealed. Therefore local anesthetics, which have a tendency to produce vasodilation, benefit more from the addition of epinephrine.\(^\text{16}\)

Since the addition of epinephrine decreases the peak plasma concentration of local anesthetic after giving a nerve block, its addition is judicious unless contraindicated, such as in patients with ischemic heart disease.

Patient’s clinical condition

Patients with existing liver or kidney disease exhibit impaired metabolism and excretion of the LA. Thus, it is a requisite to reduce the dose of local anesthetic. In patients with congestive heart failure, higher plasma concentrations are achieved with the regular dose of LA due to decreased volume of distribution and clearance of local anesthetic.\(^\text{14}\) Presence of acidosis and hypoxemia further accentuates the local anesthetic toxicity. Literature shows evidence of 2-3 times prolonged elimination half-life of amide local anesthetics in neonates.\(^\text{33}\)

Psychogenic Reactions

Thought of injection produces anxiety in most patients. The events associated are regarded as the most common adverse reaction associated with local anesthetics in dentistry. The manifestations are diverse, of which syncope being the most common. The symptoms include increased rate and depth of respiration, nausea, vomiting and changes in heart rate and blood pressure. These reactions are often overlooked or confused with allergic reaction as some features such as urticarial, edema and bronchospasm are seen in both.\(^\text{10}\)

Allergic Reactions

Esters are considered to be more allergic than amides. The main component responsible for ester allergy is the breakdown product para-aminobenzoic acid, as a result of metabolism. Allergy to epinephrine is considered impracticable.\(^\text{11}\)

Nevertheless, allergy to other compounds contained in the anesthetic cartridge, such as methylparabens used as preservatives for multidose vials has been reported.\(^\text{10}\) It is advocated to avoid vasoconstrictors in cases if the patient presents prevailing allergy to sulfites as metabisulfite is added as an antioxidant when vasoconstrictor is used. Yet vasoconstrictor do not exult cross-allergenicity with sulfite and can be used in patients with an allergy to the sulfonamide antibacterials, commonly called sulfa.\(^\text{10}\)

Interactions

Drug interactions of epinephrine with various drugs
have been identified. Interaction with Nonselective β-blockers Eg. Nadolol, pindolol, propranolol, sotalol, timolol and Tricyclic antidepressants Eg. Imipramine, amitriptyline, desipramine, nortriptyline may result in increased blood pressure. When local anesthetics are combined with an opioid and an antihistamine, there may be a predisposition to seizure activity, particularly in children.12

Pregnant and Lactating Women
Administration of local anesthetics and vasoconstrictors used in dentistry has been documented safe in pregnant or lactating patient. However, the operator must be exacting to aspirate the needle before injecting the local anesthetic in order to avoid the possibility of intravascular injection.13

Elderly Patients
Often veteran patients possess compromise in liver function. Though response to vasoconstrictor is not overwhelming, but still degree of cardiovascular deterioration can be expected, even without an apparent history of heart disease. Therefore, it may be considered judgmatic to reduce the dose of epinephrine.14

Children
Maximum dose of local anesthetic should be calculated according to the weight of the child before administration to help prevent unintended overdose. Since toxicity is more prevalent in children, it is advisable to use a low concentration solution. 2% lidocaine with epinephrine 1:100,000 may be considered ideal local anesthetic for a child. Bupivacaine should be avoided in children owing to its long duration of soft-tissue anesthesia.15

SIGNS AND SYMPTOMS
The manifestations of Local anesthetic toxicity can be divided into three categories: local, systemic, and allergic reactions. Local toxicity may present in the form of neurotoxicity, transient neurological symptoms, or myotoxicity, while systemic toxicity embrace central nervous system (CNS) and cardiovascular system (CVS).

A. Local toxicity
1. Facial Nerve Palsy20
Facial nerve palsy is the most common neurological complication as a result of an inferior alveolar nerve block.

Such patients will present the following signs:
- Generalized weakness of the ipsilateral side of the face
- Inability to close the eyelids
- Obliteration of the nasolabial fold
- Drooping of the corner of the mouth
- Deviation of the mouth to the unaffected side
- They may also complain of pain in the retroauricular area and a decreased taste sensation.

2. Total Body Hemiparesis21
Unintentional intravascular injection of local anesthetic with subsequent retrograde internal movement in branches of the internal carotid artery has been identified as a mechanism. The features present as drooping of eyelid, occipital and neck stiffness, loss of sensation on the right side of the face with difficulty in swallowing, and led to complete loss of chewing ability and a right hemiparesis. These are transient in nature and can be attributed to excess pressure created during the administration of the injection leading to a retrograde flow into the internal carotid artery.

3. Post-injection Paraesthesia22
Pricking of the needle on withdrawal from the tissues may damage the inferior dental nerve causing paraesthesia. In other cases, direct injection of local anesthetics contaminated with sterilizing agents, into the nerve may cause damage leading to the development of hemorrhage or hematoma around the nerve sheath causing necrosis of the neural tissue. Patients report such accidents as electric shock feeling. If such a complaint is raised the injection must be stopped immediately.

4. Horner’s Syndrome
Campbell et al24 reported a rare complication following an inferior dental nerve block, that is the development of Horner’s syndrome. The possibility arises due to penetration of the local anesthetic through the lateral pharyngeal and prevertebral spaces, causing blockade of the stellate ganglion. The features of the syndrome manifest as:
- Flushing of the face on the same side
- Ptosis of the eyelid
- Vasodilatation of the conjunctiva
- Pupillary constriction
A rash over the neck, face, shoulder and arm of the ipsilateral side (occasionally).

It may at times be associated with transient hoarseness of voice and difficulty in breathing due to involvement of the recurrent laryngeal nerve.

5. Sudden Unilateral Deafness

Administration of inferior dental nerve blocks has been linked with immediate loss of hearing. This has been explained, as the anesthetic reaches the middle ear along the venous systems within the mandibular region and causes localized vasospasm of the cochlear division of the internal auditory artery, leading to dysfunction of the cochlear nerve. This effect is augmented in the presence of vasoconstrictor.

6. Complications due to the local anesthetic solution

Rapid injection of local anesthetic directly into a blood vessel results in dangerously high concentrations in the brain causing toxicity. These effects may occur in two distinct phases: initially causes stimulation of central nervous system followed by a marked cerebral depression. During the phase of stimulation, symptoms range from anxiety, restlessness, hallucinations, increase in rate and depth of respiration, gagging, vomiting and in extreme cases tremors and convulsions may become noticeable. However, the patient lapses into unconsciousness with the advent of medullary depression, followed low in the blood pressure and a striking reduction in the respiratory rate. Death often results from respiratory failure.

7. Fear of Injection

It is usually fear of the injection that is responsible for psychogenic signs and symptoms. Cerebral hypoxia and anemia sets in as a result of reflex dilation of the splanchnic blood vessels. Clinical picture depicts a low blood pressure and a rapid but weak pulse. Skin appears cold accompanied by pallor and sweating. Convulsive are often noted.

8. Local anesthetic myotoxicity

Direct injection of these agents into adjacent muscles causes reversible myonecrosis. The signs manifest according to the site muscle anesthetized causing extreme weakness and quivering of the muscles. Clinical picture for diagnosis presents tenderness, increased intensity on stretching, relief on shortening.

B. Systemic toxicity: CNS

The clinical features of systemic toxicity are in proportion to the blood concentrations of the local anesthetics. In majority of cases, CNS symptoms are anticipated than cardiovascular complications. Symptoms associated with lower concentrations are ringing sensation in ears, light-headedness, altered taste sensation, and peri-oral numbness. With higher concentrations, the symptoms are grieved ranging from convulsions and unconsciousness, followed by respiratory failure. Convulsions may manifest as the first sign, if large bolus of local anesthetic is injected intravenously. In pregnant woman, the features related to lower concentrations are masked due to large doses of diazepam or midazolam as premedication, and may ultimately exhibit in the form of convulsions. Incidence of increased PaCO2 and low pH, increases the chance of convulsions by decreasing the convulsive threshold and enhances drug delivery to the brain by increasing cerebral blood flow. Toxic potential of local anesthetics closely parallels their relative potency: bupivacaine > lidocaine >> chloroprocaine.

C. Systemic Toxicity: Cardiovascular System

Initial features manifest as increased heartbeat and hypertension progressing to reversal of features depicting slowing of heart rate and dysrhythmias leading to cardiac failure. Associated features are changes in the QT interval and decrease in cardiac conduction. With increasing concentrations, LA causes depression of spontaneous pacemaker activity in the SA node resulting in sinus bradycardia and arrest.

D. Allergic reactions: The reactions range from hypersensitivity to anaphylaxis.

PREVENTION

Patient assessment

Elective decision must be before administration of local anesthetic based on proper record of patient history and physical examination. Meticulous attention must be paid to the patient's age and debilitating medical conditions. The choice of anesthetic agent, concentration and
volume must be made that best responds to the patient's medical profile.

**Preparation**

Resuscitative equipment and drugs must be acquired beforehand. Airway resuscitation equipment including Ambu bag, laryngoscopes and endotracheal tubes must be secured. Proper patient consent should be obtained. Consider pre-medication with a benzodiazepine. Vitals should be monitored continuously.

Syringe containing the local anesthetic must be labeled, aspiration before injection is prudent and discarded in case discolored with blood. Injection must be slow and incremental. Maintain verbal contact with patient such that any overt symptoms of toxicity can be reported immediately.

**MANAGEMENT**

Routine aspiration is utmost essential in order to avoid accidents with jeopardized results. Intravascular injection of local anesthetic results in immediate and transient toxicity. Injection must be immediately stopped and supportive measures to support the airway and prevent seizure activity are initiated. Patient is placed in supine position along with oxygen administration. Vital signs such as pulse, respiratory rate and blood pressure must be continuously monitored. In case convulsions occur, a slow intravenous infusion of 10 mg/2minutes diazepam should be administered.

Flumazenil must be approachable to antagonize the effects of benzodiazepam. To manage the secondary phase of toxicity involving CNS depression elevate feet of the patient, continuous administration of oxygen and respiration and circulation must be monitored and supported until the symptoms have waved off. Hospital-based treatment involving methoxamine hydrochloride should if the blood pressure fails to respond. If the symptoms continue to worsen, Intralipid kits should be available. It consists of two 500ml bags of 20% lipid emulsion, infusion tubing, and dosing information. It is mainly used for treatment of cardiac complications associated with local anesthetic toxicity. Maximum dose should not exceed 12ml/kg, as recommended. Potential side effects of Intralipid infusion are allergy. Attempts to use propofol should not be made as it is a cardiac depressant and available in formulation containing only 1% lipid emulsion in comparison with Intralipid containing 20%.

A class of drugs that can effectively manage Cardiac arrest after LA overdose are K channel openers eg. pinacidil and bimakalim. These drugs shorten the action potential in the Purkinje fibers and ventricular cells. They negatively the resting membrane potential and prolong the plateau phase. Pharmacologically, they have negative inotropic effects. As a result Ca^{+++} influx is decreased and hence contractility is reduced.

Note: liver is responsible for hydrolysis and metabolism of the amide type of anesthetic solutions e.g. lignocaine and prilocaine before being eliminated from the body. Any patient suffering from seriously impaired liver function is predisposed to danger of inadequate elimination of the anesthetic. Therefore, such patients become prone to severe toxicity even with normal recommended doses of local anesthetic. Another possibility of toxicity is seen in patients with impaired kidney function, as elimination of the metabolized anesthetic solution is excretion in the urine.

**CONCLUSION**

Varieties of anesthetic agents have been developed since the discovery of cocaine. The decision to chose appropriate agent depends on a cascade of factors including patient's age, medical condition, addition of vasoconstrictors so on and so forth. However, the use of local anesthetic in children needs meticulous planning and history taking as the adverse effects are much more elevated and fulminant even at regular recommended doses. Low dose effects of local anesthetic toxicity are often subsided using resuscitation measures alone. However, all clinicians dealing with these agents must equip them with Intralipid kits in order to counter the serious CNS and CVS complications in severe systemic toxicity.

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An unusual case of extrauterine leiomyoma

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ABSTRACT

Leiomyomas are the common benign tumours of female reproductive system. Broad ligament is a very unusual site for presentation of leiomyoma. We are presenting here a case of large, broad ligament leiomyoma on account of its rarity or clinical and radiological diagnostic difficulties encountered.

Keyword: Leiomyoma, Broad ligament.

INTRODUCTION

Leiomyomas are most often benign smooth muscle tumours of the female genital tract. It can be intrauterine or extrauterine.¹ Uterine leiomyomas are the most common myomas, accounting for approximately 20–30% of cases in females less than 35 years. Broad ligament tumours pose specific diagnostic difficulties because of their rarity.² On account of its rarity, it leads to erroneous diagnosis and management³. These lesions can compress urethra, bladder neck or ureter due to extrauterine location and manifest clinically as varying degree of urinary flow obstruction. Rarely these tumours are of massive size and present with unusual clinical manifestations.

CASE REPORT

45 years old perimenopausal married female presented with complain of pain lower abdomen on and off along with dysmenorrhea for last 2 months. Patient reported a history of four past full term, normal vaginal deliveries last one being done 20 years back. There was no associated history of anorexia, weight loss, and bladder or bowel complaints. Patient's per abdominal examination revealed a firm, nontender, slightly mobile, lower abdominal swelling of size of 18-20 weeks gravid uterus. Ultrasound examination of abdomen and pelvis showed uterine fibroid and right tubo-ovarian mass.

MRI pelvis (Figure 1) revealed a large well defined multiseptated cystic lesion right adnexa with multiple septations and solid eccentric irregular nodular area suggestive of neoplastic etiology most likely mucinous cystadenoma. CA-125 was within normal limit.

As per patient history, physical examination, laboratory and radiological investigations, she was planned for total abdominal hysterectomy and bilateral salpingo-oophrectomy for suspected neoplastic aetiology of right adnexa in a local hospital. Operative findings revealed a normal sized uterus and a mass of approximately 10x15cm size which was misinterpreted as mass from retroperitoneum and pushing the uterus towards left side. Both ovaries were found to be of normal size. Biopsy of mass was taken during exploration and patient was referred to Government Medical College & Hospital, Chandigarh for further management.

History and physical examination were reviewed. Per vaginal examination revealed normal cervix with bulky uterus deviated towards left side. Per speculum examination revealed normal vaginal and cervix.

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laboratory investigations were within normal limit. Repeat USG abdomen and pelvis was suggestive of right tubo-ovarian mass measuring approximately 6.2x6.8cm and uterine fibroid of size 2x1.8cm approximately. She underwent contrast enhanced computed tomography abdomen and pelvis (Figure 2) which also revealed bulky uterus with lobulated lesion in fundus and complex cystic lesion (12.3x10.8cm) in right adnexa with mass effect on rectosigmoid colon and right ureter. The uterus and urinary bladder were pushed towards left. Histopathological examination was suggestive of benign spindle cell tumor with no evidence of malignancy.

Operative findings revealed a large right parovarian mass in leaves of broad ligament which was pushing the uterus towards left side and compressing the rectosigmoid colon and ureter. She underwent total abdominal hysterectomy with bilateral salpingooopherectomy with excision of broad ligament spindle cell tumor (Figure 3 and 4).

On gross examination, a mass was identified, which measured 14 cm x 8 cm x 7 cm. On microscopic examination, it showed circumscribed tumor composed of interlacing fascicles of smooth muscle cells. The cells are spindle shaped with elongated nuclei having blunt end and bland nuclear chromatin. Areas of hyalinization, extensive hydropic changes and calcification were noted suggestive of leiomyoma.

**DISCUSSION**

Leiomyoma is a benign smooth muscle tumor that most commonly arises from the uterus but may also be found in the cervix, uterine ligaments and rarely in the ovaries or fallopian tubes. Broad ligament is a two layered peritoneal fold connecting the sides of uterus to lateral walls of pelvis and its floor. Mesenchymal tumours of broad ligament are rare, leiomyoma being the most common. Broad ligament leiomyoma are of two types: false broad ligament leiomyoma (uterine tumour which grows into the broad ligament) and a true broad ligament leiomyoma arising from the sub peritoneal connective tissue of the ligament. Symptoms vary depending on location of tumour. Leiomyomas can present with menstrual disturbances, reproductive dysfunctions and pressure symptoms like bladder and bowel dysfunctions. Secondary changes can occur that include degeneration, infarction, necrosis, haemorrhage and rarely sarcomatous changes.

Unusual growth pattern and varying locations often make identification of leiomyomas challenging, both clinically and radiologically. In our case, patient presented with abdominal mass which clinically and
radiologically was suspicious of ovarian neoplasm and intraoperative misdiagnosed as retroperitoneal tumor. Consistent with our finding Bansal P and Garg D reported a case of massive broad ligament leiomyoma imitating an ovarian tumor. Similarly Godbole et al also reported a case of broad ligament leiomyoma which mimicked an ovarian tumour.

The most common degenerative forms which are observed in leiomyomas are calcific degenerations. Calcifications are observed in our case which are also reported in a case of broad ligament leiomyoma by Bose et al.

In leiomyoma, cystic degeneration is considered as an extreme sequel of oedema with degenerative changes and its incidence has been reported to be as 4%. In the present case, the leiomyoma underwent hydropic changes. Similar to our finding, two cases of broad ligament leiomyomas with hydropic degenerative changes have been published.

The differential diagnosis of large cystic lesions in female pelvis includes masses of ovarian origin (both primary neoplasms and metastasis), broad ligament cysts, peritoneal inclusion cysts, paraovarian cysts, hydrosalpinces, and broad ligament leiomyomas with cystic degenerations, cystic degenerations of lymph nodes, haematomas, abscesses and lymphoceles. As has been exemplified in the present case, extrauterine leiomyomas can cause errors in radiological diagnosis. Ultrasound/CT guided preoperative percutaneous biopsies of the lesions can be helpful for determining their exact histologic compositions before doing surgeries.

So, the differential diagnosis of extra-uterine leiomyoma should be considered in cases of pelvic masses with normal uterus and ovaries. Careful evaluation and correct operative technique does provide good outcome even in such cases.

CONCLUSION

The rare case of a broad-ligament leiomyoma with a massive size and secondary changes may pose diagnostic difficulty in differentiating it from an ovarian tumor. The diagnosis of broad ligament leiomyoma is difficult owing to its rarity, unusual presentation, clinical and radiological features. This case will facilitate in creating a clinical awareness of this difficulty and it will help in making better and early diagnoses of such cases.

REFERENCES

Anaesthesiologists' perspective in meningoencephalocele: A case report

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ABSTRACT

Meningoencephalocele is a midline defect of cranial bone fusion which occurs most frequently in the occipital region (75%). The anaesthetic management of this subset of patients in the perioperative period is a formidable task for anaesthesiologist because of difficulty in securing the airway, problems associated with prone position, blood loss and hypothermia. Anaesthesia care givers should take utmost precautions during prone position; conscientious airway management, accurate blood loss assessment, measures to prevent hypothermia and management of problems associated with congenital abnormalities. We report the anaesthetic management and considerations in a 2 month old child with huge occipital encephalocele.

Keywords: Meningoencephalocele, Occipital, Anaesthesia

INTRODUCTION

In meningoencephalocele, there is a herniation of brain tissue cerebrospinal fluid, and meninges through the skull defect. Its incidence varies depending upon the ethnicity. Expertise is needed during manipulation of airway, positioning, managing intraoperative blood loss, associated anomalies, and hypothermia.

CASE REPORT

A 2 month old child weighing 4 kg presented to neurosurgery outpatient department of our institution with a large swelling on back of head. There was no neurological deficit or associated other congenital anomaly. The child had the defect since birth. The swelling made supine position of the child nearly impossible with limited neck extension (figure 1). A diagnosis of occipital meningoencephalocele (6x7) was made which required excision and repair. Preanesthesia check up revealed normal cardiovascular and respiratory system and even normal laboratory evaluations (haemoglobin, platelet count). The child was kept fasting for 4 hours. In the operation theatre, standard anesthesia monitoring were applied which included non-invasive blood pressure (NIBP), electrocardiogram (ECG), skin temperature and pulse oximetry (SPO2). Inhalational anaesthesia was induced with sevoflurane in 100% oxygen by mask in lateral position. Initial check laryngoscopy was done using miller blade size 0 which showed only tip of epiglottis (Cormack-Lehane Grade 3). Anticipating difficult intubation in lateral position; we made certain modifications for accommodating the large swelling for obtaining optimum supine position for orotracheal intubation. We made a platform using rings and rolled up sheets and placed the child as shown in the figure (2). Laryngoscopy in this position dramatically improved visualization and improved the grades (Cormack-Lehane Grade 1). After administering atracurium 0.5mg.kg-1 IV to facilitate muscle relaxation, trachea was intubated with a 3.5-mm ID uncuffed endotracheal...
tube (Portex) and was secured. Subsequently child was positioned in prone position as shown in figure 3. Anaesthesia thereafter was maintained with sevoflurane 2-4% in air-oxygen mixture (50:50) and fentanyl 1mcg.kg-1 was given for analgesia. Child exposed body area was covered with forced air warming blanket to protect from hypothermia. Prewarmed isolyte P was infused intraoperatively as maintenance fluid. Gliotic tissue was excised and total duration of surgery was 1.5 hours. The case underwent uneventfully intraoperatively and child's trachea was extubated at the end of surgery. Patient was kept under observation in post anaesthesia care unit (PACU) for next 2 hours and subsequently shifted to neonatal ward.

DISCUSSION

Encephalocele, Latin name cranium bifidum, is a neural tube defect which is characterized by sac-like protrusions of the brain and its membranes that cover it through openings in the skull. These defects are caused by failure of the neural tube to close completely during fetal development. Usually these are diagnosed immediately after birth. Though it occurs rarely, incidence of encephalocele is 1 per 5,000 live births worldwide. The most common location of this congenital anomaly is the occipital region.

Early surgical repair is definitive management in this subset of patients. The goal in such patients is to prevent rupture and infection with a view to obtain good neurological outcome.

We fasted our patient for 4 hours according to ASA fasting guidelines as pharyngeal incoordination, poor sucking reflex and absent gag reflex makes them prone for aspiration. Occipital swelling makes supine position difficult so one adopts lateral position naturally but this limits the neck extension although preventing rupture of meningoencephalocele. We managed to place the child in supine position by constructing a space using 2 head rings made of bandage as shown in figure 2. The meningoencephalocele was placed in the well shaped space which accommodated it as well as prevented its rupture. Review of literature mentions various other techniques like constructing platform of rolled-up blankets needle decompression of the encephalocele sac under sterile conditions placing the baby's head beyond the edge of table to intubate in the lateral position and even do awake intubation in the lateral position.

Risk of hypothermia is high as head in children occupy large surface area and liability of autonomic system below the level of defect. So due care should be exercised to prevent hypothermia. We used warmed forced air warming blanket and warm intravenous fluids. Accurate assessment and simultaneous replacement of...
blood loss is very essential in this surgery as it involves potential bleeding from the suboccipital bone and the dural sinus.¹⁰

Meningoencephalocele is associated with various congenital and neurological malformations. Recognition and its affect on the perioperative management should be assessed. Latex allergy may be present and sensitization must be prevented. The associated anomalies with meningoencephalocele are depicted in table no 1.

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<tr>
<th>Table 1</th>
<th>Showing congenital and neurological anomalies associated with meningoencephalocele</th>
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<td>Congenital</td>
<td>Neurological</td>
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<td>Clubfoot</td>
<td>Chiari malformation</td>
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<td>Extrophy of bladder</td>
<td>Hydrocephalus</td>
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<td>Prolapse of uterus</td>
<td>Vision problems</td>
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<td>Kippel fel syndrome</td>
<td>Developmental delay</td>
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<td>Cardiac defects</td>
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<td>Ataxia</td>
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<td>Seizures</td>
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<td>Spastic quadriplegia</td>
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Post operative back up of mechanical ventilation must be present as structural derangement of pontomedullary respiratory control centre or defective afferent efferent pathways may make extubation challenging due to inadequate respiratory efforts.⁴⁻⁵ Ultimately neurological outcome depends upon the extent and nature of the herniated contents and associated congenital anomalies.¹⁰

CONCLUSION

Perioperative care of patients with occipital encephalocele is challenging and thus requires close communication between anaesthesiologist and neurosurgeon. Careful attention to positioning and airway, prevention of hypothermia, latex allergy precautions and accurate estimation blood and fluid requirement is necessary for good outcome.

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Non union in an open Smith fracture: a case report

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ABSTRACT

Open Smith fracture is an extremely rare injury. There are no laid down standard guidelines for the management of such an injury. Nonunion in an open Smith fracture, to the best of our knowledge, has not been reported in the literature. We report a case of a young male who presented to us with a nonunion of Smith fracture which he suffered as an open injury 3 months back.

Keywords: Smith Fracture, Non union

INTRODUCTION

Smith fracture (also known as Goyrand fracture) is a fracture of the distal radius with associated volar angulation of the distal fracture fragment. Classically, this extra articular transverse fracture can be regarded as a reverse Colle's fracture. Smith's fracture is a comparatively uncommon injury accounting for less than 3% of all fractures of radius and ulna.¹ ² The most common mode of injury reported is a fall on the back of the hand which results in a typical garden spade

![Type I Fracture](image1.png)

- Type I
  - Extra-articular transverse fracture through the distal radius
  - Most common: ~85%

- Type III
  - Juxta-articular oblique fracture
  - Uncommon: <2%

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deformity.\textsuperscript{1,2} No attempt appears to have been made in the literature to classify the different varieties of Smith's fractures. However, three distinct types can be recognized radiologically.\textsuperscript{2}

There appears to be a paucity of data in the literature regarding management of open smith fractures. The present case report cites one such case and its management.

**CASE REPORT**

A 24 years old, right hand dominant, male presented to our outpatient department with chief complaints of deformity (Figure 1a & 1b), reduced grip strength and restricted motion of the left wrist of 6 weeks duration. Patient had a past history of road side accident 3 months back, in which he sustained an open fracture (Gustillo Anderson Grade II), of the left distal end radius (Figure 2, 3a and 3 b). Patient was treated with debridement and external fixator (Figure 4a and 4b). Additionally 3 K wires were used to stabilize the distal radio ulnar joint. External fixator and K wires were removed 6 weeks after application and patient was advised active and active assisted range of motion exercises of the wrist joint and was advised to follow up in OPD.
On examination in OPD at 3 months, the left wrist joint was found to be deformed with restricted range of motion (Figure 5) as follows:

- Supination = 45 degrees (Figure 5 a)
- Pronation = 60 degrees (Figure 5 b)
- Palmar flexion = 90 degrees (Figure 5 c)
- Dorsiflexion = 0 degrees (Figure 5 d)

The Radiographic parameters of left wrist 3 months were also found to be deranged (Figure 6 a and 6b) suggesting a secondary collapse at the fracture site.

- Palmar tilt = 40 degrees (Average = 11 degrees; Range = 0 to 28 degrees)
- Positive Ulnar variance = 6 mm (Range = 0 to +2 mm)
- Radial height = 7 mm (Average 12 mm; Range = 8 to 18 mm)
Radial inclination = 18 degrees  (Average 22 degrees; Range = 13 to 30 degrees)

Patient was planned for open reduction and internal fixation. A Volar Henry approach to distal radius was taken and fracture was found to be not united with volar impacted fragments. Fracture ends were lifted, margins freshened and gap filled with a wedge shaped iliac bone graft (Figure 7 a and 7b). Internal fixation was performed with a five hole volar locking 'T' plate. (Figure 8 a and 8b)
DISCUSSION

Nonunion of distal radius fracture is extremely uncommon accounting for 0.2% of distal radius fractures.6,7,8,9 The low incidence of nonunion of distal radius fractures is probably because of the metaphyseal location and the impaction of fracture fragments during the injury.8 Several contributing factors had been elaborated including: concomitant distal ulnar fracture, inadequate immobilization, inadequate fixation or excessive distraction during application of external fixator.6,11,12 Furthermore, open Smith fracture, in itself being a rarity, nonunion in open Smith fracture has not been reported in the literature. The aims of treatment for nonunion of distal radius fracture are correction of deformity, providing solid fixation to maintain fracture stability and preservation of functional motion at the wrist joint. In our patient the nonunion is likely to have been caused by the open nature of the fracture, concomitant distal radio ulnar joint disruption and probably the excessive distraction at the fracture site due to external fixator.

Furthermore, in the present case, the external fixator was used as a definitive treatment in a rigid mode of fixation, the external fixators in rigid mode are known to cause nonunion. Thus, nowadays, the external fixators are recommended to be mainly used for healing of the wounds and then definitive fixation with plates and screws is better option for such fractures.

In our revision surgery, once the fracture site was opened, fracture was not united with fibrous tissue between the fracture ends. Fracture ends were lifted, freshened and gap was filled with autologous iliac bone graft. Fracture was then stabilized with five hole volar locking t plate. Initially an ulnar shortening was also planned for a suspected ulno-carpal impingement due to a positive ulnar variance but the need for the same was not felt after opening the fracture site and lengthening the radius by adding a wedge shaped graft from the iliac crest.

Through this case we underscore the complication of nonunion which can result when external fixator is used in rigid mode as a definitive mode of treatment; the literature has highlighted the nonunion rate in fractures treated with external fixator as up to 61%.13,14 We feel that in the present case, the external fixator should have been used as a temporary means of reduction and fixation until the time soft tissue and wound got healed. Once the soft tissue had healed a stable fixation in the form of plating should have been employed at the earliest.

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