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Editorial

Health for All

There is often no better way to cope with the totality of health problem than by preventing it from occurring.[1] The Centre for Disease Control (CDC and Prevention CDC 24/7: Saving Lives. Protecting People) gives a list of simple things which we can propagate for healthy living. I would like to highlight only a few here.

When we think of disease prevention, starting from birth the logical chain would be safe birth (preventing hypoxic injury), immunizations to prevent infectious diseases, good nutrition - preventing malnutrition and obesity in our children, ensuring mental health - one of the safeguard being intake of iodised salt; safeguarding oral health - with simple strategies like brushing and flossing of teeth, promoting physical activity to promote bone health and long term disease prevention, preventing diseases caused by tobacco and alcohol by active teaching and limiting production and availability. All these strategies appear to be so simple and straightforward.

Yet, when individual and collective greed and sloth supervenes, all the above can go horribly wrong. The midday meals leading to children's death, the mushrooming of fast food joints leading to an epidemic of obesity - the 'Ahatas' selling alcohol attracting teenagers and older people, the tobacco companies being promoted for the Government to earn revenue - the examples are too many. Our country needs good governance. If that is lacking, the onus of responsibility comes on each of us to do our best to publicize and propagate the message of 'prevention' for promotion of good health. Another copy of Journal of GMCH brings to you varied and useful information.

Be healthy, be happy.

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Reference

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Review Article

Tracheostomy care in critical care settings: evidence based practice guidelines

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Tracheostomies have become popular amongst varied patients in intensive care units and emergency wards where long term ventilatory support is anticipated. This had improved patient management and reduced mortality though long term morbidity and complications are still to be pondered upon. There have been several guidelines for tracheostomy care over the past decade to improve patient outcome but no universal standards were established. Most popular and commonly used are Guidelines for Tracheostomy Care by NHS foundation trust (National Health Service, U.K.).[1] The Tracheostomy Care Bundle was initially devised by St. Mary's Milne NHS trust in 2004 based on best practice guidelines at a London teaching hospital (St. George's Healthcare, NHS), 2000 and Royal Marsden Hospital's manual of clinical nursing procedures, 2000.[2-4] [Table 1]

Ever since there have been studies and audits that showed improved compliance with 'tracheostomy care bundle' results in better patient outcomes.[2,5,6] This is further enhanced by multidisciplinary approach that comprises a physiotherapist, an otolaryngologist (ENT specialist), a speech and language therapist, an outreach and resuscitation practitioner, an intensive care medicine practitioner, a respiratory medicine practitioner and a diet specialist together with regular teaching sessions of nursing staff.[5,6] An extensive literature search done by Mitchell et al,[7] included 53 guidelines, 99 systematic reviews and meta-analyses and several RCTs, had come up with 77 consensus statements to be followed for tracheostomy care. With background of these published guidelines, audits and review of literature, we suggest following evidence based guidelines for tracheostomy care in the ICU and emergency ward.

Table1

The St. Mary's Tracheostomy Care Bundle Checklist
Humidification – Each patient with tracheostomy should receive adequate humidification. This should be documented 2 hourly.
Tube Patency/Inner tube care – Inner tube to be removed, checked for secretion build up, cleaned and replaced 2-4 hourly.
Safety Equipment – All bedside equipment relating to tracheostomy care are checked at the beginning of each shift.
Cuff – Cuff status to be checked each shift.
Tracheostomy dressing/tapes – To be changed at least 24 hourly.
Weaning plan documented
Care plan documented

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TRACHEOSTOMY CARE BUNDLE

When caring for a patient with tracheotomy, a thorough assessment needs to be completed in each shift. The patient should be observed for hypoxia, infection, stoma site for redness, purulent discharge and abnormal bleeding around the stone.

Tracheostomy care includes following points:

1. Essential/ Safety equipments for tracheostomy care
2. Humidification
3. Suctioning
4. Cleaning the inner cannula of tracheostomy tube
5. Tracheostomy site care and dressing change
6. Tracheostomy ties care
7. Maintaining optimum cuff pressure
8. Changing the tracheostomy tube
9. Communication and weaning plan
10. Decannulation

1. ESSENTIAL/ SAFETY EQUIPMENTS FOR TRACHEOSTOMY CARE[1,8]

- Should be immediately available at all times for a patient with a tracheostomy in the event of the tube needing to be replaced urgently.
- Should be checked at the beginning of each shift and / or nursing staff handover.

- Essential / Safety equipments for tracheostomy care are:
  - Suction unit, tubing and yankeur sucker (should be checked daily)
  - Suction catheters (a selection of sizes)
  - Sterile water, sterile bowl for suctioning
  - Sterile and non-sterile gloves, aprons, eye protection
  - 2 spare tracheostomy tubes (one should be the same type as the one inserted and the other one - a size smaller)
  - Tracheal dilators
  - Spare inner cannula
  - Rebreath bag and tubing
  - Tracheostomy mask
  - Oxygen cylinder and humidifier
  - Nebulizer mask and tubing (special tracheotomy nebulisers are available)
  - Tracheostomy tube holder and dressing
  - 10ml syringe
  - Artery forceps
  - Sputum trap
  - Catheter mount
  - Normal saline
  - Clinical waste bag (orange)
  - Lubricating gel
  - Communication aid (nurse call bell)

2. HUMIDIFICATION

- Check adequate humidification and document every 2-4 hours.
- Adequate humidification is essential as tracheostomy bypasses nose & upper airway mechanisms for humidification, filtration and warming of inspired gases, which can lead to life threatening blockage of tracheostomy. (Table 2)
- Can be achieved in patients with minimal or low oxygen requirements using a heat moisture exchanger (HME) or cold water venturi humidifier system connected to a T-piece or tracheostomy mask.[1]
- Equipments:
  - Oxygen outlet/cylinder
  - Tracheostomy mask
  - Bottled sterile water
  - Room Humidifier

Types of Humidifiers

a) Heated Humidifiers:

- Recommended for patients with new tracheostomy tubes.
- Dehydrated patients.
- Immobile patients.
- Patients with tenacious secretions

b) Heat Moisture Exchange Filters:

- Recommended for patients who are adequately hydrated.
- Mobile patients.
- Not suitable for patients with copious secretions.

c) Nebulizers:

- Nebulization with normal saline is effective in helping to loosen secretions and soothing irritable airway. Currently in critical care areas humidification with nebulizers is in vogue, as prescribed by Doctor, with normal saline, duolin, etc.

3. SUCTIONING (Table 3)

- Essential component: secretion control and maintenance of tube patency.
- Frequency of suction will depend on the patient's needs and is assessed as :
  - Patients' ability to cough
  - The amount and consistency of secretions

Table 2
Shows the stepwise technique of humidifier

Action	Rationale
★ Explain the procedure to the patient.	★ To gain consent and co -operation
★ Wash hands	★ To minimize risk of cross infection
★ Fill reservoir of the humidifier with sterile water and attach to the oxygen supply.	★ Humidification prevents formation of crusts which could occlude the airway. Sterile water reduces the risk of infection
★ As prescribed, set the oxygenrate at required percentage, according to the patients' needs (usually 10-15 minutes of humidification every 4 hours) unless the patient has high oxygen demands. (If the patient does not require oxygen, a room humidifier can be used)	★ This provides humidified air without the need for an oxygen supply.
★ Replace the sterile water every 24 hours or when the reservoir is empty.	★ To minimize the risk of infection.
★ Record procedure in patient's care plan	★ To ensure continuity of care.

- The patient's oxygen saturation
- Whether there is any infection present
- Selection of the correct size suction catheter

- Side effects of suctioning include hypoxia, mucosal trauma, cardiac arrhythmia, increased intracranial pressure and infection risks.[1]

A. Basic guidelines for effective and safe suctioning

- Suctioning should be performed using aseptic technique.
- The patient should be upright and their head in a neutral alignment.
- Always suction with the inner tracheostomy tube in place.
- Use the lowest suction possible < 100-120 mm Hg (13-16KPa)
- Patients may require pre oxygenation prior to suctioning to prevent hypoxia.
- Due to the possible adverse effects of suction the oxygen saturations, respiratory rate, and heart rate should be monitored, during suction.
- Suction should only be performed for a maximum of 10 seconds.[1]

Equipments:

- A functional suction unit.
- Sterile suction catheters of appropriate size.
- Universal personal protection precautions (apron, gloves and goggles).
- Bottle of sterile water [label "for cleaning suction tubing", include date when opened.
- Oxygen therapy, wall flow meter.
- Ambu bag.
- Yellow bag for disposal of waste.[9]

CALCULATION OF CATHETER SIZE

Divide the internal diameter of the tracheotomy by two, and multiply the answer by three, to obtain the French gauge of the correct suction catheter). For example: When a size 8 tracheostomy tube is used, the internal diameter of the tracheostomy will be (8mm/2) X 3 = 12 Fr. Therefore, a size 12 French gauge catheter is suitable for use.[10]

$$ID\ (Fr) = \frac{3}{2} * ID\ (mm)$$

- Mini-tracheostomies should use a maximum of 10 Fr only.

B. Procedure[1]

Table 3
Shows the stepwise procedure of appropriate suctioning

No.	Action	Rationale
1.	Explain the procedure to the patient.	To gain consent and co-operation
2.	Wash hands and apply apron and eye protection	To minimize the risk of infection
3.	Set the suction machine to the appropriate level (<100 - 120 mmHg or 13-16kpa)	If the suction is too low, it will be ineffective. If the suction is too high, it will damage mucosa.
4.	Place pulse oximeter on patient's finger	To record oxygen saturation and heart rate throughout the procedure
5.	Open the end of the suction catheter pack (suction catheter should be less than half the size of the tracheostomy tube) and use the pack to attach the catheter to the suction tubing. Keep the rest of the catheter in the sterile packet.	To minimize the risk of infection.
6.	Apply sterile gloves (they should be worn as single use items)	To minimize the risk of infection.
7.	Insert suction catheter **10-15cm (about 1/3 rd of its length) into tracheostomy tube** advance until cough reflex/resistance is felt. Then **withdraw 0.5cm before applying suction**. Slowly withdraw the suction catheter with a rotating motion. The duration of **suctioning should not exceed 10 seconds** . Wrap the catheter around a gloved hand, and then pull back glove over soiled catheter and dispose of into the clinical waste bag. Re-apply oxygen to the patient if they require a high percentage of oxygen. If the patient requires further suction, repeat the above action using new gloves and new suction catheter. The secretions should be observed for amount, colour and consistency.	In order to minimize damage to the tracheal mucosa as this can lead to trauma and infection. To remove secretions from the mucous membranes. The longer the duration, greater the risk of mucosal damage. To minimize risk of cross-infection. To prevent hypoxia. To re-oxygenate the patient. To ensure that the airway is completely clear. To evaluate patient progress and observe for signs of infection and deterioration & document inpatients' notes
8.	Dispose of equipment and protective clothing.	To ensure safe disposal of waste.
9.	Wash and dry hands.	To prevent cross-infection.

4. CLEANING OF INNER CANNULA OF TRACHEOTOMY TUBE

- This should be carried out as needed, but at least every 4 hours.
- If the inner cannula contains no obvious secretions it may be reinserted. Loose secretions can be flushed through with sterile water. If soiled or partially occluded by dried secretions the inner tube should be disposed of.
- Correct sized inner cannula must be used as a replacement.
- The use of brushes to clean inner cannula is not recommended. As this may cause abrasive damage to the inner cannula.
- After cleaning of inner cannula of tracheotomy tube patient's comfort level needs to be assessed. Ensure that the patient is not in distress.[1]

5. CARE AND DRESSING OF STOMA SITE

- First assess the site for any redness and/or skin breakdown.
- Clean the stoma with a Q-tip or gauze square moistened with normal saline solution. Avoid using hydrogen peroxide unless the site is infected, as it can impair healing.[11]
- Occasional redness and purulent drainage may be expected. Topical treatment can be used for minor infections.
- A new dressing should be applied to the stone site to absorb secretions and insulate the skin once per shift / day.[1]
- Dressings around the stoma are changed for excessive exudates.
- Dressings may be uncut gauze or sponges and changed as frequently to keep the area clean and dry. Pre-cut foam dressing (Lyofoam) should be used due to their absorbency.[1]
- Tracheostomy dressing changes help to maintain skin integrity and to prevent infection.[11]

6. TRACHEOSTOMY TIES

- First time change of ties of a new tracheostomy should be not before 24 hours, to lower risk of accidental dislodgment. Thereafter, ties are changed on a daily basis.
- To lower the risk of accidental decannulation, the tie changes should be performed by two people or with new ties secured before old ties are removed.
- There are many options available to choose from, like Twill tapes, Velcro tapes, metal chains, and plastic IV tubing etc.
- Always check that ties should not be too tight or loosely tied, as this may lead to dislodgment or obstruction of blood flow. For proper fit it must be one or two fingers loose.
- If the patient is disoriented or is trying to pull the tube, then Velcro ties must not be used.[12]

7. CUFF PRESSURE

- The main complication of cuffed tubes is tracheal stenosis which is usually due to excessive cuff pressures. It is important to only use enough air in the cuff to prevent air escaping around the tube (usually identified by the patient being able to speak or gurgling in mouth). If large amounts of air are required to prevent air escaping (i.e. above manufacturers' recommendations) then the cuff may be faulty or the tube is too small; in either case the doctor should be informed of the problem and the tracheostomy tube should be changed.[9]
- Cuff pressure should be maintained in a range from 20 to 25 mm Hg.[10] Cuff pressures should be measured in every shift with a manometer.

a. Minimal Occlusive Volume

This technique is used to prevent over inflation of the cuff and hence avoiding the trauma it may cause. The cuff is inflated by 10 ml syringe, slowly, while placing a stethoscope on the side of the trachea. When no air is heard passing over the cuff, one should stop inflation. If a leak is required in the cuff for weaning purposes, withdraw 1 -2 ml of air. There should be no more than 10 ml of air in the cuff unless advised by the anaesthetist.[13]

b. Synchronized Cuff Deflation Technique

- This technique is particularly used to clear the secretions collected above inflated tracheostomy cuff along with relieving pressure on tracheal walls, hence preventing aspiration and stenosis.
- The technique requires 2 personnel, as one person deflates the cuff; and second (trained nurse) carry outs tracheal suctioning. The timing is crucial to prevent hypoxia and aspiration. [14]

8. CHANGING THE TRACHEOSTOMY TUBE

a. For the first time:

- Changing a tracheostomy tube for the first time depends whether stoma is formed surgically or percutaneous tracheostomy is performed.
- For surgical stoma, first time changing must not be before 72 hours and usually done within 5-7 days. [7, 14]
- For percutaneous tracheostomy : ideally within 7-10 days.[7,14]

This should only be carried out by first level nurses / anaesthetist along with on call ENT team who are trained

and competent in doing this procedure.[1]

b. For subsequent tracheostomy changes (7-14 days are considered appropriate):

   Sudden blockage may also be considered for change of tube.

Equipments

- Good light source
- Two tracheostomy tubes (one same size, one smaller in case of difficulties)
- Syringe (if a cuffed tube is being used)
- The assistant in case of an emergency - should hold tracheal dilators ready for insertion into the tracheostomy site.
- Alcohol hand gels
- Suction equipment (ready and turned on). Pressure should be at 150mmHg/20kpa.
- Oxygen source
- Sterile dressing pack
- Tracheostomy dressing
- Normal saline
- Lubricating jelly
- Apron, gloves (sterile and non-sterile) eye protection
- Clinical waste bag
- Pulse oximeter (to monitor patient during)

Procedure

The Procedure of Changing Tracheostomy Tube[1]:

The patient is made to sit upright and vitals recorded. Tracheostomy tube of appropriate size is prepared (cuff checked, lubricated and ties attached). With aseptic technique, the dressing is removed, a suction catheter / guidewire is placed, soiled tube removed after deflation of the cuff, stoma cleaned and fresh tracheotomy tubes placed over the guide wire. Then introducer/ guidewire is removed, position confirmed, cuff inflated and tube secured by ties. Ensure patient is comfortable and document the procedure.

9. COMMUNICATION AND WEANING PLAN

Simple means of communication between the patient and others should be agreed such as call bell, blinking, pen and paper/alphabet board, lip-reading.[1] Constant encouragement and support are particularly important in this phase. Weaning from dependence on a tracheostomy to decannulation is a multi-professional decision. Many factors need to be considered to ensure that the patient can protect their airway from aspiration of secretions.[9]

Patient's assessment for successful weaning is done in terms of:-

- Improvement in the disease process for which tracheotomy was done.
- Neurological status (conscious, oriented), comprehension, effective coughing and able to maintain airway.
- Can tolerate cuff deflation and capping/plugging for more than 24 hours.
- Haemodynamically stable.
- Lung x-ray clear and minimal secretions.

10. DECANNULATION[9]

The optimum time to decannulate is when the patient has rested (full night rest), preferably in the morning.

Equipment

- Dressing pack
- Correct size of tracheotomy tube (in case of breathing difficulties)
- Tracheal dilators
- Tapes
- 10ml syringe (for cuffed tubes)
- Sachet or clean tube of water-soluble lubricant
- 0.9% sodium chloride sachet
- Sterile gloves
- Protective eye wear
- An occlusive dressing (not "sleek")

Procedure

- The patient must be nil per orally for at least 4 hours.
- Naso gastric tube must be aspirated before decannulation.

- Baseline vitals recorded and oxygen saturation monitored..
- Explain the procedure to the patient and make him/ her comfortable.
- Position the patient upright/ sitting
- Suction the patient via the tracheostomy tube and oro-pharynx.
- Ensure that the cuff is FULLY deflated with tapes undone and insert a suction catheter to 0.5-1cm beyond the tube tip.
- Apply suction and withdraws tube out smoothly with an outward and downward movement.
- When the tracheostomy is removed clean the site (if necessary) with 0.9% Sodium Chloride and dry.
- Place occlusive dressing on stoma.
- Instruct the patient to cough while putting gentle pressure on dressing.
- Assess the patient for any signs of distress, e.g. changes in vitals or LOC.
- Emergency intubation trolley and tracheostomy equipments must be at the patient's bed side for 24 hrs.
- Be supportive.

CONCLUSION

Tracheostomy care requires a multidisciplinary comprehensive approach to expedite the decannulation of patients with tracheostomy and subsequently reducing the duration of ICU stay. Health care professionals managing tracheostimised patients must adhere and develop guidelines feasible in their institution to cater this subset of the population. There should be regular multidisciplinary tracheostomy team meetings with documentations and implementation of care bundle checklists to safeguard the standard of care. These practice guidelines may further enhance the knowledge and confidence of nursing staff when dealing with tracheostimised patients. This prevent unpropitious incidents and hence reducing the tracheostomy-related complications and the number of re-admissions to critical care units.

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Review Article

Inhibitors of coagulation cascade: A new era of anticoagulants

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ABSTRACT

The thrombotic disorders are one of the major causes of morbidity and mortality worldwide. There is a need to develop anticoagulants which are oral, effective and also do not require continuous monitoring or dose adjustment during the treatment protocol. Two distinct drug groups that have come out as useful anticoagulants are - direct thrombin inhibitors (drugs inhibiting factor II) and Factor Xa inhibitors.

Keywords : *Coagulation cascade; Anticoagulants; Dabigartan; Apixaban*

INTRODUCTION

The thrombotic disorders are one of the major contributors to the current huge rates of morbidity and mortality worldwide. In spite of the availability of numerous classes of anticoagulants, there are many unresolved issues related to the treatment of thrombotic disorders, which need to be addressed.[1] The currently available anticoagulants like heparin and its derivatives, vitamin K antagonists (VKAs), though effective, have their own set of limitations. Heparin group of anticoagulants are very rapidly effective but their parenteral route, need for monitoring, unpredictable pharmacokinetics and pharmacodynamics are the problem areas. VKAs are given orally, take a long time for the onset or offset of action, have narrow therapeutic effect and are associated with multiple drug and dietary interactions. [2] (Figure 1) Therefore, there is a need to develop anticoagulants which are oral, effective and do not require continuous monitoring or dose adjustment during the treatment protocol.[3] In this direction, much work was done on the agents who can inhibit coagulation cascade at different stages and two distinct drug groups have come out in open as useful anticoagulants. They are direct thrombin inhibitors (drugs inhibiting factor II) and Factor Xa inhibitors. The main advantage with these two drug groups is that some of them could be given orally, thereby finally filling the space that had crept after the discovery of VKAs.[1] Some recently done studies have shown that both these drug groups have the potential of being more useful and safe when compared with VKAs, thereby it is presumable that they might replace VKAs, as oral anticoagulants, in the clinical setting in the near future. [4,5]

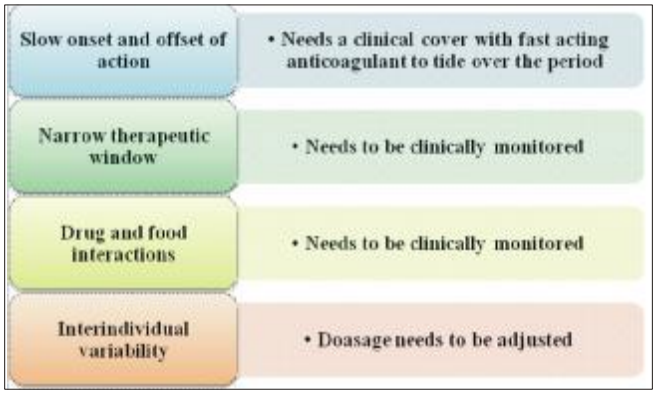

Figure 1: Limitations of traditional oral anticoagulants (Vitamin K Antagonists)

Inhibitors of coagulation cascade

After the vessel wall injury platelets, collagen and clotting factors in a highly interlinked cascade lead to thrombus formation. Direct thrombin inhibitors (DTIs) inhibit the factor II, thrombin, which plays the central role in clotting cascade. Factor Xa inhibitors specifically inhibit the activated factor X which lead to the formation of thrombin from prothrombin. In a way, factor Xa inhibitors hold an advantage over DTIs as the former do not inhibit the other activities of thrombin.They prevent the formation of thrombin, hence are seemingly associated with lesser bleeding risks. [6] Apart from them, there are natural

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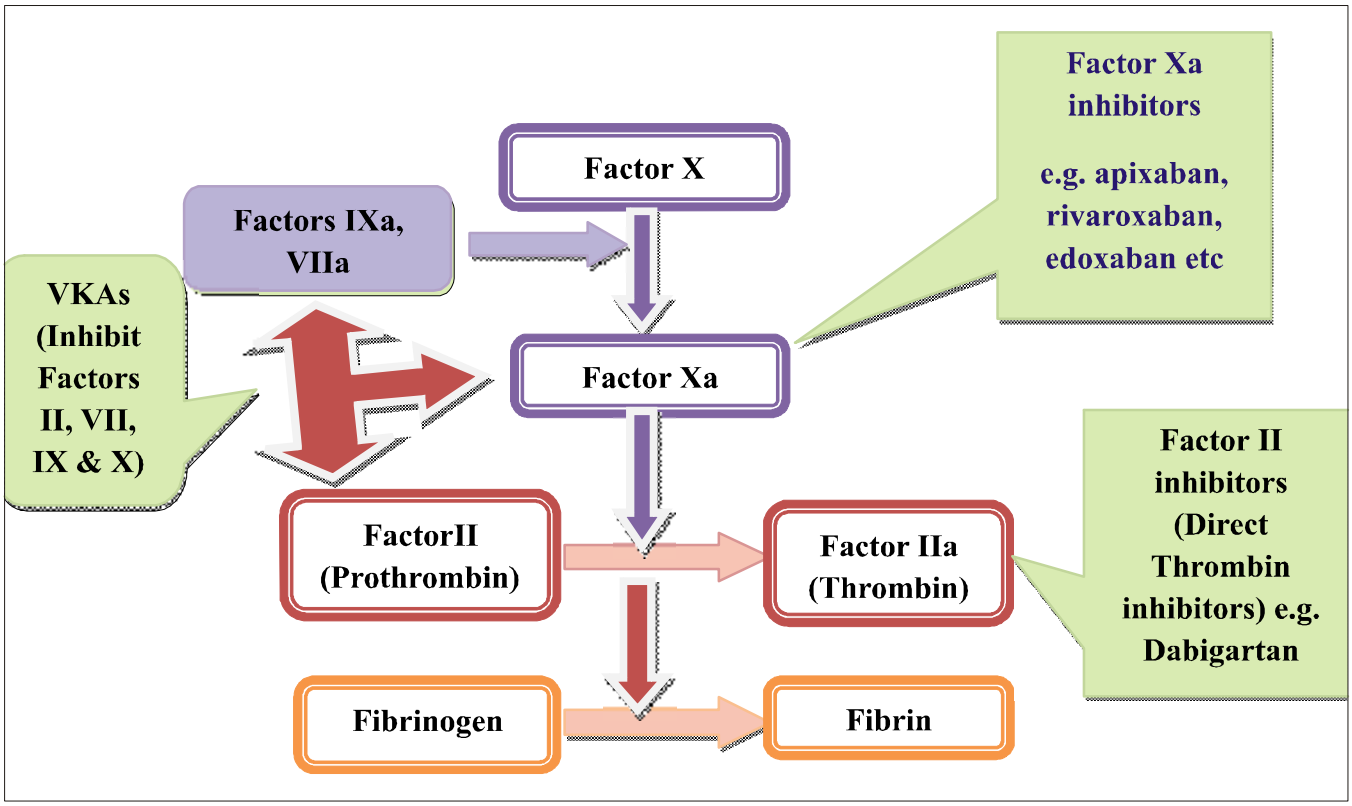

Figure 2: Site of action of various oral anticoagulants

inhibitors of coagulation cascade like protein C and S, antithrombin and tissue factor pathway inhibitor. [7] The inhibitors of clotting factors that are currently in the nascent developmental stage are those of factors VII, VIII, V, IXa, XI, XIIa. [7] Also work is going on to inhibit only the procoagulant properties of thrombin, as thrombin also has some natural anticoagulant properties.[8] (Figure 2)

NEW ORAL ANTICOAGULANTS

Among the direct thrombin inhibitors, dabigartan etexilate, a prodrug, is the most upcoming agent on the block. Oral factor Xa inhibitors include apixaban, rivaroxaban and edoxaban.[8] (Figure 3). Amongst these, apixaban is fast gaining importance because of its favourable pharmacokinetic and pharmacodynamic profile and has been approved for use in various conditions like patients needing anticoagulant treatment during and after the knee or hip replacement, atrial fibrillation (AF) etc. [9]

Dabigartan etexilate

It is a prodrug, which reversibly and directly inhibit thrombin at its active site. It inhibits both free and bound

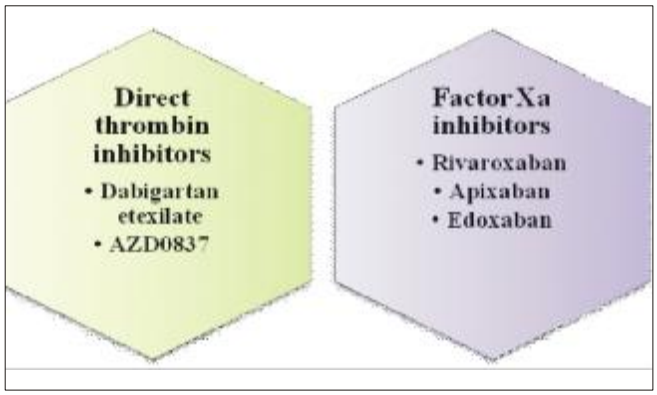

Figure 3: Novel oral anticoagulants

thrombin effectively, thereby preventing the conversion of fibrinogen to fibrin. It is given orally and gets changed into active form by the action of esterases, peaking approximately two hours after the administration. It can be given once or twice daily, as it has a long half life of 14-17 hours. Most of it is excreted in the unchanged form in kidney, through the P-glycoprotein. Since it is a substrate of P-glycoprotein, it should be taken with caution with the drugs that inhibit this transporter (e.g. quinidine,

amiodarone etc.) as it can lead to its high plasma concentrations. [10,11]

Dabigartan has been tested in several clinical trials for its use in the prophylaxis of venous thromboemobolism (VTE), and most of the results pointed towards its non inferiority, when compared to enoxaparin, in different doses. [12-14] It was also tested for non inferiority against warfarin, for the treatment of VTE in RE-COVER trial, and results showed that it was equally efficacious and safe as compared to Warfarin. [15] Dabigatran has been approved and marketed in Europe and Canada for prevention of VTE following elective hip or knee arthroplasty, at a dose of 220-mg for most of the patients. Lower doses can be used for the patients who are taking drugs which inhibit P glycoprotein e.g. amiodarone, or those who are at a higher risk of bleeding e.g. elderly patients, compromised renal function etc. [8]

In another trial, dabigartan was compared with Warfarin, for the prevention of stroke or systemic embolism in patients with AF and dabigartan, at a dose of 150 mg BD oral, was found to be at par with warfarin and associated with lesser bleeding risk.[16] It is also evaluated for reduction of risk of recurrent ischemia in patients with acute coronary syndrome (ACS), where it was seen to significantly reduce coagulation activity but with a high bleeding risk as compared to placebo.[17]

Apixaban

Among the factor Xa inhibitors that can be given orally, apixaban is one of the most tested and efficacious currently. Many trials have proved its efficacy in different thrombotic disorders and many trials are still underway. It is an active drug, with 50% bioavailability after oral administration. It has half life of 9-14 hours, and has a rapid onset of action, with plasma concentrations peaking in three hours. It has high plasma protein binding (almost 80% or more). There are many ways in which it is excreted e.g. renal, hepatic, biliary etc. Since it is metabolized by cytochrome enzyme CYP3A4, and is transported by P glycoprotein so any drug which inhibits or induces the enzyme or inhibits the transporter is going to affect the plasma levels of apixaban.[18,19]

Apixaban was evaluated in patients undergoing either total knee or hip replacement surgery, for the prevention of VTE, and it proved to be superior to enoxaparin, with lesser bleeding events.[20,21] In a trial evaluating apixaban as a treatment modality in VTE, it was shown to be effective, and was not associated with increased risk of bleeding, even if the treatment was extended with apixaban, in an another trial, for the same purpose. [22] Apixaban was also found to be useful in the treatment of symptomatic deep vein thrombosis (DVT) in a dose ranging study and was found to be useful and more convenient treatment modality compared to the complex dosing regimen of heparin group. [23]

Apart from these indications, apixaban is also useful in the prevention of stroke or systemic embolism in patients who have had AF and has been recently only approved for the same. [24,25] However, in the patients of ACS, apixaban failed to demonstrate its safety, inspite of reducing the risk of recurrent ischemic event, as it was associated with higher bleeding risk and the trials had to be terminated early because of that. [26,27]

Clinical roadblock with the new oral anticoagulants:

Both dabigartan and apixaban have transformed the clinical picture since their advent because their use in different thrombotic disorders has now been established in various trials, so they are rapidly moving towards the goal of eventually replacing the age old oral anticoagulants, i.e. VKAs. [8] However, both the groups have their own set of unresolved issues. Direct thrombin inhibitors inhibit thrombin, in both free and bound form. Thrombin however, doesn't only have a role in coagulation. It plays an important role in endothelial function, immune responses, infection etc. So whether inhibition of thrombin is really safe in the long run remains to be established. Apart from that, risk benefit ratio also needs to be established for lower doses of dabigartan used in elderly or patients with compromised renal function. The reversal of effect of dabigartan takes almost 24-48 hours, so rapid reversal in certain cases where it is required, remains a problem. [28] Since dabigartan is a P glycoprotein substrate; caution should be exercised when it is used with the drugs that inhibit P glycoprotein.[29] There is also no exact method to monitor the therapy in emergency cases, with dabigartan currently. It should be used cautiously with other antiplatelet or anticoagulants because of the risk of higher bleeding. [28]

The most common issues with the use of factor Xa inhibitors, especially apixaban, are the abnormality in liver and renal function tests. [30] They are also associated with higher bleeding risk when used concomitantly with other antiplatelets or anticoagulants. Since apixaban is metabolized by CYP3A4 and is a substrate of P glycoprotein drug interactions might be a concern for

apixaban.[31] Factor Xa inhibitors face another problem in reverting their effects as there are no available antidotes for them and also the drugs are not dialyzable because of their high plasma protein binding. The effect of a dose of apixaban can last as long as 24 hours.[32]

CONCLUSION

The arrivals of new oral anticoagulants have changed the face of treatment of coagulation disorders and related problems. It will still take a lot of time for these agents to uproot and replace the traditional oral anticoagulants, i.e. VKAs, as the latter have been firmly entrenched in the minds of clinicians as well as are effective, along with the fact that they cost less than what the newer oral anticoagulants will cost. In spite of all this, there is lot of optimism for these novel oral anticoagulants regarding their efficacy and safety and also the fact that they have revolutionized the anticoagulant therapy by simplifying it and making it all the more convenient for the patients to take. Further testing in clinical trials is ongoing to prove their long term efficacy and safety and to properly streamline these agents for their clinical use, so it is not long away that these agents will eventually take the place of VKAs as oral anticoagulants.

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Review Article

Cervical cancer vaccine: A review

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ABSTRACT

Cervical cancer is the first cancer to be almost 100 per cent attributable to an infection with high risk oncogenic types of Human Papilloma Virus (HPV). A proportion of other cancers anal, penile, oropharyngeal, vaginal and vulvar cancers in young women are also attributable to these oncogenic viruses. As with other vaccine preventable diseases, it is reasonable to expect that a subclinical exposure to the attenuated virus or a component of virus can produce immunity against the disease. This forms the basis of currently available prophylactic HPV vaccine that has been widely accepted and also included in the school health immunization programmes in United Kingdom, United States, Australia and many other countries. While the vaccine has inherent limitations, due to existence of multiple subtypes of the virus which can cause disease, the available vaccines appear to prevent precancerous and cancerous lesions caused by the two most prevalent high risk oncogenic HPV types, provided that prior exposure or infection does not exist. In the countries where well managed cervical cancer screening programmes are being run, the vaccine may decrease the anxiety and morbidity in patients as well as the expense incurred on management of precancerous lesions. In low resource countries where such programmes do not exist, the vaccine may decrease the morbidity and mortality due to cervical cancer. However, the vaccine cannot replace an effective cervical cancer screening programme. This article reviews the literature available from PubMed database and 'Science Direct' for efficacy and limitations of the currently available vaccine.

Keywords : Human Papilloma Virus; Cervical cancer; Cervical cancer vaccine

INTRODUCTION

The causal association between Human Papilloma Virus (HPV) and cervical cancer has been conclusively established by epidemiological, molecular and experimental studies.[1] Cervical cancer is the first cancer to be almost 100 per cent attributable to an infection. This forms the basis of the HPV vaccine (cervical cancer vaccine).

The focus of this article is on the rationale behind the use of HPV vaccine, the short-comings of the presently available vaccine and the ongoing research in this field.

PubMed database and Science Direct were searched for literature and references using the key words: Human Papilloma Virus, Cervical cancer, cervical cancer vaccine. The date of the last comprehensive search was February 14, 2013. The relevant articles were reviewed for the latest available information on HPV vaccines.

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HPV Virology

HPVs are small (~55 nm), non-enveloped viruses with a double-stranded circular DNA genome wrapped into a protein shell of icosahedral symmetry. The genome of HPV is made up of 7 early (E) genes and 2 late (L) genes. The early genes are necessary for replication of the viral DNA, transcription of the nonstructural early proteins E1, E2, E4, E5, E6 and E7 and assembly of newly produced viral particles. The late genes (L1 and L2) encode for the proteins making up the major viral capsid. Most of the host immune response is directed to the conformational epitopes on the L1 protein displayed on the outer surface of the intact virion.[2]

Over a hundred genotypes of HPV have been cloned to date[3]. These genotypes show varying tissue tropism; i.e., there are skin types (e.g., HPV 1-4, 10, 26-29, 37, 38, 46, 47, 49, 50, 57), and genital types (e.g., HPV 6, 11,

16, 18, various 30s, 40s, 50s, 60s, 70s). Around 40 genotypes are able to infect the genital tract. Of these, some have oncogenic potential (established high risk types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82; those with probable high risk are types 26, 53, 66) while others are low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).[3,4] Of the high risk group, HPV genotypes 16 and 18 contribute to around 70 per cent of cervical squamous cell carcinomas, and around 80 to 85 per cent of adenocarcinomas.[5]

HPV infection and clinical manifestations

HPV are epitheliotropic gaining entry through minor abrasions of the squamous epithelium or through the single cell junction of the squamocolumnar junction of the transformation zone at the cervix. Viral particles of genital HPVs infect the basal cellular layers of epithelium maintaining a low copy number of the viral genome in these cells. In contrast the complete and complex life cycle of HPV only occurs in the suprabasal compartment where the keratinocytes lose their ability to replicate, but initiate terminal differentiation. As the epithelium is shed, so the full virions are ready to infect the next host.[6, 7]

The clinical spectrum of disease ranges from asymptomatic infection, to benign warts (condylomata accuminata) to anogenital malignancy.[8, 9] While benign warts are primarily caused by low risk HPV genotypes 6 and 11, oncogenic HPVs are the necessary causative agent for cervical cancer (with more than 2/3 cases being caused by high risk types 16 and 18).[10] Similarly, a proportion of other cancers vaginal (around 50%), anal (around 90%), penile (45 to 50%) and oropharyngeal cancers (20%) occur due to infection with oncogenic HPV.[11] These viruses, particularly HPV 16 are also responsible for squamous HPV related vulvar cancers in young women, as well as for the respective precursor lesion, vulvar intraepithelial neoplasia (VIN grade 2/3). In addition there is recurrent respiratory laryngeal papillomatosis due to HPV 6 and 11. This is a rare disease occurring at an incidence of 0.3-1.0/100,000, with both paediatric as well as adult onset types, and with significant morbidity and mortality.[12,13]

HPV immunology

With HPV infection of squamous epithelium, since the virus remains confined to the epithelial cells (hides in the epithelial cells), there is no associated viraemia. Innate immunity which is nonspecific (consisting of responses from phagocytes, macrophages, monocytes, cytokines, complement and epithelial barriers), clears off some of the transient infections. This does not result in immune memory.

In addition, weak systemic adaptive immune responses occur in around 60 per cent of those found to be HPV DNA positive in the genital tract. This immune response is antigen specific and shows immune memory.[6] These antibodies prevent an individual from further re-infection due to the particular genotype. Since this immunity may wane over a period of time, it is not clear whether this immunity can give continued protection against re-infection. Also, the virus can remain within basal epithelial cells at non-detectable levels, in a latent state for many years and then become reactivated, particularly with immune senescence or immune-suppression.

HPV epidemiology

HPV are one of the easiest viruses to transmit, with a probable transmission rate of about 40% per active intercourse (based on computer modeling). The estimates of HPV prevalence among women range from 2 to 44 per cent, depending on age and numbers of partners, with a lifetime risk of infection being 50-80 per cent .[14] As the predominant route of transmission for genital HPVs is sexual, the prevalence of HPV infection is very common in the sexually active women. The majority of young women clear infection within one to two years, without ever having overt clinical disease.[15]

In a small proportion of women (approximately 5%), persistent (or chronic) infection occurs probably in presence of cofactors like cigarette smoking, high parity, long-term use of oral contraceptive pill, other sexually transmitted infections such as genital herpes and Chlamydia trachomatis infection. Persistent HPV infection may lead to cervical intraepithelial neoplasia (CIN) of mild, moderate or severe grade (CIN1, CIN2 or CIN3 respectively). It can also lead to adeno-carcinoma in situ (AIS), a precancerous lesion involving cervical glandular cells. If untreated, CIN2-3 has a high probability of progressing to squamous cell cancer, and AIS has a high probability of progressing to adeno-carcinoma.[15]

The HPV vaccine

Currently, 2 HPV vaccines are widely marketed internationally. Using recombinant technology, both are prepared from purified L1 structural proteins that self-

assemble to form HPV type-specific empty shells or virus-like particles (VLPs). Neither vaccine contains live biological products or viral DNA, so they are non-infectious. These two vaccines are designed for prophylactic use only; they do not clear existing HPV infection or treat HPV-related disease.[16] The mechanisms by which these vaccines induce protection have not been fully defined but seem to involve both cellular immunity and neutralizing immunoglobulin G antibodies.[17]

The quadrivalent vaccine

The quadrivalent vaccine, currently available by the name of Gardasil®, which was first licensed in 2006, contains VLPs for HPV types 6, 11, 16 and 18. The vaccine is produced using yeast substrate and includes amorphous aluminium hydroxyphosphate sulfate as adjuvant. Each 0.5 ml dose of this vaccine contains 20 μg of HPV-6 L1 protein, 40 μg of HPV-11 L1 protein, 40 μg of HPV-16 L1 protein and 20μg of HPV-18 L1 protein adsorbed onto 225 μg of the adjuvant. The formulation contains no antibiotics, or preservatives.[18]

The bivalent vaccine

The bivalent vaccine, currently available by the name of Cervarix®, which was first licensed in 2007, contains the VLPs of HPV types 16 and 18. It is produced using a novel baculovirus expression system in insect vector Trichoplusiani cells. Each 0.5 ml dose of the bivalent vaccine contains 20 μg of HPV-16 L1 protein and 20 μg of HPV-18 L1 protein adsorbed onto a more complex adjuvant system, designated AS04, consisting of monophosphoryl lipid A (MPL) and an aluminum salt (aluminum phosphate). MPL is a detoxified form of bacterial lipopolysaccharide and is a toll-like receptor (TLR)-4 agonist. TLRs are an evolutionarily conserved class of host sensors of microbial constituents that activate innate and adaptive immune responses to invading microbes.[18]

Vaccination schedule

Both the bivalent and quadrivalent vaccines are available as a sterile suspension in single-use glass vials or single-use pre-filled syringes that should be maintained at 2-8 °C and not frozen.

The quadrivalent vaccine is given at baseline and again after 2 months and 6 months. A minimum interval of 4 weeks between the first and second dose, and a minimum interval of 12 weeks between the second and third dose, are recommended by the manufacturer if flexibility in the schedule is necessary. The bivalent vaccine is given at baseline and again after 1 month and 6 months. If flexibility in the schedule is necessary, the manufacturer recommends that the second dose be administered between 1 and 2.5 months after the first dose[18]. Alternative schedules are being explored for both the bivalent and quadrivalent vaccines. Restarting the 3-dose series is not necessary if the programme has been interrupted, but remaining vaccine doses should be administered as close to the recommended schedule as possible.

Currently, the manufacturers do not recommend a booster dose following completion of the primary series.

Vaccine availability

To date, licensure or registration of the quadrivalent vaccine has occurred in more than 180 countries worldwide. The quadrivalent HPV vaccine was approved in June 2006 by the US Food and Drug Administration (FDA) as well as the Therapeutic Goods Administration (TGA) in Australia for the prevention of HPV 6/11/16/18-associated cervical cancer, adenocarcinoma in situ (AIS), and cervical intraepithelial neoplasia (CIN) grades 1 to 3, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) grades 2/3, and genital warts in women aged 9-25 years. It has also been approved for the prevention of anal intraepithelial neoplasia (AIN) and anal cancer in both men and women. For the bivalent vaccine, licensure for prevention of CIN and cervical cancer first occurred in Australia in May 2007, in Europe in September 2007 and in USA in October 2009.[19]

In June 2007, WHO's Global Advisory Committee on Vaccine Safety (GACVS) concluded that both vaccines had good safety profile. This was endorsed by GACVS again in December 2008 after reviewing data on early post-marketing surveillance of the quadrivalent HPV vaccine.[20]

Both vaccines were licensed for clinical use based on the interim reports of extensive multicentre, randomized, double-blind trials. Two phase III studies, FUTURE I[21] and FUTURE II,[22] evaluated Gardasil® and two, PATRICIA[23] and the Costa Rica HPV Vaccine Trial (CVT),[24] evaluated Cervarix®. All of the trials were relatively large (5,500-18,500 vaccinees) trials of young women (mean age 20, range 15-26) . The CVT was a U.S. government sponsored community-based trial, centered in the Guanacaste province of Costa Rica,

whereas the other trials were company-sponsored and multi-centric, involving multiple trial sites in Europe, North, Central and South America, and Asia Pacific, including Australia.

Trial Outcomes in terms of vaccine safety and efficacy profiles

End of study analyses of the phase III trials of prophylactic HPV vaccines in young women are now largely completed. Both the vaccines have demonstrated remarkably high and similar efficacy against the vaccine-targeted types of HPV. Since the immunological correlates of vaccine protection are unknown and the development of cervical cancer may occur decades after HPV infection, regulatory authorities have accepted the use of CIN grade 2 or 3 (CIN2-3) and AIS as clinical end-points in vaccine efficacy trials instead of invasive cervical cancer. Also, using cervical cancer as the outcome in such trials is precluded for ethical reasons. Precancerous lesions usually develop in <5 years after HPV infection.[25]

John T. Schiller et al have recently reviewed the analyses of phase III clinical trials of HPV prophylactic vaccines in detail.[26] A brief description of the results with respect to various end points is presented here.

Since the clinical efficacy was expected to vary depending on the population, the trial population basically included two types of cohorts:

Intention-to-Treat (ITT) cohort also designated Total Vaccine Cohort (TVC) which included all individuals that participated in the trial (for vaccine trials "participation" is usually defined as receiving at least one dose of the vaccine). These cohorts included women with evidence of prior HPV exposure and hence current infection/ lesions by vaccine-targeted as well as other HPV types. ITT analyses can be viewed as an approximation of the effectiveness of the vaccine in general use, at least for individuals with similar demographic and risk characteristics as the subjects in the trial.

According to Protocol (ATP) also designated Per Protocol Efficacy (PPE) cohort was restricted to individuals who adhered to all aspects of the study protocol: for example, they received the three vaccine doses within specified intervals, and events were not counted until after receiving all three doses. Importantly, individuals included in ATP cohorts had no evidence of exposure to the vaccine-targeted type under analysis. Thus ATP analyses can be viewed as the best-case scenario for the effectiveness of a prophylactic vaccine when it is given in unexposed individuals.

Having defined these two cohorts the vaccine efficacy in terms of various parameters is discussed below:

1. Immunogenicity

With both vaccines, practically all adolescent and young female vaccinees who were initially naive to vaccine related HPV types developed an antibody response to these antigens after 3 doses. Virtually all women maintained stable detectable responses for more than 4 years. For Cervarix®, maintenance of plateau levels above the levels detected after natural infection for up to 8.4 years have been observed[27]. Similar results were reported for Gardasil®, with the additional evidence for immune memory in that antibody responses could be boosted by revaccination at month 60.[28]

2. Prophylactic efficacy in young women

The quadrivalent vaccine demonstrates 100% efficacy in preventing condylomata and vulvovaginal precancerous lesions and 98% efficacy in preventing high-grade cervical lesions among HPV naïve sexually active women.[29,30] In trial populations which included women with known infection or disease associated with vaccine types prior to vaccination, the quadrivalent vaccine was 44% effective in preventing CIN 2-3 and 73% effective in preventing condylomata and other HPV associated vulvovaginal lesions.[30] Similarly, the bivalent vaccine demonstrated 100% efficacy in preventing persistent high risk HPV cervical infection; and development of vaccine type CIN lesions[31,32,16] in HPV naïve women.

3. Cross-type protection

Bivalent vaccine demonstrated significant efficacy against HPV 31, 33, and 52[33] whereas quadrivalent vaccine demonstrated significant efficacy only against HPV31[34]. This cross protection from non-vaccine virus infection was 100% for the first 3 years only. Subsequently incident infections began to appear over the next 3 years.

4. Efficacy in women with prior exposure to vaccine type infections

There was a significant proportion of vaccinees who were either seropositive or PCR DNA-positive for at least one of the vaccine type of virus at the time of enrollment in the trials. From analyses in these subgroups it is clear

that prevalent infection by one type does not impede vaccine-induced protection from incident infection by another vaccine type.[35]

5. Therapeutic efficacy

The therapeutic activity of the quadrivalent vaccine was evaluated in FUTURE II study group[22]. No significant difference in the rate of progression of HPV16/18 infection to CIN2+ was observed in VLP vaccinees versus controls, 11.1% and 11.9%, respectively. Similarly, there was no difference in the rate of clearance of vaccine or non-vaccine HPV types in those receiving bivalent vaccine versus controls.[36] Thus the VLP vaccines do not appear to alter the course of established cervicovaginal HPV infection or disease.

6. Safety

No serious adverse affects attributable to vaccination were seen in placebo controlled trials.[21,31,37-39] Local reactogenicity at the immunization site, systemic malaise and fever were slightly more common than with placebo but did not lead to discontinuation of the vaccination schedule. Redness and swelling at the vaccination site was increased with the bivalent vaccine adjuvanted with monophosphoryl Lipid A compared to placebo.[31] Since vaccine licensure, over 12 million doses of the quadrivalent vaccine have now been given to young women. The vaccine adverse events reporting service (VAERS) indicates no rare, serious adverse events occurring with greater frequency among vaccine recipients than might be expected in the age-matched unvaccinated population.[29,30] Fainting after vaccination is the most common adverse event.

7. Pregnancy outcomes

This has received special attention, given the target ages of catch up vaccination programs. A pooled analysis of the PATRICIA and CVT trials found no significant increase in miscarriages in the Cervarix® arm (11.5%) compared to the control arm (10.2%).[40] Similarly, in a combined analysis of phase III trials involving Gardasil®, the proportions of women with live births, spontaneous abortions and congenital abnormalities were similar in the vaccine and control groups.[22,41]

8. Efficacy in mid-adult women

The end of study results (median follow-up of 4 years) of a multicentre quadrivalent vaccine trial in 3819 mid-adult women (ages 24-45) were recently published.[42] The results confirm that older women without evidence of prior exposure to the vaccine types can benefit from the vaccine.[43] However vaccination cannot replace screening in mid-adult women.

9. Efficacy in males

The efficacy of Gardasil® was examined in a placebo-controlled, double-blind trial in 4065 men ages 16-26 from 18 countries.[44] The primary endpoint of the study was protection from HPV 6, 11, 16 or 18-associated external genital warts (condylomata acuminata) or penile, perianal or perineal intraepithelial neoplasia (PIN) of any grade, or cancer at these sites. Protection against this combined endpoint was 90.4% in the HPV naïve population and 65.5% in the intention to treat population. The differences in vaccine efficacy in the two populations reinforce the desirability of vaccinating males before they become sexually active. This has led to U.S. FDA approval of Gardasil® for the prevention of anal intraepithelial neoplasia (AIN) and anal cancer in both men and women.

10. Safety and efficacy in adolescents

For practical reasons, efficacy studies have not been conducted in the primary target populations of current vaccination programs, adolescent girls and boys (cervical or penile examination and collection of cervical swabs will be unethical in this group). Immunogenicity bridging studies were critical in extending regulatory approval for the vaccines to pre- and early adolescent girls and boys.[45,46]

11. Efficacy data in HIV-infected individuals

Immunodeficiency in HIV-infected individuals puts them at an increased risk of persistent HPV infection, HPV-associated benign lesions and HPV-associated cancers. The vaccine was safe and well tolerated in separate studies of HIV infected adult males (ages 22-61) and children (ages 7-12).[47,48] These findings encourage targeted vaccination programs for young HIV positive individuals.

The basic profiles of the two licensed HPV VLP vaccines are now well established. According to the American Cancer Society's Guideline for HPV Vaccine Use[49], the limitations of current vaccines are: (i) the vaccines do not protect against all carcinogenic HPV types; (ii) the vaccines do not treat existing HPV infections; (iii) the duration of protection and the length of protection required to prevent cancer are unknown; (iv) the cost of vaccination and the possible need for

booster doses may limit vaccine use among poor and uninsured women; and (v) the three-dose regimen may not be feasible in poor and medically underserved populations.

Recent Advances

Several second-generation HPV prophylactic vaccines are under development with the goal of addressing some of these inherent limitations of the current vaccines. The approach that is by far the most advanced is to simply increase the valency of an L1 VLP vaccine to address the issue of type-restricted protection. Phase III efficacy trial of a nonavalent vaccine, which, in addition to the four types in Gardasil®, contains L1 VLPs of types 31, 33, 45, 52 and 58 are being conducted.[50]

Vaccines based on L1-pentameric subunits produced in E. coli have been generated to address the cost of production in eukaryotic cells.[51]

Vaccines based on the minor virion protein, L2, have generated increasing interest in recent years[52] as they can induce cross-neutralizing antibodies, raising the possibility of an inexpensive monovalent vaccine with the potential to be broadly protective. However, neutralizing antibody titers to L2-based immunogens are invariably lower than homologous type neutralizing titers elicited by L1 VLP-based immunogens.

Therapeutic vaccines that attack already persistent HPV infections to prevent cervical cancer may regress disease progression in women infected with high risk HPV, where the prophylactic vaccines have failed to be of much value. Since it may take 10 to 20 years for development of invasive cervical cancer after incident HPV infection, it may take decades to perceive the benefits of prophylactic vaccines. Therapeutic vaccines may bridge this temporal deficit. Several therapeutic HPV vaccines are in phase I and phase II clinical trials.[53-54] Most efforts have been directed towards the early proteins, HPV E6 and E7, mainly because these are the major transforming viral proteins that are responsible for HPV-related carcinogenesis.

Despite the ongoing research, the timeline for clinical development and licensure of these second generation vaccines is uncertain. We may have to wait several more years till we have adequate data in this regard.

CONCLUSION

The available prophylactic HPV vaccines have good safety and efficacy data with regards to newly acquired infection with vaccine specific HPV types and consequent prevention from premalignant lesions but with certain limitations. The other limiting factors in Indian scenario are high cost of the vaccine, inadequacy of trials in Indian population and social resistance to vaccine due to fear of behavioral dis-inhibition (vaccinees may presume that HPV vaccine makes sex safe). With or without widespread use of HPV vaccination in India, we do need an organized cervical cancer screening programme. Such a programme has substantially reduced the cervical cancer burden by about 70-75% in developed countries during the past four decades. Until such time when we are ready to implement universal cervical cancer vaccination in India , it is most essential to disseminate correct information to improve understanding of both HPV and cervical cancer among medical and paramedical personnel, social workers, policymakers, parents, young adults and the public at large.

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Anesthesia versus Anaesthesia: Does it really matter?

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The Oxford dictionary definition of Anaesthesia is "insensitivity to pain, especially as artificially induced by the administration of gases or the injection of drugs before surgical operations". The Merriam-Webster dictionary defines Anesthesia as "loss of sensation and usually of consciousness without loss of vital functions artificially produced by the administration of one or more agents that block the passage of pain impulses along nerve pathways to the brain" Synonymous: yes? Anyone would agree that the difference between Anaesthesia (British English) versus Anesthesia (American English) lies above and beyond the addition of a single alphabet of the the English language.

I started my journey as an anesthesia resident in a country where Anaesthesia was the correctly spelt version of the branch of medicine that dealt with this specialty. Today, three years after re-training the art and re-learning Anaesthesia to be spelt as Anesthesia in the United States, it is time to look back and ponder on the finer points.

The decision to leave your own country after finishing a residency always comes with a pinch of salt. As you look to expand your clinical and academic training beyond the horizon, you are faced with the uncertainty of the unexpected. The challenge is a system of medicine distinctly different from your home country and a culture to healthcare that demands considerable understanding. A question that I am very often faced with when I make my frequent trips back home is " What is different about Anesthesia practice in the United States?" It might come as a surprise to a lot of people if I say "nothing at all" in reply. Well, what is different is not Anesthesia or Anaesthesia, only the fine print!! The other very frequent question that is thrown at me is the almost rhetorical " Is it better there?" Let me step back today and say lets keep all this better worse talk aside. It never was and it will never be fair to intricately compare two vastly different systems of medicine. As I direct this piece to those friends of mine who are faced with doubts and internal struggles before they leave the comfort of there own homes I say forget about quality of medicine or quality of life. For me, the biggest challenge is the ability to train to re-train or put in more simple words another residency program.

Starting a residency program in Anesthesia under the Accreditation Council for Graduate Medical Education (ACGME) at the Cleveland Clinic Foundation, I realized early on that the essence of getting the most out of this education is to wipe my slate clean and restart again. Tell the world that you are trained in your specialty in your own country and you are capable of doing your thing does provide you with the much-needed independence of clinical work at times, but can be your worse enemy if you want to acquire new knowledge. It is important to understand that there will be days where the attending will hold your hand when you are doing a procedure that you have done so many times before or might tell you that " this is the way it is done here". Days, when you need to leave your ego at home. Days when you will feel your neurons are struggling to cope with erasing old skills and acquiring new skills for the same procedures again. But, hey did you want to do things the way you were doing them in your own country? That said, what is the reason you made this trip across 4000+ miles half way across the planet? The answer to these questions will help you know that unless you let your guard down in this foreign land and say that you are an open book you will never learn anything new and in essence never grow as a clinician. Medicine is repetitive science; it is very easy to be lulled into a false sense of satisfaction practicing the same things over and over again, the same very way every day. The only way to appropriately imbibe your area of expertise and to mature as a clinician is to step out and see what else can be done and is being done. My message here is not to train in the United States after training in India, but to train at different places and in that process acquire a new set of skills all the time.

Going further, another area of distress for the physician from India as he or she steps onto alien soil is the cultural aspect of medicine. The interaction between peer groups as resident doctors and patient physicians as healthcare providers is different to say the least. As you move away from the "yessir/ma'am" policy to "yes

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Dr.XYZ" even when that Dr.XYZ might be your department chair, you will quickly realize that you have to prove your worth as a resident by the sheer quality of your work and not the weight of your courtesy and multiple salutations to your staff. Decision making for the betterment of your patient is another area where the young resident here is thrown into the deep end every single day. An ICU attending will ask you for your plan, and so will your anesthesia attending in the operating room. And yes, your plan will be plan that will be executed as long as you can justify it. And that holds true for every provider from the lowest level of an intern to upwards.

Protecting patient privacy and respecting that the patient is true owner of his or her healthcare information is another moot point here. Not to discuss patients with there names or anything that could identify them, not to talk about them in the hospital corridors or the escalators was a tendency that was difficult to get out rid of initially for me. The tendency to try to force your decision as a clinician on the patient or the patient's family is also something that we live by all the time. The patient is the master of his/her own destiny here and whether it be morbid obesity, chronic smoking in a vasculopath or narcotic abuse in a chronic pain patient, your job will be to ask them whether they feel they can change there lifestyle and not to enforce that change on them.

Difficult times will also revolve around "End-of-Life" decisions in the ICU and DNR statuses. The ability of families here, to think extremely practically for their dying loved ones and to let go of them when there is point of futility is commonplace. Another challenge which is beyond the understanding of Anesthesia and different from back home, and is something that you have to deal with on a regular basis.

How can I forget to include in my set of challenges also, the change from using pharmaceuticals as brand names versus names of salts back home. Or the different abbreviations that come inherent with another healthcare system. Yes, I gave my senior resident a quizzical look when he said " Did you tube your patient" (a.k.a intubation) or "Can you do the A-line first?" (a.k.a arterial line) or " Is he off the vent ?" (weaning from the ventilator) or "When is your ICU patient going to the sniff?" (a.k.a skilled nursing facility). There is numerous more such which define the distinct cultural differences in healthcare here in the United States.

As I look back today, I know that things have evolved for me as a clinician but also more importantly as a human being. I look at medicine differently; I look and understand a patient's emotions differently. That to me is the pivotal change. For all those fellow friends who are getting ready to step out on this often-treaded path of training in another country after training as a specialist in India, I hope this writing will give a better idea of what to expect. All said and done, the difference is not in quality of healthcare or the quality of life that you can expect to live, but in what you can assimilate from the new system of medicine. In the end, it is not Anesthesia versus Anaesthesia, and it really does not matter!

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Original Article

Comparison of antimicrobial efficacy of neem extract with 3% sodium hypochlorite and 2% chlorhexidine as endodontic irrigants against Enterococcus Faecalis -an in vitro study

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ABSTRACT

The present study was aimed to evaluate alternative inexpensive, simple and effective method for the sanitization of the root canal system. The antimicrobial efficacy of neem leaf extract as irrigant was evaluated and compared with the standard irrigant 3% sodium hypochlorite and 2% chlorhexidine gluconate. Neem leaf extract was prepared from neem leaves and pure ethanol. To check the antimicrobial efficacy of neem leaf extract, 2% chlorhexidine gluconate and 3% NaOCl, agar well diffusion method was performed. Nutrient agar plates were prepared and cultures were spread onto agar plates. The plates were incubated for 24 hours at 37°C aerobically. Following incubation the diameters of zone of bacterial inhibition (clear zone) were measured in millimetre.The results were tabulated and statistically analyzed using analysis of variance (ANOVA). There was significant difference between the zone diameters of neem extract and 2% chlorhexidine against E. faecalis ($p < 0.05$). The 2% chlorhexidine showed maximum zone of inhibition and control group i.e absolute ethanol did not show any antimicrobial effect against E.faecalis whereas 3% sodium hypochlorite showed more area of zone of inhibition as compared to neem leaf extract.2% chlorhexidine offers maximum antibacterial advantage over 3% NaOCl and Neem leaf extract.

Keywords: *E. faecalis; Neem leaf extract; Sodium hypochlorite; Chlorhexidine gluconate*

INTRODUCTION

Microorganisms and their by products are considered to be the primary etiologic agents in endodontic diseases. Failure, during and after endodontic treatment are linked to the presence of bacteria in the root canal.[1] Enterococcus faecalis is commonly detected in asymptomatic, persistent endodontic infections. Its prevalence in such infections ranges from 24% to 77%.[2] This finding can be explained by various survival and virulence factors possessed by Enterococcus faecalis, including its ability to compete with other micro-organisms, invade dentinal tubules, and resist nutritional deprivation.[3]

Complete debridement and adequate elimination of microbial irritants is a fundamental prerequisite for successful endodontic therapy. Numerous irrigants have been recommended for irradication of root canal infections.[4]

Sodium hypochlorite (NaOCl) has been widely used as an irrigant since its introduction in endodontics by Walker in 1936.[5] Sodium hypochlorite has been widely recommended as an irrigant for chemicomechanical debridement of root canals because of its tissue dissolution and antimicrobial activity, thus making it an irrigating solution of choice irrespective of its several undesirable characteristics such as tissue toxicity, risk of emphysema, allergic potential and disagreeable smell and taste.[6,7]

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2% Chlorhexidine gluconate has been used as an irrigant and intracanal medicament in endodontics.CHX is a bis-biguanide that acts by adsorbing onto the cell wall of microorganism resulting in leakage of intracellular components.CHX has broad-spectrum antimicrobial activity, targeting both gram-positive and gram-negative microbes. 2% Chlorhexidine gluconate when used as an irrigant has the advantage of substantivity and inactivates many endodontic resistant organisms in as little as 15secs of contact time.[8] But it may have toxic effect on host tissue if expressed beyond the confines of root canal and impair healing. It also under goes chemical reaction with NaOCl forming brownish orange precipitates p-chloroaniline (PCA) which may be cyanotic. So in recent past herbal products are coming up in the field of dentistry.

Medicinal plants are part and parcels of humans since the dawn of civilization. In India, they form the backbone of several indigenious systems of medicine. Azadirachta indica (Neem) is one of the versatile medicinal plants having a wide spectrum of biological activity.[9]

In dentistry, Azadirachta indica has been widely investigated, due to its antimicrobial potential against oral microorganisms especially those associated with gingivitis and periodontitis, and concluded to be highly efficacious as an alternative to 2% chlorhexidine gluconate in cases of periodontal disorders.[6]

Currently none or very few natural products that might be used as an alternative to sodium hypochlorite or 2% Chlorhexidine gluconate as an effective root canal irrigating solution have been identified. Literature has shown that neem has antimicrobial and therapeutic effects suggesting its potential to be used as an endodontic irrigant, but there is lack of any documentation or data regarding neem research in endodontics.

The purpose of this in vitro study, was to compare the antimicrobial efficacy of 3% sodium hypochlorite, 2% cholorhexidine and Neem leaf extract against E. faecalis.

MATERIALS & METHODS

Neem leaf extract, 3% sodium hypochlorite, 2% chlorhexidine, absolute ethanol (control group), Enterococcus faecalis , petridishes, nutrient agar , incubator , micropipette, vernier calliper were the materials used in this study.

Preparation of neem leaf extract

Mature fresh Azadirachta indica leaves were collected. Leaves were washed in sterilized distilled water and weighed in a sterile disposable cup. 25gms of fresh neem leaves were added to 50ml of absolute ethanol. Mixture was macerated for 1-2 mins. Extract was filtered through muslin cloth for coarse residue. Extraction process was repeated again using coarse residue and 25ml ethanol. Both the extracts were pooled together and filtered through filter paper. Ethanol part was removed from the extract on water bath till the volume was about 25ml. Extract was prepared and stored in airtight amber coloured container.

Agar - diffusion test

Strain of E. faecalis was collected from IMTECH institute, Chandigarh. Eighteen petridishes of nutrient agar were incubated aerobically (Fig- 1). Cultures of E.faecalis were grown overnight at 37°C in peptone water (Fig-2) and bacterial growth was checked by evaluating the changes in turbidity at 24 hrs (Fig-3).

To check the antimicrobial efficacy of neem leaf extract, 3% NaOCl and 2% chlorhexidine agar well diffusion method was performed. Agar plates were prepared and cultures (200µl) were spread onto agar plates (Fig- 4). Wells of 3mm diameter were made in the agar surfaces.

Neem leaf extract, 3% sodium hypochlorite, 2% chlorhexidine and absolute ethanol (control group), 50µl of each were added to the respective wells(Fig- 5) and the plates were incubated for 24hrs at 37°C in an incubator (Fig- 6). After incubation period, plates were removed and zones of inhibition were recorded. The irrigant with high antimicrobial effect showed more area of zone of inhibition (Fig- 7).

RESULTS

The results were tabulated and statistically analyzed using analysis of variance (ANOVA). There was significant difference between the zone diameters of neem extract and 2% chlorhexidine against E. faecalis. ($p < 0.05$)

The 2% chlorhexidine showed maximum zone of inhibition of about 13.33mm and control group i.e absolute ethanol did not show any antimicrobial effect against E.faecalis whereas 3% sodium hypochlorite showed more area of zone of inhibition as compared to neem leaf extract. (Table-1 & Graph-1)

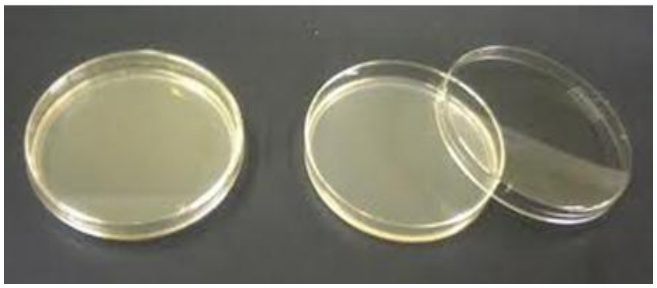


Figure 1: Petridishes with nutrient agar-Incubated aerobically

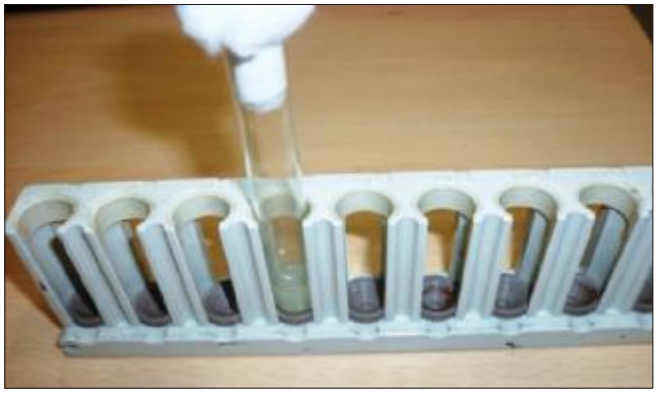


Figure 2: Purpuric rashes all over the body

Figure 3: Bacterial growth was checked by changes in turbidity at 24hrs

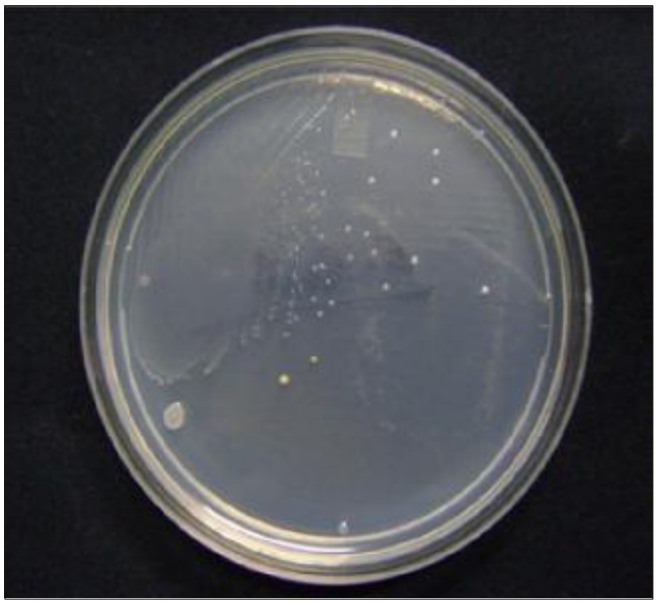


Figure 4: Bacteria on nutrient agar

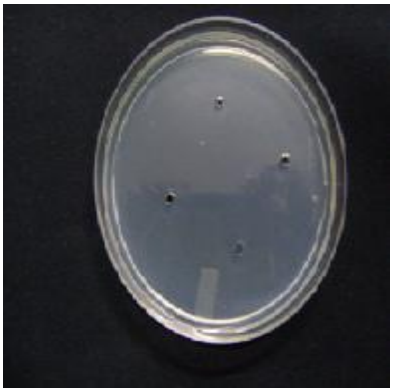


Figure 5: Irrigants added in the wells

Figure 6: Petridishes were incubated for 24hrs at 37°C in an incubator

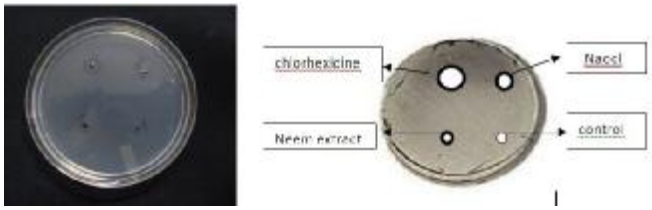


Figure 7: Zone of inhibition against Enterococcus faecalis

Table 1

Irrigant with high antimicrobial effect showed more area of zone of inhibition

Irrigant	Zone of inhibition
2% Chlorhexidine	13.33mm ± 1.3
3% Sodium hypochlorite	10.22mm ± 2.0
Neem leaf Extract	0.75mm ± 0.1
Ethanol (Control group)	0mm

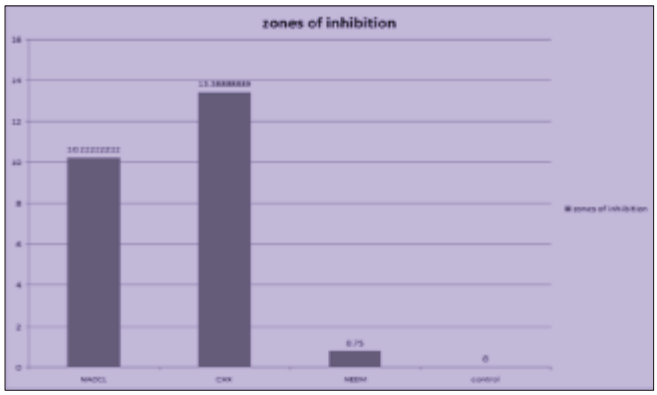
ability of antimicrobial action.[4]

The use of best possible irrigant during chemicomechanical preparation is of great importance. Ideal irrigant should combine antimicrobial action and a capacity to dissolve organic and inorganic remnants.

Botelho et al and Behl et al in their experiments concluded that Azadirachta indica is highly efficacious in the treatment of periodontal disease thus exhibiting its biocompatibility with human PDL fibroblasts.[11,12]

Use of neem as an endodontic irrigant might be advantageous because it is a biocompatible antioxidant and thus not likely to cause the severe injuries to patients that might occur via Sodium hypochlorite accidents. But in the present study Neem leaf extract showed less antimicrobial efficacy as compared to Sodium hypochlorite because sodium hypochlorite is an effective antimicrobial agent and an excellent organic solvent for vital, necrotic and fixed tissues. However, it is highly irritating to periapical tissues, especially at high concentrations.[7]

2 % chlorhexidine gluconate has been recommended as a root canal irrigant and medicament. In the present study chlorhexidine has shown maximum zone of inhibition as compared to sodium hypochlorite and neem leaf extract. Studies have shown that it is a potent antimicrobial agent that holds substantivity and has a low grade of



Graph 1 - Irrigant with high antimicrobial effect showed more area of zone of inhibition

toxicity.[13] However chlorhexidine is unable to dissolve pulp tissue and debris may remain on canal walls, obstructing the dentinal tubules.[14]

The results obtained in this in vitro study showed that neem leaf extract is not viable medicament against E. faecalis as compared to sodium hypochlorite and chlorhexidine. Although 3% sodium hypochlorite showed comparatively less antimicrobial effect than 2% chlorhexidine.

CONCLUSION

Under the limitations of this study, it was concluded that neem leaf extract has an insignificant antimicrobial effect against E.faecalis as compared to 2% chlorhexidine and 3% sodium hypochlorite. As the global scenario is now changing towards the use of non toxic plant products that have traditional medicinal use, extensive research and developmental work therefore should be undertaken on neem and its products for their better economic and therapeutic utilization. Further research is needed to conclusively recommend herbal solutions as a root canal irrigant.

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Large ameloblastoma of mandible: Surgical management with immediate reconstruction

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ABSTRACT

Ameloblastomas constitute 11 percent of all odontogenic jaw tumors. A majority of them involve the mandible with 70 percent arising in the molar-ramus area. The treatment includes curettage and broad bone resections with or without reconstructive surgery. The lesion is radio-resistant. A 60 year old lady presented with a painless slow growing swelling on right side of the face. An orthopantomogram (OPG) showed multilocular radiolucency affecting most of the right side of mandible involving condyle, coronoid, ramus, angle and body region. The patient underwent hemimandibulectomy and immediate reconstruction using titanium reconstruction plate. This paper highlights the management of large ameloblastoma with immediate reconstruction resulting in good functional and esthetic outcome.

Keywords : *Ameloblastoma; mandible; reconstruction; management*

INTRODUCTION

Ameloblastomas constitute 1-3 percent of tumours and cysts of jaws. It is one of the most common odontogenic tumour which does not differentiate to the point of enamel formation.[1-2] The term Ameloblastoma was coined by Churchill in 1933 and its first detailed description was given by Falkson in 1879.[3] Regezi and Sciubba reported that ameloblastomas account for 11 percent of all odontogenic tumours in the jaws.[4] Its peak incidence is in the 3rd to 4th decades of life and has an equal sex distribution. The tumour is often asymptomatic, presenting as a slowly enlarging facial swelling or an incidental finding on a radiograph. The presence of the tumour may sometimes cause symptoms such as pain, ulceration, malocclusion, or loosening of teeth. These tumours more commonly occur in the mandible than maxilla and 70 percent of them arise in the molar-ramus area.5 Radiographically, the tumour is seen as a multilocular radiolucency with moderately well defined margins, sometimes giving a soap bubble (honeycomb) appearance. In some cases it can also appear as a unilocular radiolucency. There are three forms of ameloblastoma, namely multicystic (86%), unicystic (13%) and peripheral (1%).[4] Treatment may vary from curettage to broad bone resections, with or without reconstruction. Radiotherapy has no role as it is a radioresistant tumour. In the present case report we describe a large ameloblastoma managed surgically with immediate reconstruction and good functional and esthetic outcome.

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CASE REPORT

A 60 year old lady reported to the outpatient department of Oral Health Centre at Government Medical College

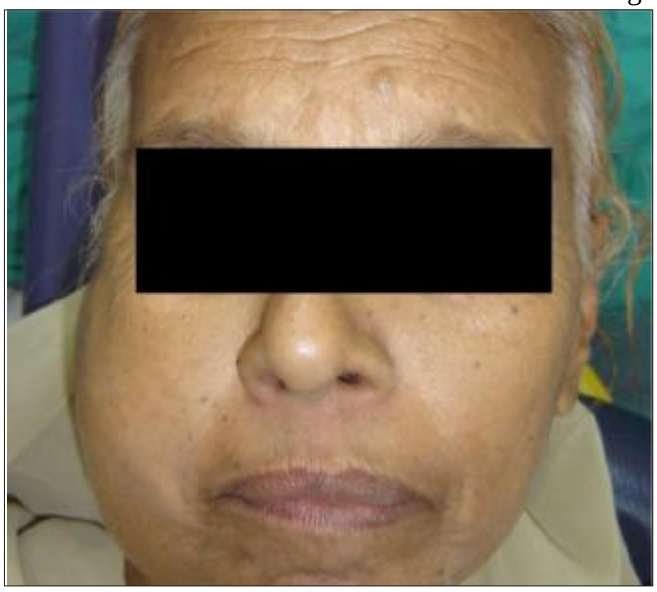

Figure 1 (a): Preoperative photograph showing swelling over left side of face.

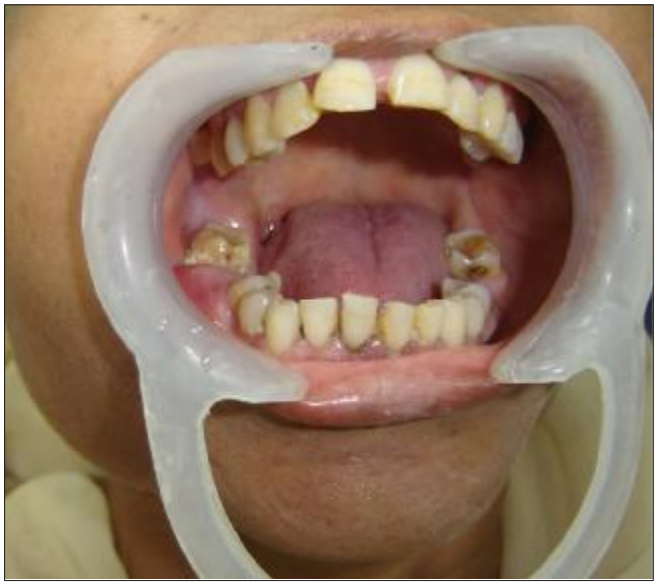

Figure 1 (b): Preoperative intraoral photograph showing swelling and displacement of teeth.

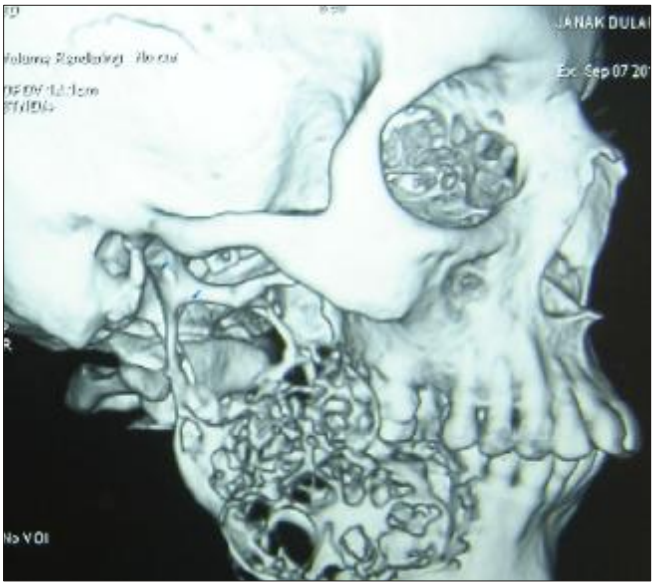

Figure 1 (d): CT scan (3D reconstruction view) showing almost complete involvement of left mandible with multiple areas of perforation.

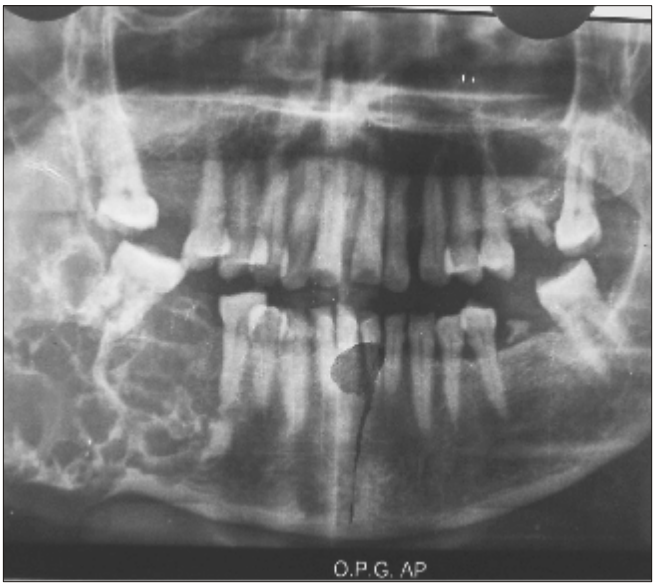

Figure 1 (c): Preoperative radiograph (orthopantomogram) showing large multilocular radiolucency involving condyle, coronoid, ramus, angle and body region of left mandible with expansion of lower border.

Hospital, with a painless slow growing swelling on right side of face since 6 months. Examination of the patient revealed a hard, non-tender swelling on right side of face measuring 10 cm × 7 cm × 5cm in size which extended from zygomatic arch to lower border of mandible supero-inferiorly, and from angle of mouth to posterior border of ramus antero-posteriorly [Fig 1(a)]. Both buccal and lingual expansion was present on the mandible. Intraorally, the swelling was present on right mandibular region with obliteration of buccal vestibule. The displacement of teeth was also present on right mandibular region extending from first premolar to second molar [Fig 1(b)]. The patient was having paresthesia on right side of lower lip. There were no palpable cervical lymph nodes. An orthopantomogram (OPG) was done, which showed multilocular radiolucency extensively involving the right side of mandible including the condyle, coronoid, ramus, angle and body region [Fig 1(c)]. The anterior portion (parasymphysis) of right mandibular region was spared resulting in preservation of the muscular complex at the symphysis region. CT scan showed multilocular cystic lesion confined to the right side of mandible with a thinned out cortex and multiple areas of perforations [Fig 1(d)]. The patient was taken up for surgery under general anesthesia after routine blood investigations. The patient underwent resection of right mandible along with teeth, and disarticulation of the right condyle (hemimandibulectomy), preserving the articular disc. An angled eighteen holes titanium reconstruction plate with condylar head was fixed at resection site using six bicortical screws [Fig 2(a), (b), (c)]. Intraoperatively, the tumour bed where perforations of cortex were present was chemically cauterized using carbolic acid to prevent recurrence. The resected specimen was reported to have histopathological features consistent with multilocular ameloblastoma. In the postoperative recovery period,

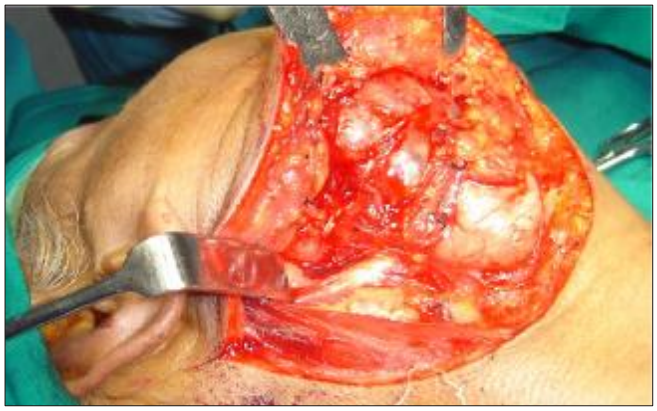

Figure 2 (a): Intraoperative photograph showing exposure of tumor via extended submandibular approach.

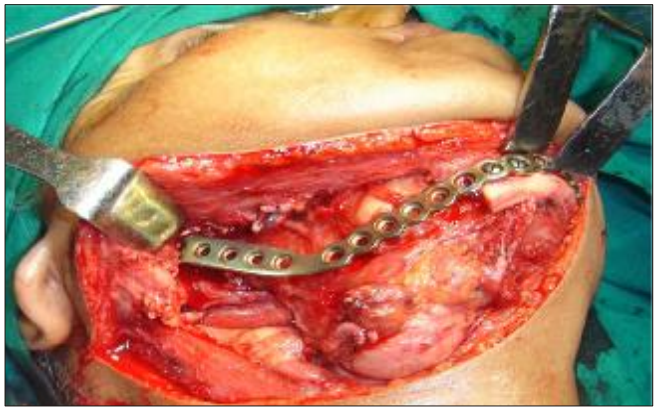

Figure 2 (b): Intraoperative photograph showing hemimandi bulectomy and reconstruction of mandible with titanium reconstruction plate with in-built condyle.

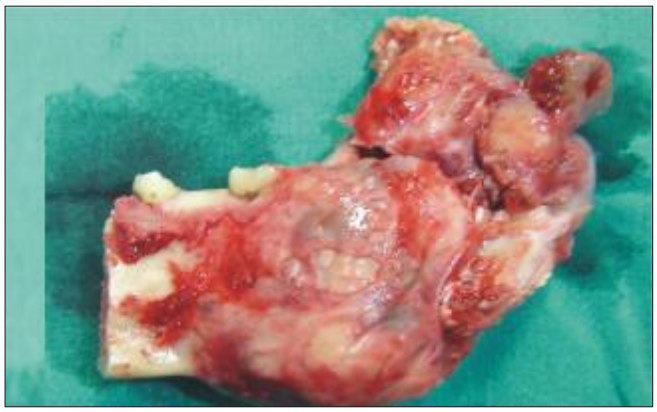

Figure 2 (c): Specimen of disarticulated resected mandible (lingual view) and normal bone in anterior portion for clinically clear bony margins.

patient had no complications and at two year follow up she is having good esthetic and functional outcomes without any recurrence [Fig 3 (a), (b), (c)]. Patient is still on follow up to observe for late recurrences.

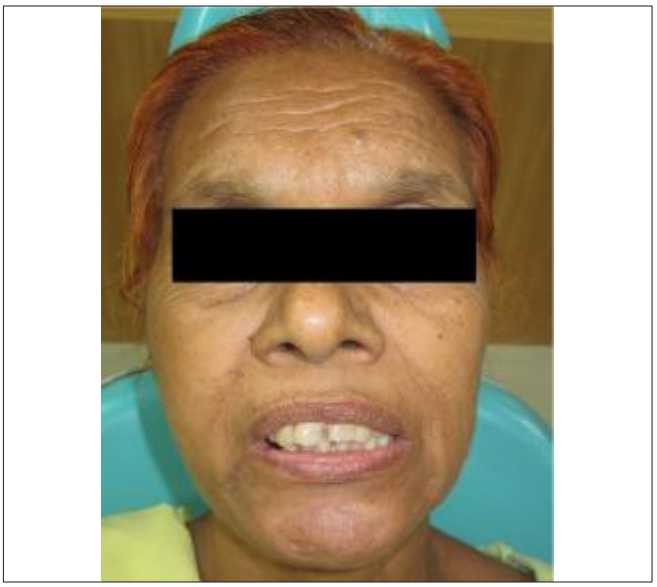

Figure 3 (a): Postoperative (one year) photograph showing facial symmetry and normal facial nerve function.

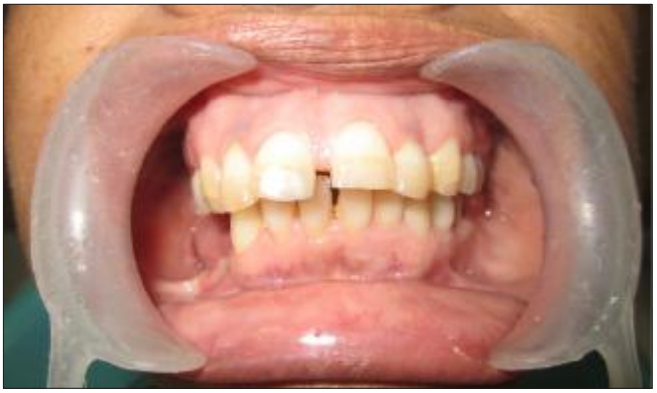

Figure 3 (b): Postoperative photograph showing normal occlusion.

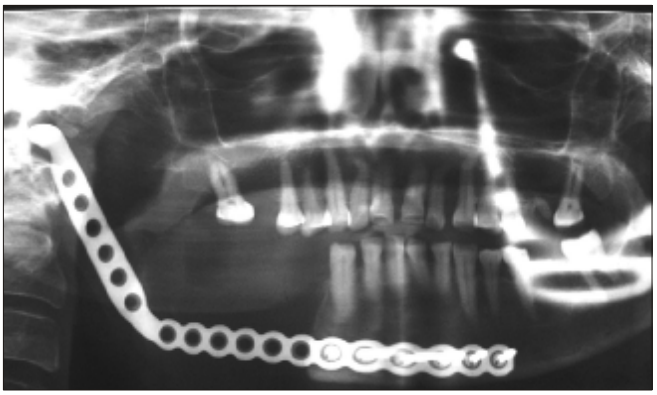

Figure 3 (c): Postoperative radiograph (orthopantomogram) showing resected right mandible and titanium reconstruction plate with good positioning of prosthetic condyle in glenoid fossa.

DISCUSSION

Ameloblastoma is a benign but aggressive lesion. It may arise from enamel organ, remnants of dental lamina, the

lining of an odontogenic cyst (dentigerous) or possibly from the basal epithelial cells of oral mucosa.[6] A few studies showed that HPV might have a role in its pathogenesis.[7] Compared to its multicystic counterpart the unicystic ameloblastoma tend to be less aggressive, has a lower recurrence rate and is less common.[8] In general, incomplete excision of an ameloblastoma results in a high recurrence rate. Therefore, treatment of choice is surgical excision with wide free surgical margins. Conservative modalities include enucleation, curettage and cryosurgery which are usually preferred for less aggressive lesions.

The challenge in treating ameloblastoma is in achieving complete excision and reconstruction of the defect when the tumour is large. The reconstruction mode to be employed depends mainly on the defect size. Mandibular segments larger than five centimetres treated with bone grafts tend to have a higher rate of postoperative complications. Such defects must be preferably rebuilt with micro-surgical flaps from the fibula or iliac crest.[9] Wherever microvascular facilities are not available, the large defects can be bridged using reconstruction plates. Reconstruction plate is sometimes used for temporary purpose for secondary microvascular reconstruction in young patients or as a permanent measure in old patients where long duration surgeries are not advisable due to poor health conditions.[10] The drawback of this approach is that the reconstruction plate cannot provide adequate alveolar height for denture construction. Hence, resection and immediate reconstruction using titanium reconstruction plate is an effective procedure in the management of large ameloblastoma, and it also provides good functional and aesthetic outcomes. Further rehabilitation with artificial teeth may be required in future if patient needs.

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Case Report

Primary Candida pneumonia in a non-immunocompromised patient

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ABSTRACT

We present the case of a 59 year old female who presented with complaints of fever, dyspnea and hypoxemia not responding to one week of antibiotics therapy. After the chest x ray showed bilateral non homogenous infiltrates, a sputum examination and later broncho-alveolar lavage were performed. Candida pseudohyphae were present in abundance with no other organism being isolated. She responded very well to micafungin therapy. Primary Candida pneumonia is a very rare entity in a patient with neither any obvious immunosuppression nor any other comorbidity.

***Keywords**: Candida; Pneumonia; Micafungin*

INTRODUCTION

Candida pneumonia either occurs as a primary process because of aspiration from the oropharynx or secondary to haematogenous dissemination from a distant source.[1,2] Most of the cases encountered in clinical practice are of latter type in immunocompromised patients. This case was unique and rare as there was no underlying malignancy or immunosuppression. The choice of antifungal is another matter of debate with multiple options available now a days.

CASE REPORT

A 59 year old female presented with complaints of fever and dyspnea for last seven days. She was non diabetic, non hypertensive and there was no history of any alcohol intake/smoking. Her chest radiograph and CT-chest showed non homogenous infiltrates predominantly in right upper and left lower lobes (Fig.1-3). She was hypoxemic with a spO_2 of 85% and pO_2 of 52 mm Hg on room air. She was tachypneic with a respiratory rate of 28/minute. She was on injectable ceftriaxone for last one week without any improvement. Sputum examination was done the same day of admission which showed pseudohyphae. Other investigations namely total leukocyte count, serum electrolytes, renal function tests, liver function tests and serum HIV were non contributory. Also, her blood cultures were sterile.BAL was done to exclude any concomitant pathology such as tuberculosis keeping in view the high prevalence of the disease in the region.BAL examination also revealed the same findings as sputum. Sputum culture by the time had shown the growth of Candida tropicalis only.

Regarding her treatment, we decided not to use fluconazole because of patient being in respiratory distress, hypoxemia and isolation of a non albicans species. The choice was between Amphotericin B and Echinocandins and the latter was opted for in view of better safety profile. Amongst echinocandins, micafungin was used based on personal experience of the authors of this particular drug. The patient improved rapidly and significantly with this treatment and she was discharged after two weeks of therapy. She was switched over to oral voriconazole for another two weeks at the time of discharge as her chest radiography showed some residual infiltrates. The patient is currently doing well under follow up.

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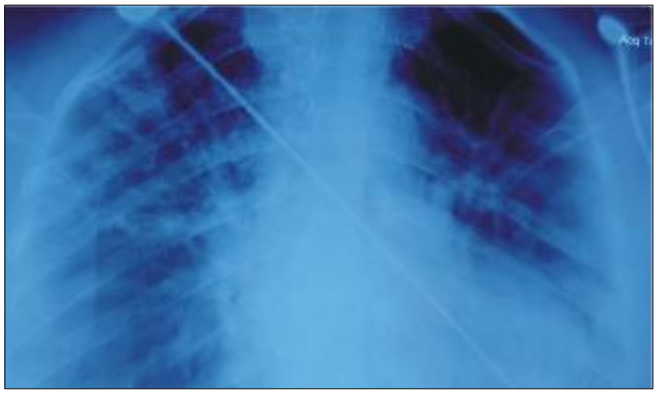

Figure 1: X-ray chest showing non-homogenous infiltrates

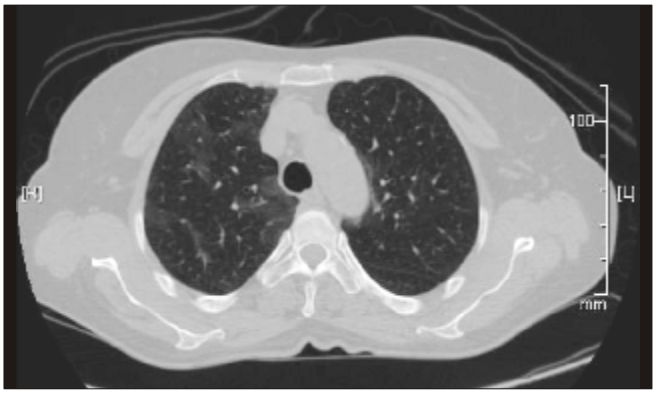

Figure 2: CT scan of lung with infiltrates

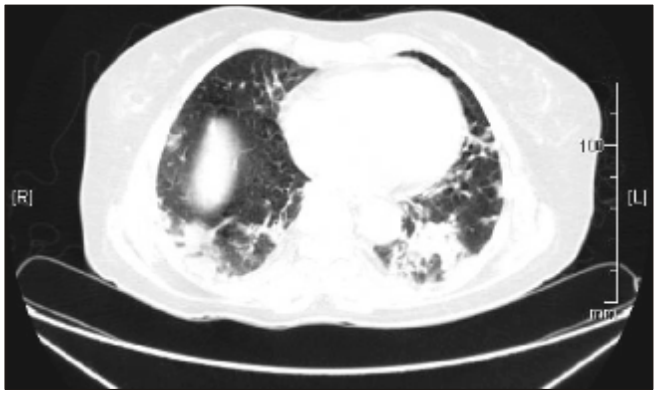

Figure 3: CT scan of chest

DISCUSSION

Candida pneumonia is a rare event. Two forms of it have been described in literature. The first one is primary pneumonia, which follows aspiration of Candida laden macrophages[1] and second one is secondary to haematogenous dissemination of Candida (especially in immunocompromised individuals) [2].The latter form has been more commonly described probably in view of HIV and more number of patients being prescribed immunosuppressive medications. In an autopsy study, only two out of eleven tissue verified pulmonary candidiasis were attributed to aspiration as the etiology.[3]In another autopsy study of critically ill mechanically ventilated patients, candida was isolated from pulmonary biopsies in upto 40% of the patients.[4]In such patients, pulmonary candidiasis usually arises from a focus of infection implanted during haematogenous dissemination. However, in patients without any definitive immunodeficiency, Candida pneumonia has been described in patients with chronic parenchymal lung disease e.g from nicotine [5].It has also been reported in an alcoholic patient [6]. Haron et al reported a large case series of 31 patients of primary candida pneumonia but amongst patients of malignancy,9 of them having severe neutropenia.[1]It has been suggested that trivial viral infections may trigger primary candida pneumonias.[5]This patient of ours neither had any chronic/ structural lung damage nor there was any history of any substance abuse.

Because pulmonary candidiasis is more commonly seen in critically ill patients, the diagnostic criteria of this entity have been more oftently discussed in this subgroup of patients only. Mustafa et al in their post-mortem study found that candida colonization is uniform throughout different lung regions but its presence in respiratory samples alone is not a good marker of candida pneumonia in critically ill patients.[4] We believe the same should apply to community acquired candida pneumonia as well. Though mere isolation of yeast from sputum does not prove the pathogenic presence of yeast in the respiratory tract[7] but isolation of this only organism in abundance in both sputum and BAL was probably sufficient to make the diagnosis in this case. In absence of other organisms and abundance of candida pseudohyphae (as in this case), clinical suspicion of invasive candidiasis should be high.[8] The demonstration of tissue invasion by candida is definitive, might not always be practical. The patient here improved soon after initiation of therapy and hence no further diagnostic intervention was sought for. In the last few years, rapid nucleic acid assays using PCR have become available for C. Albicans whereby specific DNA can be detected in culture positive specimen.[9]

The choice of the antifungal agent usually depends upon a number of factors. They include clinical status of the patient, identification of the species, antifungal susceptibility of the fungus, presence of organ dysfunction that may affect drug clearance and patient's prior exposure to antifungal agents, if any.[10] Local

epidemiological data should be taken into consideration before starting antifungal therapy.

In patients with documented candidemia or clinical instability, the choice remains between amphotericin-B and echinocandins in chest. Some authors have suggested using fluconazole for non-neutropenic patients[11] but we went ahead with micafungin 100mg/day(for initial two weeks)in view of significant hypoxemia. The patient was continued with oral voriconazole for another two weeks after receiving micafungin. Though we did not come across any evidence of combination/sequential therapy of different class of antifungals in such patients, we continued with oral voriconazole after two weeks as patient still had some residual infiltrates on chest radiograph. The patient continued to improve and was symptom free with no residual radiological shadows after two weeks of stopping the drugs.

In a large double blind study in patients of invasive candidiasis, caspofungin was found to be as efficacious as amphotercin-B but with fewer side effects.[12] Micafungin is a water soluble antifungal agent that is derived from Coleoptioma empedri. It acts in a concentration dependent manner as a noncompetitive inhibitor of the formation of the enzyme 1,3 beta d glucan synthase.[13]Available data support the use of this drug against Candida(albicans and non albicans) and Aspergillus but not against zygomycetes or Cryptococcus. Though micafungin and caspofungin have quite similar microbial spectrum of activity, the former has exhibited better in vitro activity against candida species.[13]Also, the feasibility to be used in presence of liver dysfunction and having less of drug interactions supports the use of micafungin over the latter in many cases. In a recent study, micafungin at a dose of 100 mg/day has been found to be equally efficacious to 150 mg /day and to caspofungin as well in patients of candidiasis.[14]We believe the choice of antifungal rests on the clinical condition of the patient, the species of candida isolated and sensitivity pattern of the organism.

CONCLUSION

Community acquired Candida pneumonia is a rare entity. In the absence of any underlying malignancy or immunosuppression, the clinical suspicion is usually low. Because of widespread use of fluconazole, the isolation of candida non albicans is more common than before. High index of suspicion should be kept in patients not responding to more than a week of antibiotics. Though most of the guidelines usually recommend azoles as an alternative treatment to echinocandins/amphotericin B, our patient recovered using the two different drugs (micafungin and voriconazole) in a sequential manner. Larger trials on these newer antifungals in different clinical spectrums are needed to reach definitive conclusions.

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Oral rehabilitation of a patient with partial anodontia - A case report

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ABSTRACT

This clinical case report describes the oral rehabilitation of a 19 year old male patient diagnosed with true partial anodontia. Conservative approach was used without extracting the retained deciduous teeth which had good periodontal support. A combined dental therapy approach was used which included fabrication of maxillary and mandibular cast partial dentures followed by direct composite veneers on central incisors. Functional and esthetic results were achieved improving the psychology and personality of the patient.

***Keyword**: Partial anodontia; cast partial denture*

INTRODUCTION

True partial anodontia is the characteristic feature of hereditary ectodermal dysplasia which is characterized by deformity of at least two or more of the ectodermal structures like hair, teeth, nails and sweat glands. It is typically inherited as a cross – linked recessive trait so that the frequency and severity of the condition is more pronounced in males than in females[1]. The clinical feature include sparse, fine blond hair of the scalp, eye-brows and eyelashes, nail defect, prominent forehead, depressed nasal bridge and protuberant lips[2,3]. A complete anodontia of both primary and permanent dentition is rare. A partial anodontia is more common with the patient showing a few widely spaced malformed teeth. Patient affected with partial anodontia offer a significant treatment challenge to the restorative dentist. Deciduous teeth are often retained into the third decade of life. Teeth in the permanent dentition are frequently conical, tuberculoid and tapered toward the coronal surface. Lack of alveolar bone growth may be associated with a marked mandibular protrusion on closure or a deep vertical overlap. Depending upon severity of the condition various treatment options are available to improve appearance, mastication and speech.[2,3]

- Prosthetic management in patients with complete Anodontia includes fabrication of complete dentures (conventional or implant supported).
- Removable cast partial denture or Fixed partial denture (tooth supported or implant supported) or removable overlay dentures may be considered in patients with partial Anodontia.

This article presents a case of a 19 year old male patient with partial anodontia in which prosthetic rehabilitation was done using cast partial denture.

CASE REPORT

A 19 year old male patient presented with chief complaint of missing upper & lower teeth and difficulty in mastication. Intra-oral examination revealed tuberculoid[1] and conical shaped upper central incisors, retained

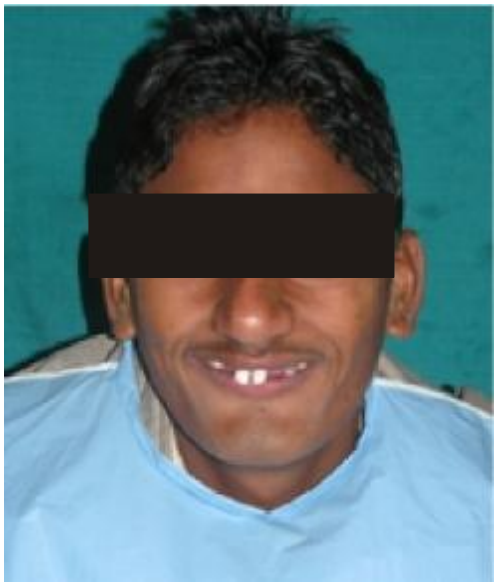

Figure 1: Extra – Oral frontal view

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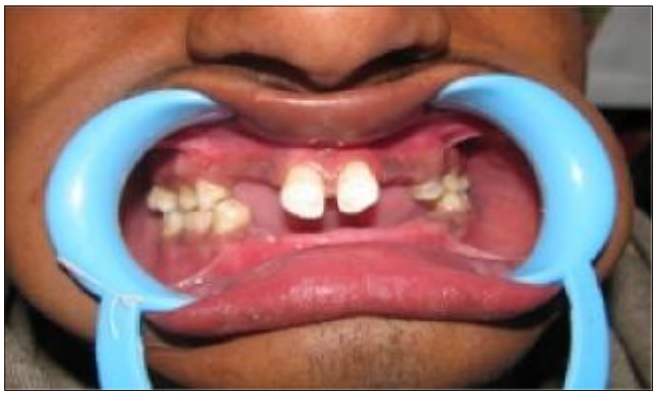

Figure 2: Pre-operative intra-oral examination.

deciduous teeth and underdeveloped knife edged alveolar ridges. Maxillary arch presented five permanent teeth (11, 21, 16, 26, 14) and three deciduous teeth (55, 65, 63). Mandibular arch presented with three permanent teeth (36. 46. 44) and two deciduous teeth (75, 85). The periodontal support of all the primary teeth was satisfactory on OPG. All the present posterior teeth (permanent or deciduous) had good occlusal relation and occlusal stops(Fig. 2). Extra-oral examination revealed normal hair pattern of eye brows and eyelashes, normal nasal bridge and protuberant lips (Fig. 1). A diagnosis of true partial anodontia was made from clinical and radiographic features.[5]

Maxillary and mandibular cast partial dentures were planned at the present vertical dimension of occlusion.

Preliminary impressions were made using alginate hydrocolloid impression material. Diagnostic casts were made, duplicated and mounted on semi-adjustable articulator (Hanau H2 Model) using face – bow transfer and interocclusal records. Diagnostic casts were surveyed and enameloplasty was done to remove the undesired undercuts. Prosthetic mouth preparation was performed according to the proposed design of cast partial dentures. Maxillary and mandibular final impressions were made using polyvinyl siloxane impression material. Cast partial denture framework was fabricated. Framework fitting and occlusal try-in was checked. Jaw relation records were made at the existing vertical dimension and transferred to the articulator.

In adolescence, selection of teeth requires more precision to satisfy their aesthetic requirements.[6,7] Anterior mold was selected according to the existing central incisor and changes to be made in it by composite veneer. A vigorous looking mold was selected to give a masculine appearance, but considering the age and soft facial features, little alteration in shape and position were made to give natural appearance. Trial dentures were checked for retention, phonetics, occlusion and esthetics. Cast partial dentures were processed (DPI heat cure acrylic resin, DPI) through compression molding and polished dentures were inserted (Fig. 3). The boy was trained for insertion and removal of dentures and was given post insertion instructions for denture care and hygiene maintenance.

Direct composite laminate veneers were made on maxillary central incisors to change the shape of tuberculoid, rotated, conical incisors (Fig. 3). All-ceramic veneers were suggested, to which patient did not agree. Oral hygiene instructions were given. Orthodontic correction of the central incisors was considered but was not done due to the lack of patient acceptance and presence of few permanent teeth. While doing the direct composite veneering, special emphasize was given to provide dominance of central incisor, masculine appearance for overall personality of patient and to reduce the midline diastema (Fig. 4).

Following the insertion of maxillary and

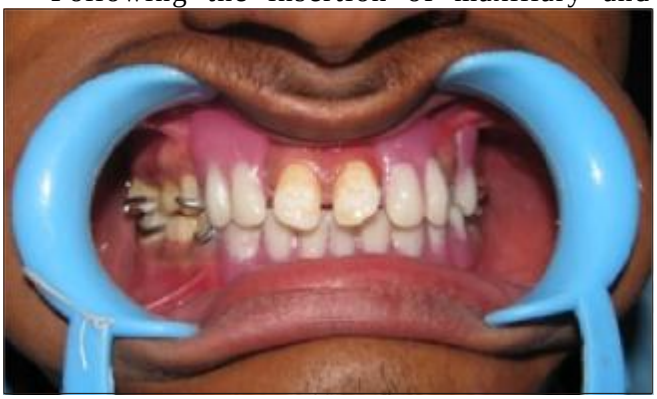

Figure 3: Tuberculoid, rotated central incisor and maxillary, mandibular cast partial denture in Occlusion.

Figure 4: Direct Composite Veneers on upper central incisors

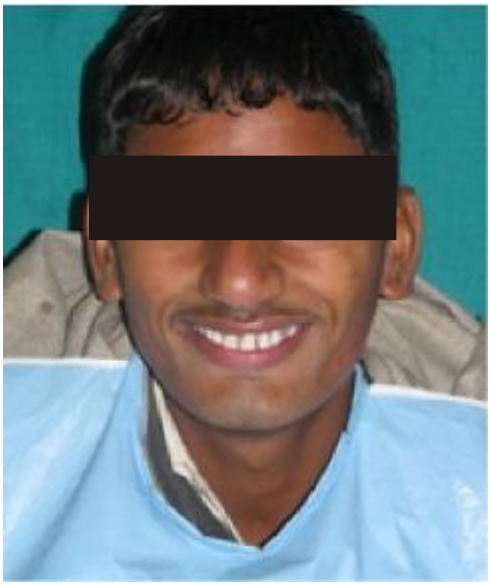

Figure 5: Completed oral rehabilitation. (frontal view)

mandibular cast partial denture and composite veneering, patient's facial esthetics changed dramatically (Fig 5). Periodic review was done for one year to make necessary adjustments and monitor the patient's oral hygiene (Fig. 5).

DISCUSSION

The treatment of true partial anodontia includes not only the management of the defect but also the psychological management of the patient as a whole.[7-9] So the treatment plan involves the role of prosthetic management fulfilling the psychological demands of the patient. This clinical case report demonstrates the treatment of partial anodontia patient with cast partial dentures without extracting the deciduous teeth and with direct composite veneering. This treatment plan is relatively simple, reversible, inexpensive and conservative and may be used in treatment of partial anodontia patient. In this case, treatment resulted in a functionally improved esthetics, development of personality and a favourable change in the psychology of the patient. After bone augmentation, implants can be given in future if primary teeth are lost.

SUMMARY AND CONCLUSION

Prosthetic rehabilitation with combined dental therapy was provided for a patient having partial Anodontia which restored the function, esthetic and confidence of the individual.

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Why the Proximal Femoral Nail (PFN) failed: Lessons to be learnt!

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ABSTRACT

Proximal femoral nails have revolutionised the surgical management of unstable pertrochanteric fractures particularly in the elderly by virtue of their intramedullary placement and anchorage in osteopenic bones. However, however, less attention towards technical aspects of procedure may herald the beginning of the failure of such devices. We report a case of intertrochanteric fracture in a 72 year old female which was well fixed with a proximal femoral nail. The fixation however failed due to 'innocuous' looking increased length of the superior screw. The newer implants although are biomechanically superior to the conventionally available fixation systems, failures still can occur.

Keywords : PFN; fracture femur

INTRODUCTION

Proximal femoral fractures constitute a major source of morbidity and mortality in the elderly population. The incidence of pertrochanteric fractures is on the rise partly because of increase in life expectancy of the populationand in part due to rise of vehicular trauma.[1] Even after surgical fixation of these injuries, morbidity remains high in these patients due to factors like poor hold of the osteoporotic bone on the metal implants and the reduced potential of healing in elderly patients.

Unstable intertrochanteric and subtrochanteric fracture patterns benefit from newer generation of intramedullary nails like proximal femoral nails which allow immediate mobilisation with lower risk of loosening of the implant.[2] However concern still remains regarding the use of such fixation modalities since they are technically more challenging and less forgiving. Minor inattention to the details and biomechanical principles can give rise to problems, which both the surgeon and the patient won't like to be a part of.

The purpose of this case report is to highlight the importance of a minor yet essential step while fixing a pertrochanteric fracture with a proximal femoral nail.

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CASE REPORT

A 72 year old female reported to the emergency department with complaints of inability to bear weight on right lower limb after a trivial fall on level ground. She was hypertensive; controlled on anti hypertensive medication. Radiographs revealed a comminutedunstable

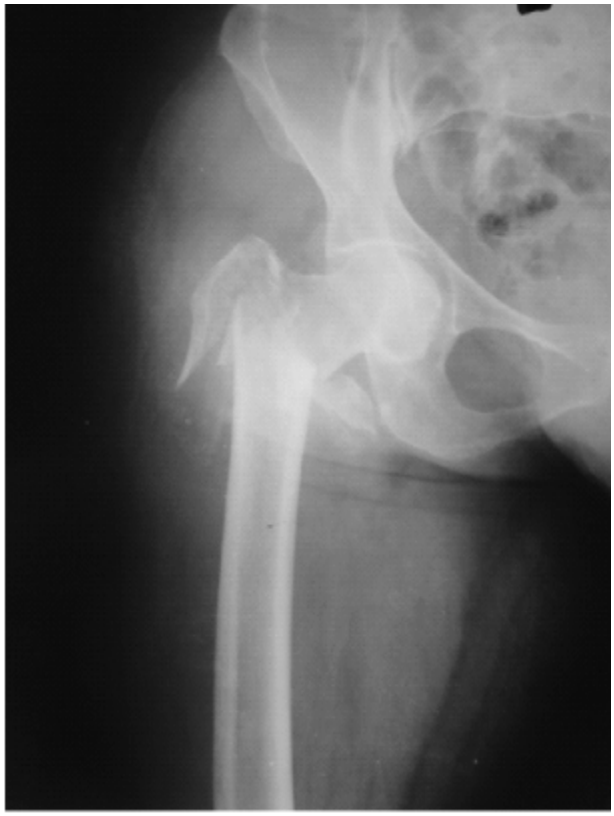

Figure I: Radiographic appearance of the fracture sustained. Note the comminution and gross osteopenia

(reverse oblique type) intertrochanteric fracture with extension along the intertrochanteric line (Figure 1). There was no distal neurovascular deficit and no associated skeletal injury. DEXA scan showed that the bones were severely osteoporotic with a 'T' score of -3.4. Surgical fixation of the fracture was carried out two days after injury with a short proximal femoral nail with achievement of perfect alignment (Figure 2). Non weight bearing mobilisation was started on post operative day 1 and partial weight bearing starting after 2 weeks. The patient was discharged from the hospital with an advice to use the walking stand so that the fractured hip in not fully loaded during walking. However, since the gait was painless, the patient, at her own, started walking with a stick after 6 weeks of surgery. She reported to the emergency department again after 2 months with severe pain in right hip region and inability to bear weight. Fresh radiographs demonstrated a failure of fixation with broken superior (derotation) screw and backing out of the inferior (weight bearing) screw (Figure 3). The fracture was viewed under dynamic fluoroscopy and was found to be ununited. Implants were then removed and the fracture was then fixed with a 95^0dynamic condylar screw with bone grafting (Figure 4).

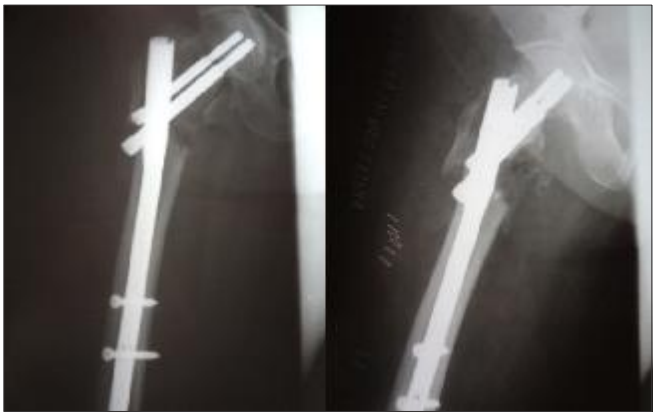

Figure 2 : Postoperative anteroposterior and lateral view after fixation

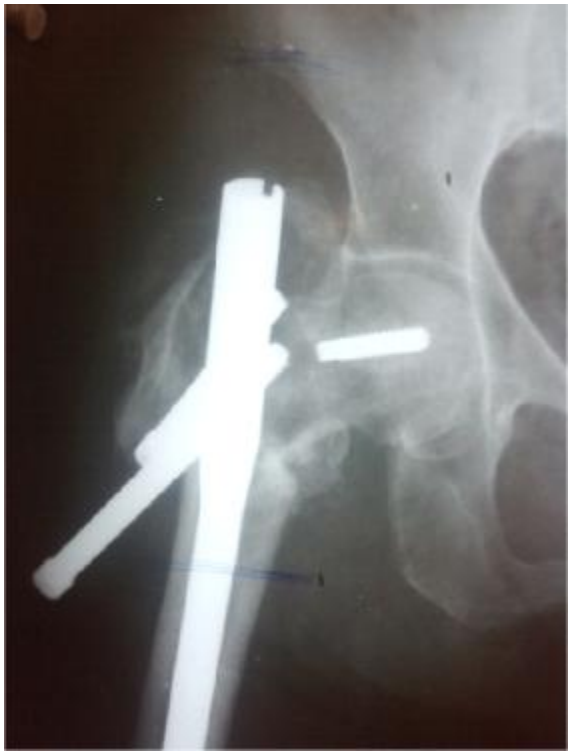

Figure 3 : Proximal femoral nail failure with breakage of superior screw and backing out of inferior screw; note the varus at the fracture site.

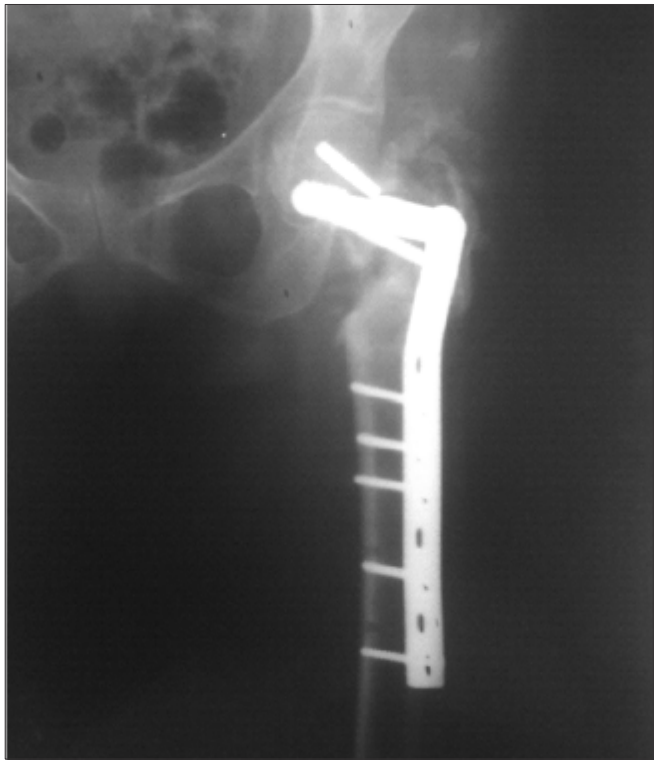

Figure 4: Postoperative anteroposterior and lateral view after fixation

DISCUSSION

Intramedullary nail fixation has revolutionised the management of unstable pertrochanteric fractures in the elderly. The fulcrum of these implants lie within the medullary canal and the load to failure is significantly higher as compared to extramedullary implants (sliding hip screw).[2] However these newer implants demand a high level of technical expertise and a slightest deviation from the mechanical principle can result in failure.

The implant failure in a well fixed fracture in the above said case without any trauma is unwarranted. After careful scrutiny of the radiographs and minute introspection, it was found that the superior (derotation) screw was longer in length than the inferior (weight bearing) screw). The design of the PFN implant is such that there are two transfixing proximal screws which get hold in the femoral neck (proximal fragment of the fracture) and there are two transfixing distal screws which get hold in the shaft of the femur (distal fragment of the fracture). Of the two proximal screws, the superior screw is thinner in diameter which is meant to prevent the rotatory forces acting on the fracture during the rotations at the hip joint while the inferior screw is thicker in diameter which is meant to bear the load of weight bearing. It is recommended that during fracture fixation, it should be ensured that the length of the superior screw should not exceed a level so that it starts acting as a weight bearing screw. If the superior screw is longer and it starts acting as load bearing screw, then there is a possibility that the inferior screw starts retracting out due to poor hold of the osteoporotic bone and the two screws make a configuration of 'Z' which has been described as Z effect by Werner Tutshcku et al in 2002.[3] Howeverthe real cause and effect relationship in such failures is yet to be elucidated fully.[4] A laboratory study conducted by Strauss et al proposed that the different bone densities where the two screws take hold in the femoral head are responsible for the success or failure of the construct.[5] They recommended that nails with two interlocking screws should be avoided in communited and osteoporotic fractures. However it is also known that two screw nail construct have higher strength to failure than a single screw nail construct.[6] Furthermore, the quality of metal is also an important factor for the strength of the implant. Although, like majority of the standard implants being used internationally, the present implant was made from stainless steel. However, the present implant was indigenously manufactured to reduce the cost of the surgery to the patient because in our country the cost of the implant is borne by the patient and majority of the patients visiting the public hospitals belong to low socio-economic strata. It is well known that apart from the quality and type of the metal, the process of manufacturing the implant has a significant share in the final strength of the implant.

Initial placement of the screws is paramount to the outcome of the fracture fixation.[7] The failure in our case was a bit different from the classical Z effect which has been reported consisting of lateral migration of the inferior screw and medial migration of the superior screw. The former component was present in the aforesaid case while the superior screw was broken. Pires et al[4]have observed that the failure can result even if one screw migrates to an extent so that the superior screw starts acting like a weight bearing screw rather than the derotation screw. We believe that apart from the indigenously manufactured implant another important facture for the failure of the superior screw in our case was attributed to longer length of the superior screw which made it to assume the role of a primary weight bearing screw. This screw being weaker due to its smaller diameter could not withstand the stresses of mobilisation and eventually failed at the fracture site. The fracture then collapsed into varus causing the inferior screw to migrate laterally owing to absence of medial cortical support and comminution.

During the revision surgery, we removed the PFN assembly and replaced it with another design of the implant: the dynamic condylar screw because the hollow created by the earlier screws in the neck of the femur would not allow the hold of the two similar screws in the same track. The distal tip of the broken screw was not removed by us because it required lot of surgical morbidity which carried a risk of damage to the bone stock of the neck of the femur. Since the metals being used for the manufactured of the implants are relatively inert metals, it is well recommended that broken metal implants may be left in situ at the time of a revision surgery if they require significant surgical morbidity and if they do not interfere with placement of the new implant.

We conclude that every failed surgery has multiple factors of failure. Some of the factors like bone quality and fracture geometry are not under the control of the surgeon. While the factors like proper selection of implant and use of the mechanical principles during the insertion of the implant are under the control of the surgeon. If we take care of the factors which are controllable, many failures can be avoided.

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Lorcaserin: A new drug for obesity

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INTRODUCTION

The burden of obesity is increasing worldwide. The increasingly unfavourable lifestyles along with availability of high density food, including processed and junk food have played a major role. Obesity is associated with a host of co-morbidities which include- most importantly- diabetes mellitus, hypertension , dyslipidemia and other cardiovascular diseases as well as cancer and arthritis. Management of obesity is a challenging since it incorporates a multifaceted approach aimed at various contributing factors. Lifestyle changes including dietary changes and exercise are the mainstays of obesity management. The results are often disappointing and not long-lasting. Bariatric surgery has been added as an option, especially for the morbidly obese patients. High cost and invasiveness of the procedure are two important limitations of this therapy.[1]

Pharmacotherapy with drugs seems an attractive option in management of obesity. However, both safety and efficacy of weight loss drugs has been a major hurdle in pharmacotherapy of obesity.[2] Though a number of drugs had been approved earlier many of these have been associated with severe adverse effects leading to their withdrawal from the market. Sibutramine and rimonabant were two major drugs that have been withdrawn of late. Sibutramine was a centrally acting serotonin/noradrenaline reuptake inhibitor that mainly increased satiety. Rimonabant was a selective antagonist of cannabinoid type 1 receptor which, by inhibiting the overactivation of the endocannabinoid system, produced anorectic stimuli at the central nervous level. However, long term studies showed sibutramine was associated with increased cardiovascular events and strokes while rimonabant was found to have a high risk of serious psychiatric problems and even suicide. Thus the quest for a safe and effective agent is on. Prior to approval of lorcaserin orlistat was the only approved drug for long term use in weight loss.

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Lorcaserin (Belviq^{R}), is an oral agent approved in 13 years by the US FDA for use as adjunct to diet and exercise in obese patients (BMI>30 kg/m^2) or overweight patients ie BMI >28 kg/m^2, with at least one co-morbid condition (diabetes mellitus, hypertension, dyslipidemia etc).[3] The recommended dose of Lorcaserin is 10 mg twice daily. However, it is to be noted that the decision for approval by the European Medicines Agency (EMA) is still under consideration.

Mechanism of Action

Lorcaserin is a potent, selective 5-HT(2C) agonist with ~15-fold and100-fold selectivity as compared to 5-HT(2A) and 5-HT(2B) receptors, respectively. The 5-HT(2C) receptors are present mainly in the brain including the choroid plexus, cortex, hippocampus, cerebellum, amygdala, and thalamus. The selectivity for 5-HT(2C) receptors may explain its low tendency to cause severe valvular defects like fenfluaramine. [4] It is proposed to decrease weight by decreasing energy intake and inducing satiety without increasing energy expenditure.[5]

Trials evaluating Safety and Efficacy of Lorcaserin

Three Phase III double blind, randomised , placebo-controlled trials involving over 5000 patients have assessed the safety and efficacy of lorcaserin for receiving approval nod by the FDA. One systematic review and a meta-analysis have been published recently.

Smith et al evaluated the safety and efficacy of lorcaserin for weight reduction in obese patients in a 12-week randomized, double-blind, placebo-controlled, parallel-arm study. [6] Four hundred and sixty nine men and women between ages 18 and 65 and with BMI 30-45 kg/m^2 were enrolled. Patients were given placebo, lorcaserin 10 mg once daily, lorcaserin 15 mg once daily, or lorcaserin 10mg twice daily for 12 weeks and were counselled to maintain their usual diet and activity. The primary end point of the study was change in weight

from baseline to day 85. Echocardiograms were done at screening and day 85/study exit for safety analysis. Lorcaserin was associated with progressive weight loss of 1.8 kg, 2.6 kg, and 3.6 kg at 10 mg once daily, 15 mg once daily, and 10 mg twice daily, respectively, compared to placebo weight loss of 0.3 kg (P<0.001 for each group). All the three groups receiving lorcaserin showed a weight loss of 5% of initial body weight. Transient headache, nausea, and dizziness were the most frequent adverse events. There was no apparent drug-related effects on heart valves or pulmonary artery pressure (PAP) shown on echocardiograms.

Another one year multicentric randomized, placebo-controlled, double-blind, parallel arm trial by Fidler et al (BLOSSOM trial) included 4008 patients aged 18-65 years with a BMI between 30-45 kg/m^2 or between 27 and 29.9 kg/m^2 with an obesity-related comorbid condition. [7] Patients received lorcaserin 10 mg once daily , 10 mg twice daily or placebo in addition to routine lifestyle counselling. There was a significant decrease in at least 5% of baseline body weight with both doses of lorcaserin (47.2 and 40.2%, respectively) as compared to placebo (25.0%, P < 0.001 vs. lorcaserin BID). Patients in lorcaserin group had a stastistically significant mean weight loss in comparison to placebo group. Headache, nausea, and dizziness were common adverse events associated with lorcaserin. Echocardiographic valvulopathy was noted in equal percentage of patients (2%) on placebo and on lorcaserin 10 mg BID.

The efficacy of lorcaserin in obese patients with type 2 diabetes was studied by O' Neil et al in 604 diabetic patients with BMI 27-45 kg/m^2 . [8] Patients were randomized to receive placebo, lorcaserin 10 mg once daily (QD) or lorcaserin 10 mg twice daily (BID) in addition to metformin, a sulfonylurea (SFU) or both .Usual diet and exercise counselling was given to all. Loss of e" 5% body weight was seen in more patients on lorcaserin BID or lorcaserin QD than with placebo (37.5% , 44.7%, 16.1% respectively ;P< 0.001). There was also a stastistically significant fall in glycosylated haemoglobin levels{ HbA (1c)} in both lorcaserin compared to placebo. Hypoglycemia was seen more commonly in lorcaserin groups while headache, nausea, back pain and nasopharyngitis were other common adverse events.

A systematic review concluded that about 47 percent of patients without type 2 diabetes lost at least 5 percent of their body weight compared with about 23 percent of patients treated with placebo (<"25%; p<0.05 in all studies).[9] Patients with diabetes mellitus also saw significant reductions in their HbA1c with lorcaserin (<"0.9%) versus placebo (<"0.4%; p<0.001). Another meta-analysis estimated that lorcaserin induced weight loss of 3.23 kg (95% confidence interval [CI]: 2.70, 3.75) and body mass index reduction of 1.16 kg m(-2) (95% CI: 0.98, 1.34) as compared to placebo in RCTs of 1 year duration.[10] Patients receiving lorcaserin had significantly higher headache, nausea and dizziness than patients receiving placebo.

Other safety issues

Besides the above common adverse events associated with lorcaserin, it should not be used during pregnancy. The FDA warns of serious side effects, including serotonin syndrome, particularly when taken with medicines that increase serotonin levels or activate serotonin receptor like anti depressants. Lorcaserin may also cause disturbances in attention or memory, dry mouth, and constipation.

CONCLUSION

Lorcaserin, has been approved by US FDA after a gap of thirteen years, citing an epidemic-like situation of obesity in the country. However, the delay in approval by another stringent authority on drugs, the EMA must be kept in mind. Though lorcaserin achieves modest weight loss and appears to be well tolerated further long duration clinical studies as well as active post-marketing surveillance are required to ensure its long-term efficacy and safety.

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Apixaban : newer oral anticoagulant

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ABSTRACT

For over half a century, warfarin remains the commonly used oral anticoagulant. This vitamin K antagonist has been commercially available for a very long time despite its limitations. Over the time, it has been noticed that with warfarin, the risk of hemorrhage may outweigh the benefit in stroke risk reduction in certain populations. Aspirin, on the other hand, while safer to use, is not quite as effective as warfarin. Apixaban is a new anticoagulant for the prevention of venous thromboembolic events after elective hip or knee replacement that has been available in Europe. A detailed drug description is presented here.

***Keywords**: Apixaban; oral anticoagulant*

INTRODUCTION

Oral anticoagulants are the mainstay of treatment in the prevention and management of both venous and certain arterial thrombotic disorders. Warfarin was the only available oral anticoagulant since last 60 years.[1] Due to several limitations of warfarin, such as narrow therapeutic index, dietary and drug interactions, and genetic influences, search has always been there for a better drug. Apixaban is a new anticoagulant for the prevention of venous thromboembolic events after elective hip or knee replacement and is available in Europe since May 2011.[2] It was approved by FDA in December 2012 with an indication of reducing the risk of stroke and systemic embolism in patients with non cardiac origin atrial fibrillation.[3]

Warfarin is a highly effective drug in preventing stroke in patients with atrial fibrillation but is associated with a variable response, has dietary and drug interactions, requires regular monitoring for dose adjustment, and carries a risk of bleeding (including intracranial hemorrhage).[4] In practice, only about half of patients who would genuinely benefit from warfarin therapy actually receive the drug because of these limitations.[5] Therefore a search was always there for an anticoagulant which has lesser side effects than warfarin.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was compared with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.[4] The trial was designed and led by a steering committee including academic investigators and representatives of the sponsors (Bristol-Myers Squibb and Pfizer). It was a double-blind, double-dummy study where patients were randomly assigned to treatment with apixaban or dose-adjusted warfarin. The primary objective was to determine whether apixaban was not inferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or systemic embolism among patients with atrial fibrillation and at least one other risk factor for stroke. The primary safety outcome was major bleeding, according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH). Key secondary objectives were to determine whether apixaban was superior to warfarin with respect to the primary outcome and to the rates of major bleeding and death from any cause. Apixaban 5mg or matching placebo was administered twice daily and Warfarin 2 mg or matching placebo was adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0. The primary outcome of stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27% per year) as compared with 265 patients in the

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warfarin group (1.60% per year). The rate of hemorrhagic stroke was 49% lower in the apixaban group as compared to the warfarin group, and the rate of ischemic or uncertain type of stroke was 8% lower in the apixaban group than in the warfarin group . Major bleeding, as defined according to ISTH criteria, occurred in 327 patients in the apixaban group (2.13% per year), as compared with 462 patients in the warfarin group (3.09% per year) (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001). The use of apixaban significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% when compared to warfarin in patients with atrial fibrillation and at least one additional risk factor for stroke. These findings are supported by the results of the Apixaban Versus Acetylsalicylic Acid [ASA] to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment trial (AVERROES).[6]

Apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) was compared with ASA 81 to 324 mg once daily in patients with AF and at least 1 risk factor for stroke who have failed or are unsuitable for VKA therapy. The primary outcome was stroke or systemic embolism, and the primary safety outcome was major bleeding. Apixaban regimen, as compared with low-dose aspirin, was shown to substantially reduce the risk of stroke without any difference in the rates of major bleeding and with lower rates of discontinuation.

PHARMACOLOGY

Apixaban is an oral , selective factor Xa inhibitor with a rapid onset of action. The plasma elimination half life of the drug is 12 hours. It has been given in twice daily dosage in clinical trials without the need of any monitoring or dose adjustments. Apixaban and its metabolites are eliminated by both biliary and renal routes and therefore can be administered in patients with either hepatic or renal disease.its pharmacokinetics is not affected by patient's age, sex, race or ethnicity.[7,8]

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to apixaban (i.e., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

Increased risk of stroke with discontinuation of apixaban: Discontinuing apixaban in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from apixaban to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If apixaban must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

Bleeding Risk: Apixaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Concomitant use of drugs affecting haemostasis increases the risk of bleeding including aspirin and other anti-platelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report to an emergency room. Discontinue apixaban in patients with active pathological hemorrhage. There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose (i.e., about two half-lives).

A specific antidote for apixaban is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.

Prosthetic Heart Valves: The safety and efficacy of apixaban has not been studied in patients with prosthetic heart valves and is not recommended in these patients.

Critical Care Settings: The safety and efficacy of apixaban has not been studied in patients of ICU and not yet recommended

ADVERSE REACTIONS

The most common and most serious adverse reactions reported with apixaban were related to bleeding.

DISCONTINUATIONS FOR SURGERY AND OTHER INTERVENTIONS

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.

DRUG INTERACTIONS

Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Decrease the dose of Apixaban to 2.5 mg twice daily when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking apixaban at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.

Strong Dual Inducers of CYP3A4 and P-gp: Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke. Avoid concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.

Anticoagulants and antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANC Y CATEGORY B

There are no adequate and well-controlled studies of apixaban in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. Apixaban should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Cost effectiveness

Usage of the new anticoagulants like apixaban may be associated with lower medical costs relative to warfarin.

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