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Editorial

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Obesity and Pulmonary Hypertension. What's the Link?

Roop Kaw

Severe pulmonary hypertension (PH) is a rare disorder characterized by multifactorial etiology and shared pathophysiology. The belief that primary pulmonary hypertension (PPH) is an idiopathic variety mostly affecting younger women may still be held by some. However, PH has often been reported in overweight and obese individuals and postmenopausal women.[1] Earlier studies have also suggested that combination of obesity and higher altitude favors the development of pulmonary arterial hypertension. Hypercapnic acidemia and increased total blood volume have been implicated in this group of patients. Pulmonary artery systolic pressures (PASP) greater than 40 mmHg is found in 6% of otherwise normal individuals age 50 years or older and in 5% of individuals with a BMI greater than 30kg/m^2 . [2]

Overall, the widely held view has been that alveolar hypoxia is the main pathophysiologic cause of vasoconstriction in obese patients living at sea level or higher altitudes. In 1947, Motley et al demonstrated that breathing a gas mixture containing 10% oxygen induced a rise in pulmonary artery pressure (PAP).[3] Papers dating back more than three decades have documented increases in PAP associated with hypoxemia related to sleep disordered breathing (SDB). It is well known that apneic episodes during sleep are associated with transient elevations in PAP, which return to baseline when breathing resumes after relief of obstruction. Earlier studies suggested that daytime hypoxemia attributable to abnormal lung function was the main cause of pulmonary hypertension in patients with sleep apnea. Whether transient hypoxemias and associated elevations in PAP with obstructive events during sleep are adequate to produce daytime resting "fixed" pulmonary vascular disease, or whether daytime hypoxemia is required remains unclear. It is also less certain whether daytime pulmonary arterial hypertension also occurs in OSA patients without underlying pulmonary or cardiac disease. Additionally, studies have shown that the severity of SDB as measured by apnea-hypopnea index (AHI) and the PAP elevations often fail to correlate.

Sajkov et al [4] were amongst the first to demonstrate that hypoxemia in PH patients with obstructive sleep apnea syndrome (OSAS) could not be explained by impairment of lung or cardiac function, BMI and smoking history. However, most of the studies that have tackled this question (including the one done by Sajkov) have used echocardiography based pulmonary artery pressures and the few that have used the gold standard Right heart catheterization (RHC) used a definition of mean pulmonary artery pressure (mPAP) >20 mmHg. At present, pulmonary arterial hypertension is defined as a mean PAP greater than 25mmHg at rest or 30 mmHg with exercise, as measured by RHC. The largest such study found PAH in 17% patients but it also included some patients with chronic obstructive pulmonary disease (COPD).[5] Smaller series of patients with OSA but no clinical history of COPD have reported daytime PAH as measured by RHC in 20-42% patients. [6, 7]

Thus, despite acute nocturnal increases in PAP associated with obstructive apneas, proof that OSA causes PH has been limited by other co-morbidities related to obesity. The three biggest confounders making this issue difficult to be explored are associated COPD in OSAS patients (overlap syndrome), Obesity Hypoventilation Syndrome (OHS) and underlying concomitant left ventricular dysfunction in patients with OSA. OHS as defined at present is characterized by combination of obesity (BMI ≥30kg/m^2) and chronic daytime hypercapnia ($PaCo_2$ >45 mmHg); and sleep disordered breathing in the absence of other known causes of hypercapnia.[8] PH has been shown to be more frequent and mean PAP higher in patients with OHS or the overlap syndrome when compared to patients with pure OSAS only. [9] Elevated mPAP associated with higher pulmonary capillary wedge pressure (PCWP) from underlying elevated left ventricular end-diastolic pressure and in some studies apnea associated have been other potential confounders.[10] Other difficulties related to exploring this issue are technical concerns regarding non-invasive measurement of pulmonary artery pressure in obese OSA patients and difficulties in identifying suitable controls i.e, obese patients with PH and without OSA. Studies are also needed to investigate the role of humoral vasoactive factors like natriuretic peptides, nitric oxide or norepinephrine and individual genetic predisposition to account for different remodeling responses to hypoxia in the pulmonary circulation. In OSAS patients no neutrally mediated effect of apneas on PAP has been demonstrated.

PH seen in association with OSA is generally regarded as mild and can be attributed to elevated pulmonary vascular resistance (PVR) because cardiac output and PCWP are normal atleast at rest. Although the association between left sided-heart disease and OSA is widely accepted, most studies of OSA patients with PH do not differentiate between pre-capillary (PAH) and post-capillary pulmonary hypertension (PVH). Additionally a good proportion of the studies do not even report PCWP.[6, 9] while some explain higher PAP on the basis of PCWP alone. Elevations in both PCWP and PVR have been reported to contribute to PH in patients with OHS. A recent study of referred patients who met the WHO criteria for PAH from Duke University reported PCWP> 15 mmHg in 25% of the patients. These patients were predominantly obese (58%) and all had normal LVEF%. [11] In our retrospective analysis of 8254 patients who underwent RHC for suspected PH, mean Right atrial pressure, mean PA diastolic pressure, mean PCWP and mean cardiac output increased proportionately with increase in BMI regardless of the underlying contributory disease process. [12]

The debate about whether OSA alone can be a cause of sustained pulmonary arterial hypertension continues, but based on the above literature, the latest revision of the Clinical Classification of Pulmonary Hypertension identifies SDB as a part of the category of respiratory disorders associated with PH.[13] The most direct evidence comes from observations that treatment of OSA with continuous pulmonary arterial pressure (CPAP) may lower daytime PAP. OSA patients with PH seem to have increased pulmonary vascular reactivity to hypoxia compared to patients without PH and CPAP has been reported to decrease pulmonary vascular reactivity to hypoxia.[14] In studies from Stanford as early as 1978, 50% reduction in PAP was noted in six selected patients with OSA after tracheostomy. In a recent randomized placebo-controlled cross-over trial of effective versus sham CPAP in 23 patients with OSA, effective CPAP was associated with decreases in echocardiographic measurements of PASP especially in patients with PH or left ventricular diastolic dysfunction at baseline. [15] This trial was limited by baseline differences in obesity and lung function between the two groups. Larger randomized studies are needed to identify more definitively any sustained effects of CPAP therapy on PH and right heart function and to better establish any role for CPAP as one of the rapidly evolving therapeutic options for PH.

COMPETING INTERESTS
None Declared

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Review Article

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Breast cancer and therapeutic deployment of growth factor receptors

Gajanan V. Sherbet

Abstract

Growth factors and their receptor play a major part in normal growth and differentiation and also in tumour development and progression. Mutations or over-expression of growth factor receptors is associated with aggressive cancers and poor prognosis for patients. Growth factor receptors are transmembrane tyrosine kinase proteins that transduce growth factor signals imparted by their binding to specific receptors leading ultimately to the induction of cell proliferation. HER2 is a human epidermal growth factor receptor. Approximately 25% of breast cancers show HER2 gene amplification and this correlates with aggressive behaviour and poor prognosis. The deployment of Herceptin (Trastuzumab), a humanised chimeric antibody against HER2, to treat HER2+ patients, has emerged as a successful approach to the treatment of breast cancers that over-express HER2 and are resistant to tamoxifen. These patients could benefit from anti-oestrogen therapy combined with blockade of HER2 signalling. Post-menopausal patients with advanced breast cancer appear to benefit significantly from this combination therapy. Combination of Herceptin with chemotherapy might yield considerable benefits in terms of reduction of recurrence and mortality. The efficacy of conjugates of anti-HER2 antibodies with cytotoxic drugs to achieve targeted delivery of the cytotoxic agents is being evaluated. The toxicity associated with the administration of monoclonal antibodies has been recognised. Cardiotoxicity, pulmonary toxicity and infusion-related problems such as anaphylaxis occur, albeit infrequently, with monoclonal antibody therapies. The EGFr (epidermal growth factor receptor) inhibitor Lapatinib (Tykerb) is a protein kinase inhibitor (a 4-anilinoquinazoline derivative), which inhibits growth factor signalling by binding to the ATP-binding pocket of both EGFr and HER2 receptor proteins. Lapatinib has shown much promise in clinical trials in patients with advanced metastatic breast cancer and is believed to have little cardiac toxicity. A strategy similar to that adopted with EGF family growth factor receptors has been used to target the vascular endothelial growth factor receptor (VEGFr) and inhibit signalling by VEGF. Avastin (Bevacizumab) is a humanised monoclonal anti-VEGFr antibody. Avastin combined with Paclitaxel improves progression-free survival and response rate in patients with advanced breast cancer. However, on account of possible side effects, Avastin has not received general approval.

Key words: Avastin (Bevacizumab), VEGFr inhibitor, EGFr Epidermal growth factor receptor, ER Oestrogen receptor, Growth factor signalling, HER2 Human epidermal growth factor receptor 2, Herceptin (Trastuzumab), Lapatinib (Tykerb) inhibitor of EGFr, Receptor tyrosine kinases, Tamoxifen resistance, VEGFr Vascular endothelial growth factor receptor

Introduction

Adjuvant modes of breast cancer therapy following surgical intervention mainly revolve round radiation therapy, chemotherapy, or hormone therapy designed to eliminate residual cancer cells. The increase in the incidence of breast cancer with age has sharply focused attention on the link between incidence and progression. It follows from this that approaches to successful treatment and patient management would converge on hormonal status as a beneficial mode of targeted therapy. A number of growth factors, besides the steroid hormones oestrogen and progesterone, are closely involved in the growth and metastatic spread of breast cancer. Recent years have seen intensive studies of the mechanisms of function of growth factors and the pathways by which they stimulate the growth of cancer cells. These studies have led the way to the targeting growth factor function as a means of controlling breast cancer development and secondary spread.

The growth factor receptors are transmembrane proteins. The binding of growth factors to the external domain activates these receptors which have tyrosine kinase activity. This activation therefore leads to the phosphorylation of signalling proteins down stream in the signalling cascade. This in turn leads to the expression of genes associated with cell proliferation and often also to the inhibition of apoptotic loss of cells.

Growth factors, growth factor receptors and tumour growth and progression

Growth factors and their receptor play a major part in normal growth and differentiation and also in tumour development and progression. Growth factors promote proliferation and induce cancer invasion. Certain growth factors, e.g. the insulin-like growth factor (IGF) might promote tumour growth by inhibiting apoptotic loss of cells[1]. Mutations or over-expression of growth factor receptors is associated with aggressive cancers and poor prognosis for patients. Growth factor receptor genes are amplified in a number of human cancers and this is reflected in the expression of the respective receptor proteins in the cancers. Growth factor receptors are transmembrane tyrosine kinase proteins and transduce the signals imparted by the binding of the growth factors to their specific receptors; this signal transmission ultimately results in the induction of cell proliferation.

Among growth factors of note in the context of this editorial are the epidermal growth factor (EGF) and the Heregulins constituting a family of EGF related growth factors. There are several isoforms of Heregulin generated by alternative RNA splicing of the heregulin gene; these isoforms bind to their receptors with different degree of affinity. The epidermal growth factor receptor (EGFr) family (also often referred to as the erb

family) includes HER1 (human epidermal growth factor receptor 1 also called EGFr), HER2, HER3 and HER4. These receptor proteins significantly resemble one another in aminoacid sequence[2]. Heregulin can bind HER3 and HER4 receptors but the ligand for HER2 has not been identified[3] and so HER2 is often described as an orphan receptor. The receptor protein consists of an external domain that binds growth factors, a transmembrane domain and an intracellular domain which possesses tyrosine phosphorylation sites[4]. Growth factors and their paralogues bind to these receptors and induce receptor oligomerisation. This activates the cytoplasmic kinase domains, which phosphorylate and activate target proteins that induce the expression of genes responsive to the growth factors. The binding and activation of the receptors is a highly specific process, but often more than one receptor might be involved in the signalling process. In this event heterodimerisation would occur between different receptors; this seems to enhance the affinity of ligand binding[5]. This process of engagement of co-receptors to enhance growth factor signalling has been described as cross-talk between the receptors. HER2 is known to be involved in cross-talk with EGFr, HER3 as well as HER4. So HER2 seems to occupy a pre-eminent position in the signalling cascade, but recently it has been suggested that HER3 might also be a prominent participant[6].

The EGFr family of receptors have been intensively investigated for their potential relationship to cancer progression and prognosis and as a potential route for treatment and patient management. Approximately 25% of breast cancers show HER2 gene amplification and this correlates aggressive behaviour and poor prognosis[7-10]. However, on the positive side the presence of HER2 receptors has provided a new treatment modality for many patients.

Monoclonal antibodies (Herceptin) have been raised against the external domain of HER2. Herceptin has provided a highly successful mode of treatment for metastatic breast cancer showing high HER2 expression and HER2 gene amplification[11-13]. Blocking receptor function with Herceptin inhibits tumour growth and possibly also microvascular density associated with tumours and vascular permeability. Furthermore, Herceptin treatment appears to reduce VEGF (vascular endothelial growth factor) expression, tumour associated microvascular density and cell proliferation in breast cancers xenografted into mice[14]. Also in murine tumour models, Herceptin reduces the number of circulating cancer cells even under circumstances where the tumour is resistant to Herceptin treatment[15], which could be a manifestation of its effects on the vasculature independently of its inhibition of HER2 signalling.

HER2 expression and tamoxifen resistance

Breast cancer growth is influenced by the sex steroid hormones oestrogen and progesterone and growth factors such as EGF and HER2 ligands. Patients with tumours that are oestrogen receptor (ER) positive are treated with tamoxifen. The latter binds ER and competitively blocks oestrogen signals. In the context of the deployment of Herceptin to treat HER2+ patients, it has emerged that tumours over-expressing HER2 are resistant to tamoxifen. These patients could benefit from anti-oestrogen therapy combined with blockade of HER2 signalling[16]. A randomized trial has indicated that post-menopausal patients with advanced breast cancer can benefit significantly from this combination therapy[17].

Among other factors that might confer tamoxifen resistance is AIB1, the steroid receptor co-activator, which is often amplified in breast cancers. In vitro studies with breast cancer cells and in vivo investigations of murine tumours have suggested the involvement of AIB1 in tamoxifen resistance[18] and in HER2 signalling[19]. In primary breast cancer also AIB1 has been linked with tamoxifen resistance[20, 21]. A second factor deserving discussion in this context is the possibility that EGFr and HER2 signalling systems might interact and contribute in this way to resistance to hormonal therapy. As mentioned elsewhere in this review, EGFr does recruit HER2 as a co-receptor in signal transduction. This is of some significance for patients with ER-negative tumours. For, we showed some years ago that a proportion of ER-ve tumours tended to be EGFr+ve[22-24]. So this would suggest the possibility that patients with ER-ve/EGFr+ tumours could conceivably benefit from Herceptin treatment (see below).

Another possible means by which tamoxifen resistance might arise has been suggested by the finding that tamoxifen and Fulvestrant, also an anti-oestrogen, appear to be able to induce breast cancer cell invasion in the absence of E-cadherin[25]. Cadherins are transmembrane proteins, which have considerable influence on cancer invasion because they alter intercellular and cell-substratum adhesion. E-cadherin is regarded as a suppressor of invasion and growth of carcinomas as the loss or mutation of E-cadherin leads to the acquisition of invasiveness. Borley et al.[25] showed that both tamoxifen and Fulvestrant induced invasion in E-cadherin deficient MCF7 breast cancer cells, but this did not occur after oestrogen depletion. These findings add a new dimension to tamoxifen resistance as potentially being mediated by recurrence resulting from induced invasive ability.

HER2 expression and adjuvant chemotherapy

It has been recognised of late that combination of Herceptin with chemotherapy might yield considerable benefits in terms of reduction of recurrence and mortality. So HER2 expression has come into the reckoning when considering the use of adjuvant chemotherapy. Combining Herceptin with either an anthracycline plus cyclophosphamide or with Paclitaxel, as first-line therapy for metastatic breast cancer over expressing the HER2 receptor, has provided significant benefits in terms of objective response, duration of response and survival as compared with chemotherapy alone. Furthermore, the benefits were related to the degree of HER2 over-expression[26]. A review

of 35 clinical trials has indicated that patients with HER2+ cancers might benefit more from anthracycline-based and taxane-based adjuvant chemotherapy than those with HER2-negative cancers[27]. Indeed, anti-HER2 antibody combined with chemotherapy is superior to HER2 anitibody and anti-oestrogen combination[17]. The benefits of adjuvant chemotherapy with anthracyclines to patients with HER2 over-expressing tumours seem to be beyond reasonable doubt. Gennari et al.[28] have provided a combined analysis of eight studies. HER2+ patients on anthracyclines had superior disease-free as well as overall survival in comparison with patients on non-anthracycline regimen. No such benefits emerged for HER2-ve patients, suggesting that one can exclude these patients from anthracycline adjuvant therapy. Also being investigated is potential synergy between antibodies against other growth factor receptors and anti-HER2 antibodies.

Attempts are also currently in progress to test the efficacy of conjugates of anti-HER2 antibodies with cytotoxic drugs to achieve targeted delivery of the cytotoxic agents. Laboratory studies are underway with Herceptin-platinum(II) complexes[29] and Herceptin-microtubule-depolymerising agents[30].

Contraindications of Herceptin regimen

The toxic side-effects of the administration of monoclonal antibodies were recognised some years ago. Cardiotoxicity, pulmonary toxicity and infusion-related problems such as anaphylaxis occur, albeit infrequently with monoclonal antibody therapies [31, 32]. These toxicities have been described with Herceptin treatment, more so in patients on anthracycline and cyclophosphamide combined with Herceptin[26]. Cardiotoxicity could occur in some patients when Herceptin is administered with anthracyclines[33, 34]. Herceptin itself can be cardiotoxic in patients receiving concurrent or prior anthracyclines[35, 36]. Cardiotoxicity is not due to structural abnormalities but Herceptin might cause myocardial dysfunction. The toxicity of anthracyclines and Herceptin could be brought about by different routes[37]. As Dinh et al.[38] have emphasised, many questions relating to Herceptin treatment still remain unanswered, e.g. optimising treatment, and combination with conventional chemotherapeutic agents, among others. Even with these caveats Herceptin may be regarded as a most efficacious agent in the treatment of HER2+ breast cancers.

EGFr inhibitor Lapatinib (Tykerb) in breast cancer treatment

As stated earlier, EGFr is over expressed in a proportion of breast cancers that are ER-negative. EGFr expression also correlates with the expression of metastasis promoting genes. Further, in the light of the function of EGFr in conjunction with HER2, it would be of considerable clinical benefit to test the effects of EGFr inhibitors in breast cancer treatment. Lapatinib is a powerful dual inhibitor of EGFr and HER2 with marked pharmacological potential.

Lapatinib is a protein kinase inhibitor (a 4-anilinoquinazoline derivative), which inhibits growth factor signalling by binding to the ATP-binding pocket of both EGFr and HER2 receptor proteins and so prevents autophosphorylation of the receptor and inhibits the signalling cascade leading to the suppression of the growth of tumours, including advanced or metastatic breast cancers resistant to Herceptin[39]. Objective responses have been achieved in 28% of patients with untreated HER2-positive tumours[40]. Clinical trials have provided promising results; Lapatinib is clinically very effective especially in advanced or metastatic breast cancer and patients with brain metastases. A phase III trial assessing the efficacy of combination of Lapatinib with Capecitabine, which is converted to 5-Flurouracil and inhibits DNA synthesis, seems to suggest a significant slowing down of disease progression by the combination as compared with capecitabine alone[41]. The efficacy of combining Lapatinib with other conventional chemotherapeutic agents is being evaluated. First-line Paclitaxel-Lapatinib combination gave significant benefits to HER-2-positive patients[42].

Lapatinib could be functioning synergistically with HER2 inhibitors, for its effect on prominently EGFr over-expressing cancers, such as colorectal cancer or squamous cell carcinoma of the head and neck, is said to be unexceptional and moderate[43]. According to Press et al.[44] the benefits of Lapatinib appear to be restricted to patients with HER2 over-expressing cancers. Lapatinib has no cardiac toxicity but does produce other toxic effects[45]. However, its toxicity whilst administered in combination with other anticancer agents has not been appraised.

Avastin in breast cancer treatment

A different route to control of tumour growth and metastatic spread has been afforded by inhibitors that target the microvasculature associated with tumours. Tumours induce the formation of neovascularisation so that tumour cells can access the vascular system and become disseminated to form distant metastases. The neovasculature is induced by VEGF, which transduces its effects by binding specifically to its receptors VEGFr (see[46]). A strategy similar to that adopted with EGF family growth factors has been used to target VEGFr, inhibit its function and inhibit the signalling by VEGF. Avastin (Bevacizumab), a humanised monoclonal anti-VEGFr antibody, is such an inhibitor. Avastin with Paclitaxel chemotherapy has been found to enhance progression-free survival and improve response rate in patients with advanced breast cancer[47]. However, on account of possible side effects, there is some reluctance to the use of Avastin. It has been approved in Europe for first line treatment of women with metastatic breast cancer, but has not been approved for use by the National Institute for Health and Clinical Excellence UK[48].

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Review Article

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Oral Bisphosphonates and the Risk for Osteonecrosis of the Jaw

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Abstract
Several recent reports have described osteonecrosis of the jaws (ONJ) associated with the use of bisphosphonates. Osteonecrosis of the jaws is recognized as a serious complication of bisphosphonate therapy, more commonly with the intravenous form of the drugs. However, there is limited scientific understanding about the association between osteonecrosis of the jaws and bisphosphonates. Primary care physicians treating bone diseases with bisphosphonate need, therefore, to be aware of this potential risk and plan the prophylaxis, early diagnosis and prevention of potential consequences. In this article, I review the literature on this newly described complication, with particular focus on systemic and local predisposing pathologies, preventive measures suggested before and during therapy with oral bisphosphonates, and the frequent clinical presentation of the oral lesions. The expert panel recommendations for the management of care of patients who develop ONJ are summarized also.
ONJ has been linked with high-dose intravenous bisphosphonate use in patients with bony cancers and the observation has been extended at a much lower incidence to patients on oral bisphosphonates taken for osteoporosis. The benefit-risk ratio is still heavily weighted towards therapy but primary care physicians need to be aware of this link. The risk is greatest in those with poor oral health who are undergoing dental surgery. If there is doubt, then a review by an experienced oral surgeon is appropriate.

Key words: Oral Bisphosphonates, Osteoporosis, Osteonecrosis

Osteoporotic fracture is common, expensive, and associated with increased morbidity and mortality. The incidence of osteoporosis fracture annually is greater than the risk of stroke, breast cancer, and heart attack combined. Bisphosphonates (BPs) have recently been the subject of clinical controversies because of the reported incidence of osteonecrosis of jaw (ONJ). Bisphosphonates as a group of drugs were introduced for the management of various conditions such as osteoporosis, Paget's disease, multiple myeloma, and hypercalcemia of malignancy. This group of drugs has improved the quality of life in many patients with proven efficacy in limiting pain and skeletal-related events. The efficacy of BPs as one method to prevent and treat osteoporosis and avert future fractures, particularly vertebral fractures, is well documented in large clinical trials. However, despite this evidence, many patients at risk for osteoporosis are not screened or treated. The controversy of osteonecrosis of the jaws and bisphosphonates is a recent and growing problem.

Bisphosphonates:

Bisphosphonates are fairly safe drugs to be used in the long term. There is a significant amount of safety data for up to 10 years with alendronate or Fosamax and up to 7 years with risedronate or Actonel. Every year, an estimated 30 million BP prescriptions are written in the U.S. alone.[1] The bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid are nitrogen containing compounds that increase bone mineral density (BMD) by inhibiting osteoclast-mediated bone resorption.[2] They have been shown to increase BMD approximately 2–8%, depending upon the dose and site measured, and have demonstrated efficacy in primary and secondary prevention of osteoporotic fractures.[3–10]

Nitrogen-containing bisphosphonates are used widely for the management of metastatic cancer in bone (intravenous zoledronic acid or Pamidronate), for the prevention and treatment of osteoporosis (oral alendronate, risedronate, and ibandronate and intravenous ibandronate), for the treatment of Paget's disease of bone (intravenous Pamidronate and oral alendronate and risedronate), and for the short-term management of acute hypercalcemia (intravenous zoledronic acid and Pamidronate).[11] Bisphosphonates reduce the survival and function of osteoclasts, the bone-resorbing cells. The clinical pharmacology of intravenous (IV) BPs is characterized by low intestinal absorption but highly selective localization and deposition in bone. Oral BPs have a bioavailability of less than 5%.[12] Once in the blood, BPs disappear very rapidly into the bone.[13] After BPs are buried in the skeleton, they are released only when the bone is destroyed in the course of turnover. In humans, the skeletal half-lives of various BPs range from 3 months to as long as 10 years. [14]

Osteoporosis:

Osteoporosis is a devastating disease that may lead to significant morbidity and mortality from resultant fractures. Approximately one in two women and one in four men over age 50 will have an osteoporosis related fracture in their remaining lifetime. [15] According to estimated figures, osteoporosis was responsible for more than 2 million fractures in US in 2005 [15] (including approximately 297,000 hip fractures, 547,000 vertebral fractures, 397,000 wrist fractures ,

135,000 pelvic fractures , 675,000 fractures at other sites). The number of fractures due to osteoporosis is expected to rise to more than 3 million by 2025. [15]

Osteoporotic fractures are associated with significant morbidity and mortality. Patients who sustain a fracture are more likely to have lower health-related quality of life, depression, pain, disability, physical deconditioning due to inactivity, vertebral deformities with a resultant decrease in pulmonary function and increase in gastrointestinal complications (e.g., refractory reflux esophagitis), pressure ulcers, increased likelihood of nursing home placement, and changes in self-image. [16-23] Hip fractures, which are the most serious complication of osteoporosis, are associated with significant mortality. [24–27] Up to 38% of patients may die within one year after a hip fracture, and the risk of death is approximately double that of patients who do not sustain a hip fracture. [24, 25, 27]

The economic consequences of osteoporosis are enormous. In 1995 in USA, osteoporotic fractures were responsible for approximately 432,000 hospital admissions, 2.5 million physician's office visits, and 180,000 nursing home admissions. [15] Health care costs associated with osteoporotic fractures in 2005 were an estimated $19 billion. By 2025, experts predict that these costs will rise to approximately $25.3 billion. [15] As the population of the United States continues to age, these costs will likely increase, with the number of hip fractures and associated costs possibly tripling by 2040. [15]

Oral bisphosphonate associated osteonecrosis of the jaw:

Osteonecrosis of the jaws (ONJ) is characterized by the death of bone as a natural consequence of a wide variety of systemic and local factors compromising the blood flow of the bone. Clinically it is diagnosed by an area of exposed bone in the mandible, maxilla, or palate that typically heals poorly or does not heal over a period of 6 to 8 weeks. The diagnosis is primarily a clinical one, but imaging studies such as computed tomography can be helpful. Approximately two thirds of cases involve the mandible and the rest involve the maxilla. The lesion is painful in many, but not all, patients, and infection is often present. In one unusual case, osteonecrosis of the external auditory canal developed in a patient with myeloma who had received intravenous zoledronic acid and amidronate.[28] Predisposing factors for the development of osteonecrosis of the jaw appear to be dental disease, dental surgery (e.g., tooth extraction), oral trauma, periodontitis, and poor dental hygiene. The risk factors for developing ONJ include trauma, female gender, advanced age, edentulous regions, radiotherapy, chemotherapy, steroid therapy, blood dyscrasias/metastatic disease, anemia, coagulopathy, surgical dental procedures, alcohol or tobacco use, prior infection, and bisphosphonate therapy.[29-32] Although there have been some reports in the literature about osteonecrosis caused by steroids, this form is different from ONJ in the sense that steroid-induced osteonecrosis does not cause bone exposure. [1, 33]

ONJ in connection with bisphosphonate use was first reported in 2003 [34], or 5 to 10 years after these drugs were approved in the United States for their current indications; it was rarely seen before then. Most of the reported cases (95%) have been associated with zoledronic acid or Pamidronate given intravenously to control metastatic bone disease. [35, 36, 11] Myeloma and breast cancer are by far the most common cancers associated with intravenous bisphosphonate use and osteonecrosis of the jaw.[35]

Osteonecrosis of the jaw has developed far less often among patients who have received oral bisphosphonates at the lower doses used for osteoporosis than among patients who received the higher doses used for metastatic cancer. Among several million patients who have received oral treatment for osteoporosis, fewer than 50 cases of osteonecrosis of the jaw have been reported to date.[35] Moreover, with more than 60,000 patient- years of exposure to nitrogen- containing bisphosphonates in clinical trials of treatment for osteoporosis (involving follow-up for as long as 10 years in some patients), osteonecrosis of the jaw was not reported among the adverse events. [11] The exact incidence of ONJ is unknown. However, some reports have estimated it to be about 1 in 10,000 for Intravenous use of BPs. [37] 1 in 100,000 patient years is a reasonable estimate of the incidence of osteonecrosis of the jaw in patients receiving oral nitrogen-containing bisphosphonates for osteoporosis. [11] The risk of developing ONJ for patients taking alendronate, the most commonly prescribed oral bisphosphonate, has been estimated to occur in approximately 0.7 per 100,000 persons per years' exposure [38]; on the other hand, the incidence of ONJ for risedronate and ibandronate cannot yet be quantified because too few cases have been reported (12 cases for risedronate and one for ibandronate). [38]

The Cartosos medical claims database study also surveyed 260,000 subjects with osteoporosis, and found an odds ratio for inflammatory necrosis of the jaw to be 0.65 in oral bisphosphonate users, and that for surgery for a necrotic process to be 0.86. [39] Both these values are consistent with the other data suggesting that oral bisphosphonate use does not increase ONJ risk in osteoporosis patients. These findings are very similar to those from a case-control study using a claims database, which found that receiving

at least one oral bisphosphonate prescription was associated with an odds

ratio for jaw surgery of 0.91. [40] As per one consensus panel, there have been 33 cases [reported] in the literature as of January 2007 -- out of the 33 million patients who have been treated worldwide with an oral bisphosphonate -- which translates into approximately 200 million prescriptions written. [41] In addition, there has been spontaneous reporting in 1 of 100,000 patient-years for all of the approved bisphosphonates. [41] The fact that the majority of reported cases of osteonecrosis of the jaw are associated with the use of high-dose intravenous

bisphosphonates for metastatic bone disease suggests that the dose, duration of treatment, and route of administration, as well as coexisting conditions, concomitant treatments (glucocorticoids or immunosuppressive agents), and dental health, could all be related to the incidence of this complication. [11]

Prevention and management of bisphosphonate-associated osteonecrosis of the jaw:

Published recommendations are based upon expert experience from a variety of sources. [35,36,1, 42–45] As yet, there have been no randomized, controlled trials that have evaluated strategies to prevent or manage ONJ in individuals receiving long-term high-dose bisphosphonate therapy. Before initiating BP therapy, all medical and dental practitioners are encouraged to follow these guidelines:

1. All patients should undergo a routine dental exam to rule out any dental source of infection.
2. All medical practitioners also should perform a baseline oral exam.
3. Invasive dental or/and oral surgical procedures should be completed before initiating therapy.
4. Practice preventive dentistry, involving procedures such as oral prophylaxis, dental restorations, and endodontic therapy, and check dentures for irritational foci.
5. Schedule routine follow-up every 3 months to check for any signs of developing ONJ.
6. The risks associated with oral surgical procedures such as dental implants, extractions, and extensive periodontal surgeries must be discussed with the patient and weighted against the benefits.

The following recommendations are made by the American Association of Oral and Maxillofacial Surgeons for management of patients on BP therapy and patients with proven ONJ. [46]

Management of patients with proven ONJ based on staging of the condition:

a. Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.

b. Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection.

c. Stage 3: Exposed/necrotic bone in patients with pain, infection, and 1 or more of the following: Pathologic fracture, extra oral fistula, or osteolysis extending to the inferior border.

Treatment of patients with established ONJ:

i. Patients with stage 1 ONJ: Conservative management with oral rinse such as 0.12% chlorhexidine.

ii. Patients with stage 2 ONJ: Manage with antibiotics and antimicrobial oral rinses.

iii. Patients with stage 3 ONJ: Surgical debridement/ resection in combination with antibiotic therapy.

Extraction of symptomatic teeth can be performed without any additional risks of worsening the condition.

General recommendations:

As with all dental patients, routine dental examinations are recommended. A comprehensive oral evaluation should be carried out of all patients about to begin therapy with oral bisphosphonates (or as soon as possible after beginning therapy). The dentist should inform the patient taking oral bisphosphonates that there is a very low risk (estimated at 0.7 cases per 100,000 person-years' exposure) of developing ONJ; there are ways to minimize the risk, but not to eliminate the already low risk; the consensus is that good oral hygiene along with regular dental care is the best way to lower risk; there are no diagnostic techniques to identify those at increased risk of developing ONJ.

Before undergoing any invasive procedure that involves manipulation of the bone the patient should understand that at this time, the risk of developing osteonecrosis of the jaw is considered very small, and that the vast majority of patients taking an oral bisphosphonate do not develop any oral complications. (Dental management of patients receiving oral bisphosphonate therapy: Expert panel recommendations)

Based on the currently available information, National Osteoporosis Foundation believes that in the vast majority of patient who are receiving them, the benefits of oral bisphosphonate medications outweigh the potential risk of ONJ. Patients for whom bisphosphonates are appropriate would be at higher risk of fractures without treatment, and fractures are the source of significant pain and disability that impact on function and quality of life. If a patient receiving bisphosphonates has planned dental surgery that involves the bone, a drug holiday beginning shortly before the procedure and lasting until there is local healing could be considered, although there is as yet no clinical evidence that this will affect the incidence or severity of ONJ. (Osteonecrosis of the Jaw (ONJ) June 14, 2006 / Reviewed and approved by the Science and Research Committee of the NOF Board of Trustees March 3, 2007).

Conclusion:

There is a need to clearly delineate the incidence of ONJ in osteoporosis patients treated with oral bisphosphonates, and in appropriate control populations. Based on current evidence, the risk of ONJ in osteoporosis patients taking oral BPs appears to be comparable to that in the general population. With the likely prevalence sitting at approximately 1 per 100,000 patient-years, it is quite clear that this is no different from that in the general population, since these problems can certainly occur in the absence of bisphosphonate use. The documented benefits of using bisphosphonates for established indications clearly outweigh whatever small risk of osteonecrosis of the jaw might be incurred. [11, 47] Even if the number of cases of ONJ in patients taking oral bisphosphonates are still rare compared to the total exposure, primary care physicians treating bone

diseases with bisphosphonates need to be aware there is a small risk their patients may develop this new complication, allowing for prophylaxis, early diagnosis and prevention of potential consequences. The benefits and risks of bisphosphonate therapy should be individually discussed and, when necessary and possible, alternative therapy for postmenopausal osteoporosis should be considered.

It is important to understand that, based on the information currently available; the risk for developing BON is much higher for cancer patients on intra venous bisphosphonate therapy than the risk for patients on oral bisphosphonate therapy. Therefore, there are different recommendations for dental management of these patients.

In conclusion, the risk of ONJ is extraordinarily low. The risk of being in a fatal car accident is 10-15 times as high as the risk of ONJ from taking an oral bisphosphonate. [41]

COMPETEING INTERESTS:
Serves as a speaker for Eisai Inc. and Pfizer Inc. for the 2008 ARICEPT LTC DELTA 2 (Dementia Education Leadership Training in Alzheimer's) Promotional Education Program

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Review Article

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Ventilator Associated Pneumonia – an Overview

Harshal Wagh and Devaraja Acharya

Summary
Ventilator Associated Pneumonia (VAP) is pneumonia occurring in a patient within 48 hours or more after intubation with an endotracheal tube or tracheostomy tube and which was not present before. It is also the most common and fatal infection of ICU. VAP increases length of ICU stay by 28% and each incidence of VAP is estimated to generate an increased cost of £6000- £22000.

The NICE in collaboration with NPSA is examining four technical patient safety solutions for the prevention of VAP. The Department of Health published a 'High impact intervention' for ventilated patients in June 2007. Eliminating or reducing the unnecessary use of antibiotics should be the primary goal in reducing antibiotic-resistant nosocomial infections.

Ventilator Associated Pneumonia (VAP) is defined as pneumonia occurring in a patient within 48 hours or more after intubation with an endotracheal tube or tracheostomy tube and which was not present before[1, 2]. Early onset VAP occurs within 48 hours and late onset VAP beyond 48 hours of tracheal intubation.

Incidence

Between 5-15% of hospital in-patients develop infection during admission to ICU[3]. Patients are 5-10 times more likely to acquire nosocomial infections than patients in the wards[4]and approximately 86% of hospital associated pneumonia is linked with mechanical ventilation[5].

Approximately 10-28% of critical care patients develop VAP[6]. VAP is also the most common and fatal infection of ICU[7,8] and in the United States it affects 9-27% of intubated patients and doubles the risk of mortality as compared with similar patients without VAP[9-13].

VAP may account for up to 60% of all Healthcare-Associated Infections[14]. VAP increases length of ICU stay by 28%[16] and each incidence of VAP is estimated to generate an increased cost of £6000- £22000[15].

Diagnosis

Despite the high incidence, diagnosis remains challenging because many conditions common to ICU patients like ARDS, sepsis, cardiac failure and lung atelectasis have similar clinical signs. More than 50% of patients diagnosed with VAP do not have the disease whereas upto one-third are not diagnosed[17, 18]. Unfortunately there is no clearly accepted gold standard for diagnosis of VAP[19].

Centres for disease control and prevention (CDC) national healthcare safety network definition for VAP

Radiology signs (2 or more serial chest x-rays with at least one of the following)
1)New or progressive and persistent infiltrate
2)Consolidation
3)Cavitation
Clinical signs
At least one of the following
1)Fever (temperature > 38 deg C with no other recognised cause)
2)Leucocytosis > 12000WCC/uL or leucopenia (<4000 WCC /uL)
2)For adults 70 years or older, altered mental status with no other recognisable cause
and at least 2 of the following
1)New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
2)New-onset or worsening cough, or dyspnoea or tachypnoea
3)Rales or bronchial breath sounds
4)Worsening gas exchange (eg. O2 desaturations [PaO2/FiO2 ≤ 240], increased O2 requirements, or increased ventilation demand)
Microbiological criteria (optional)
At least one of the following:
1)Positive growth in blood culture not related to another source of infection
2)Positive growth in culture of pleural fluid
3)Positive quantitative culture from bronchoalveolar lavage (≥104 colony forming units/ml) or protected specimen brushing (≥103colony forming units/ml)
4)5% or more of cells with intracellular bacteria on direct microscopic examination of Gram-stained bronchoalveolar lavage fluid
5)Histopathological evidence of pneumonia

Histological landmark of VAP is multifocal disease favouring dependant lung segments, often at different stages of development and severity with cultures growing heterogenous microbial flora.[20,21]

Risk Factors
Mechanical ventilation with Endotracheal intubation including Tracheostomy
Prolonged mechanical ventilation
Advanced age
Pre-existing sinusitis and lung disease
Micro or macroaspiration of oropharyngeal or gastric contents
Malnuitrition and immunosuppression
Obesity
Chronic lung disease

Several factors affect the aetiology of VAP
Time of onset of hospitalisation
Stress induced flora change
Antibiotic induced flora change
Exposure to contamination with nosocomial pathogens
Patient interventions

Pathogenesis:

VAP that occurs within 48 hours after tracheal intubation is usually termed as early onset often resulting from aspiration, which complicates intubation process[22]. VAP occurring after this period is late onset. Early onset VAP is often due to antibiotic sensitive bacteria (eg oxacillin-sensitive Staphylococcus aureus, Hemophilious influenza and Streptococcus pneumoniae), whereas late onset VAP is frequently caused by antibiotic resistant pathogens (eg.oxacillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa, acinetobacter species and enterobacter species) [23,24,25]

The pathogenesis of VAP usually requires that two important processes take place:

1. Bacterial colonisation of the aero-digestive tract
2. Aspiration of contaminated secretions into the lower airway[26].

Therefore, the strategies to prevent VAP usually focus on reducing the burden of bacterial colonisation in the aero-digestive tract, decreasing the incidence of aspiration or both.

The presence of invasive medical devices is an important contributor to the pathogenesis and development of VAP[27]. Many patients have nasogastric tubes that predispose them to gastric reflux and increase the potential for aspiration. Endotracheal tubes facilitate bacterial colonisation of the tracheo-bronchial tree and lower airway aspiration of contaminated secretions through mucosal injury, pooling of contaminated secretions above the endotracheal tube cuff and elimination of the cough reflex[26]. The ventilator circuit and the respiratory-therapy equipment may also contribute to the pathogenesis of VAP if they become contaminated with bacteria, which usually originate in the patient's secretions[26, 28].

Prevention:

The National Institute of Clinical Excellence (NICE) in collaboration with National Patient Safety Agency (NPSA) is examining four technical patient safety solutions for the prevention of VAP and in the process of publishing guidelines. The latest technical patient safety solutions for VAP was published in August 2008 which says

1. **Body position**-mechanically ventilated and intubated patients should be positioned with their upper body elevated for as long as possible. This may be inappropriate in some patients. eg. spinal injuries.

2. **Oral antiseptics** e.g. 2% chlorhexidine should be included as part of oral hygiene regimen for all patients who are intubated and ventilated. There is insufficient evidence to recommend any particular antibiotic regimen.

3. **Use of kinetic beds -** a lack of robust evidence meant the Committee was unable to make recommendations for action on the use of kinetic beds.

4. **Care bundles** - although the evidence supported the use of elements of care bundles; there was insufficient evidence to recommend a care bundle of any specific design.

The Department of Health published the following 'High impact intervention' for ventilated patients in June 2007

- Elevation of the head of bed to 35-40 degrees
- Sedation holding
- Deep Vein Thrombosis prophylaxis
- Gastric ulcer prophylaxis
- Appropriate humidification of inspired gas
- Appropriate tubing management
- Suctioning of respiratory secretions (including use of gloves and decontaminating hands before and after the procedure)
- Routine oral hygiene as per local policy

In addition the following also may contribute to the prevention of VAP

- Prolonged nasal intubation (more than 48hrs) should be avoided because of the association between nosocomial sinusitis and ventilator-associated pneumonia[29].
- Several investigations have suggested that secretions that pool above the inflated endotracheal tube cuffs may be a source of aspirated material and thus VAP. Endotracheal tubes with separate dorsal lumen above the cuff to suction pooled secretions from the subglottic space are now available. The pressure of the endotracheal tube cuff should be adequate to prevent the leakage of colonised subglottic secretions into the lower airway[26,30].

Antibiotic Administration:

Previous administration of antibiotics is an important risk factor for VAP because of the presence of antibiotic-resistant bacteria[31]. In an attempt to reverse the trend towards increasing rates of antimicrobial resistance among hospital acquired infections, more effective strategies for using antibiotics have been advocated that restrict antibiotic use or offer guidelines for their use [32, 33]. Eliminating or reducing the unnecessary use of antibiotics should be the primary goal in reducing antibiotic-resistant nosocomial infections[32].

The routine use of prolonged courses of empirical therapy i.e. therapy not supported by results of clinical cultures should be avoided to minimise the subsequent development of antibiotic-resistant infections.

The use of aerosolised antibiotics for the prevention of VAP has been abandoned because of its lack of efficacy and subsequent emergence of antibiotic-resistant infections[28].

Similarly the routine use of selective digestive tract decontamination has not gained acceptance in the UK and USA because of its lack of demonstrated effect on mortality, emergence of antibiotic resistant infections and additional toxicity. NICE is currently in consultation for selective decontamination of digestive tract guidelines. The technical patient safety solutions for VAP in adults were published in August 2008.

The Committee examined evidence, which suggested that selective decontamination of the digestive tract (SDD) using topical antibiotics may reduce the incidence of VAP and that SDD regimes that include systemic antibiotics may also reduce mortality. However, Specialist Advisers stated that UK intensive care specialists had particular concerns about the risk of infection with *Clostridium difficile* and the induction and/or selection of resistant, including multiresistant, microorganisms as a result of SDD. Therefore the Committee recommended further research into SDD in a UK setting.

Use of broad-spectrum antibiotics is also not recommended for the prevention of VAP because of increasing antibiotic resistance among subsequent hospital acquired infections. Targeted antibiotic therapy with appropriate dose of appropriate antibiotic is the sensible thing to do.

Vaccines:

Various vaccination programmes in adults and children have reduced the incidence of pneumonia caused by specific pathogens including H.influenzae type B, Streptococcus Pneumoniae and Influenza virus [34, 35].Vaccinations against these may prevent some hospital acquired infections. Pneumococcal and influenza vaccination must be considered before hospital discharge or included in the discharge planning for all patients at increased risk for subsequent respiratory infections including VAP.

Newer Developments:

There have been new advances in equipment and techniques to help prevention of VAP

3. Endotracheal and tracheostomy tubes with an extra subglottic port to clear pooled secretions above the endotracheal and tracheostomy tube cuff.
4. Continuous suctioning of the subglottic secretions.
5. Endotracheal tubes with specially designed cuffs that do not allow pooled secretions above the cuff to trickle down causing micro-aspiration and ultimately leading to VAP. eg. Endotracheal tubes with microthin polyurethane cuff.
6. Specially designed closed Tracheal Suctioning Systems (TSS) as compared to open tracheal suctioning systems. However a meta analysis of randomised controlled trial showed that closed suctioning system is not associated with a lower incidence of VAP or mortality as compared to open suctioning[36]

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Review Article

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Uncovering the face of racism in the workplace

Minal Mistry and Javed Latoo

"Racism at work - a crime in anyone's language" [1]

The Civil Rights Act 1964 remains of the greatest achievements in United States (US) history. It had implications internationally, making racial discrimination illegal, but its effectiveness in the employment domain remains contestable [2]. The worldwide existence of workplace racism has attracted controversy and this is drawn out by psychiatry's attempt to understand the nature of the problem [3]. Discrimination at work, based on a person's race, comes in different guises and can have negative consequences on both individuals and organisations [1]. Despite legislation to protect individuals substantial progress needs to be made to eradicate the problem.

What is racism?

The concepts of "race", "ethnicity" and "racism" are explained in figure 1.

Figure 1: Definition of race, ethnicity and racism [4, 5]	
Race	The group a person belongs to as a result of a mix of physical features, ancestry, and geographical origins, as identified by others or, increasingly, as self-identified. The importance of social factors in the creation and perpetuation of racial categories has led to a broadening of the concept to include social and political heritage, making its usage similar to ethnicity. Race and ethnicity are increasingly used synonymously.
Ethnicity	The group you belong to as a result of a mix of cultural factors that include language, diet, religion, ancestry, and race.
Racism	A belief that some races or ethnic groups are superior to others, used to devise and justify actions that create inequality between racial groups.

Racism is a *social process* associated with "overt and covert forceful establishment and maintenance of power by one social group over another" [3].

Racism can be seen as a misuse of power and, even today, power relations are signified by subtle cultural rules that perpetuate racial inequality [6].

What are the origins of racism?

That some races are superior to others has origins from the 19th century [5]. The history of racism has stimulated considerable debate in understanding racism.

Racism may have origins in experiences derived from, what is known in analytical psychology as, the collective and personal unconscious. The personal unconscious arises from the lifetime experiences of the individual. This is distinct from the "collective unconscious" which psychiatrist Carl Jung described to represent a form of the unconscious common to mankind as a whole and originating in the inherited structure of the brain [7]. This contains inherited primitive cultural and racial elements. Both the personal and collective unconscious, made from our individual and ancestral experiences respectively, may account for the manifestation of racism in society today.

In recent times the experience of overt racial bigotry and prejudice is seldom seen [8]. Nevertheless discrimination against members of a social group may persist because it is so deeply entrenched within society, by the personal and collective unconscious, that it becomes the automatic response even when no conscious intent is present [9]. "Everyday discrimination" is the discreet, pervasive discriminatory acts experienced by stigmatised groups on a daily basis [10], and highlights the modern perspective that racism is subtle.

The subtlety of racism

"Like a virus that has mutated, racism has evolved into a new form that is difficult to recognise and harder to combat" [8]

As blatant forms of racism become extinguished, particularly in the current climate of political correctness, unconscious racial biases in subtle forms, known as ambivalent or modern racism [10], are appearing. This has been referred to as *aversive racism* occurring in people who possess strong egalitarian values, and who believe they are not prejudiced, but have negative racial feelings and beliefs that they are *unaware* of [8]. These feelings and beliefs are rooted in the normal psychological processes of social categorisation, satisfaction of basic needs for power and control, and socio-cultural influences [8]. The ambivalence involving positive and negative feelings creates a psychological

tension that leads to an inconsistent pattern in their behaviour [8].

The cumulative effects of unpredictable and seemingly trivial behaviour such as avoidance of ethnic minorities, closed and unfriendly verbal and non verbal communication, and failure to provide assistance, is more damaging [10]. Apparently harmless interactions, including racist assumptions and questioning about where somebody is from, also convey messages about marginality and not belonging [11]. This subtle racism may contribute to the racism perceived by minority groups in higher status professions and organisations.

Does racism exist in healthcare organisations?

"American Medical Association apologizes for racism in medicine" (10th July 2008) [12].

This admission by the American Medical Association, of racial discriminatory practices against African-American physicians, reflects the recognition of racism in other western countries.

In the United Kingdom (UK) racism has been revealed in public institutions such as the metropolitan police [13] and widely reported in the nursing profession [14,15] within the National Health Service (NHS). Trevor Phillips, chairman of the Equality and Human Rights Commission, referred to the "snowy peaks of the NHS" [16] with a large number of ethnic minorities at the base. Less than 10% of senior managers and 1% of chief executives are from ethnic minority background [17]. There is a "glass ceiling" [18] preventing promotion and black and minority ethnic (BME) managers feel they have to work twice as hard and have twice as many qualifications to succeed [19].

Since 2000, after a survey commissioned by Department of Health (DOH) reported that half of front-line NHS BME staff had been victims of racial harassment in the previous 12 months [20], reports of racism in healthcare have increased. In 2001 a Kings Fund report, "Racism in Medicine" [21], generated powerful debate after finding that bullying and discrimination were a daily fact of life for black and Asian doctors. Then in 2003 a British Medical Association (BMA) survey revealed that in ethnic minority doctors, who form nearly one third of the NHS workforce [22], more than 80 per cent believed that their ethnicity had a negative effect on their career advancement [23]. In 2004 the Royal College of Psychiatrists accepted that racism existed in the NHS and in their own institution [24].

How does racism manifest itself in medicine?

"Discrimination can appear to be hidden when it is institutionalised, although it is not usually hidden from the person who is subjected to it" [3]

Institutional racism is "the collective failure of an organisation to provide an appropriate and professional service to people because of their colour, culture and ethnic origin" [13]. Health disparities among *patients* have been widely linked to racially biased discriminatory health practices [25, 26, 27] but how do structures, processes, and values within an organisation discriminate against those *working* in the medical profession?

There is considerable evidence to indicate that discriminatory practices against doctors evolved from medical school. For instance racial discrimination has operated at the time when students applied to study medicine [19, 28], through short-listing based on whether applications had Asian or English names [29, 30], and with downgrading of non-English names by computer [31]. Discrimination has also been reported *during* medical school in the US and Canada [11]. UK ethnic minority medical students also perform poorly in examinations compared to white students [32, 33] although the lack of evidence of explicit discrimination may suggest the involvement of more subtle communication styles and cultural differences [33].

If the problems at medical school are accountable by racial organisational processes it is not surprising that discriminatory practices persist after qualification (figure 2)

Figure 2: How BME doctors may experience racism [17, 19, 34, 35, 36]

Bullying and harassment	More likely to experience bullying and harassment.
Recruitment and career advancement	More likely to be over-represented in junior grades. Reduced promotion and career advancement also seen in relation to academic careers. Underrepresented in senior leadership positions.
Disciplinary hearings	Over-represented at disciplinary hearings with nearly a third of complaints coming form other health professionals.
Disciplinary action and dismissals	Six times more likely to be disciplined e.g. in 2006 two thirds of the 54 doctors struck off in UK had trained outside UK.
Reward systems	Disadvantaged in the allocation of discretionary grants and NHS distinction awards.

What are the consequences of racism in healthcare?

"Racial discrimination damages both those discriminated against and those doing the discriminating" [37]

The cost of workplace racism is that it acts as a chronic and acute stressor on the *individual* with a range of consequences (figure 3):

"Racial fatigue" characterises the potential emotional and psychological sequelae of feeling isolated in a work environment in which race regularly influences behaviour but is consistently ignored and nobody wants to discuss it ("racial silence") [40].

Racism may be underreported for the same reasons seen with workplace bullying: fear of making matters worse, belief that nothing will be done, concerns regarding confidentiality, fear of victimisation, and concern about being labelled as a troublemaker [41]. In addition the individual may fear being regarded as having a "chip on one's shoulder".

Figure 3: Consequences of racism on an individual [1, 10, 38, 39]	
Psychological	Poor well-being. Loss of confidence. Humiliation. Low morale. Gives a sense of thwarted aspirations.
Physiological	Increase blood pressure. Physical illness.
Behavioural	Bad work performance. Require time off work.

Organisations may also suffer with disharmony at work, high sickness levels, and resignation [1]. In medicine this results in the "double loss" of a speciality losing highly motivated people and gaining those where enthusiasm may be low [19]. In addition victims of racial discrimination in healthcare may pursue legal action. In 2003 a surgeon won over £600,000 [42] after being denied entry to the specialist registrar. Another surgeon successfully sued the BMA for more than £800,000 for racial discrimination after it failed to support his own claim against the DOH [43]. In another case a UK trust paid £2.5m, including legal costs, for wrongful dismissal of a consultant obstetrician who was investigating discrimination [44].

What can be done if you are experiencing racism at work?

In the UK there is protection by legislation. It is unlawful to discriminate against anyone on racial grounds. The Race Relation Act 1976 defined three types of discrimination (direct, indirect, and victimisation) [1, 45]. Following this was the setting up of the Commission for Racial Equality (CRE) in the UK to tackle racism and promote racial equality [45]. The Race Relations Act 1976 has now been superseded by the Race Relations (amendment) Act 2000 [46] that requires public bodies to eliminate discrimination, promote equal opportunities, and ensure good race relations. However legal processes are stressful and there are some steps you can take before pursuing this route (figure 4).

Figure 4: Steps to take if you are a victim of racial discrimination [1]
Talk to colleagues and friends who may have suffered a similar problem because it helps to share a problem and trying to cope on your own can be particularly stressful.
Keep a diary of events of who said what, when, circumstances and any witnesses – this will give a vital record of the nature of the racism.
Find out whether your employer has specific rules about racism at work or a grievance procedure you can use to raise a problem.
If you are in a union contact them to assist you with talking to management or approaching the perpetrator.
In the UK the Commission for Racial Equality is a national body that can help victims of racial discrimination.
Your local Citizens Advice Bureau or Law Centre may be able to help.
You may want to talk to a private law firm that specialises in discrimination issues.

Recommendations and Conclusion

"The law may be just but its implementation is another matter" [47]

Despite legislation and procedures, to address racism at work, healthcare organisations are slow in introducing and supporting the policies for race equality [18]. Suits come to legal action, not for a lack of policy, but because of not being enforced [48]. Practice is not synonymous with policy [19]. Reinforcement of policies depends on the degree to which upper management understands discrimination and harassment [48]. Although implementation of policies could be successful in combating *overt* racism this is not so for the *covert* form.

The covert form of racism, as in institutional racism where organisational processes are "unwittingly" enacted [13], suggests that racism is inevitable. Even people with strong motivations to avoid it are subject to automatic cognitive activation of stereotypes, which can unconsciously influence behaviour, making diversity training courses and non-discrimination policies relatively ineffective [10]. Attending to, and encouraging the reporting of, the "softer" aspects of racism may be the key to establishing a true "positively diverse climate" [10]. New forms of racism require new approaches (Figure 5):

Figure 5: The STEEP model to approaching subtle racism in organisations [8]	
Structured Support	Visibly supported by senior management.
Training and Education	Educate people about subtle bias and training to recognise it.
Experience	Frequent and constructive interracial contact to decrease bias, enhance group cohesion, and increase productivity.
Personal Commitment	Individuals must be committed to recognise and combat subtle racism.

The most important part of the solution is education. Teaching on racism should be incorporated into the undergraduate and postgraduate curriculum [19]. However of greater significance is recognising our own personal prejudices, at an early stage, so that prejudices we all harbour are challenged within ourselves.

"The hardest attitude to change is the one you don't know you have" [8]

KEY POINTS – RACISM:
Is associated with power and superiority
Has evolved from an overt to a covert form
Is commonplace in healthcare organizations
Is manifested at each stage of a doctors career
Has implications for individuals and organizations
Can be partly dealt with through policies and legislation
Requires a new approach to eradicate the problem

Useful UK online resources

- http://www.oneworkplace.co.uk - "One Workplace Equal Rights" aims to tackle racism and promote equal opportunities in the workplace.
- http://homepage.ntlworld.com/rajen/RacialEquality - Race Equality Ltd provides phone advice about racism in the medical establishment.
- http://www.bidaonline.org.uk - The British International Doctors Association protects and promotes the interests of Ethnic Minority Doctors and Dentists working in the UK.
- http://www.equalityhumanrights.com - A new commission working to eliminate discrimination, reduce inequality, protect human rights and build good relations.

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Original Article

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Laporoscopic Fundoplication: Not a simple wrap

Riaz AA, Kosmoliaptsis V and Meyrick-Thomas J

Abstract

Introduction

Laparoscopic fundoplication (LF) has been emerging as the procedure of choice for selected patients with symptomatic and problematic reflux disease. The aim of this study was to investigate post-operative complications associated with LF. Furthermore we wanted to look at the impact of a surgeons learning curve on post operative morbidity and investigate patient satisfaction after LF.

Methods

A single surgeon's series of 75 patients who underwent laparoscopic fundoplication were included in the study. The data was collected prospectively but analysed retrospectively. A satisfaction survey was performed with one to eight years follow-up.

Results

Laparoscopic fundoplication was associated with a learning curve. One of the major aims of the study was to record post-operative complications. Interestingly, post-operative dysphagia occurred in up to 40/75 of our patients. Our initial policy was to perform an OGD and dilate prophylactically; however, this was abandoned halfway through the study as it was found that the dysphagia settled in all patients with conservative management.

Conclusion

Our study confirms a real learning curve for LF. Furthermore, it has also clearly highlighted that post operative dysphagia is common and affects a significant number of patients. In our study we found that this was best managed conservatively.

Laparoscopic fundoplication (LF) has been emerging as the procedure of choice for selected patients with symptomatic and problematic reflux disease since the first described case by Dallemagne in 1991 (1). This was followed by a rapid expansion into routine clinical practice shortly afterwards. With increased acceptance and availability of laparoscopy as a safe surgical modality there has been a huge increase in the number of patients undergoing LF. This has probably been due to increased willingness of patients and referring doctors to consider the less invasive procedure, rather than the older 'open' surgical treatment, with its more rapid recovery, smaller incisions and earlier return to work and to normal daily activities.

Patient referral patterns have also changed over the last decade with the main indication for consideration of LF being patient choice, a general unwillingness to take long term medication as well as ineffective or intolerance of medications and relapse of symptoms (5-6). Several advantages of LF have been described by recent data including shorter hospital stay, less requirement for analgesia, and sooner return to work (7-9). These have to be offset against procedure specific complications including gastro-oesophageal perforation, pneumothorax, dysphagia, and bleeding (2-4). However, the other main downside to LF is the learning curve during which there are an increased number of complications. Previous reports have suggested the learning curve to be around 20 for an individual surgeon and 50 for an institution (10-12).

In a recent meeting of the Upper GI group at the Royal College of Surgeons there was discussion concerning the incidence and management of dysphagia following laparoscopic fundoplication (13 Bill Owen Day RCS (Eng) 2004). There is a paucity of data available in this regard with a general paucity of negative or unequivocal results in the literature equating to a selection bias towards only positive data and positive reporting of good results.

Therefore the aim of the present study was to look critically at the learning curve and, with respect to operative complications, with specific regard to the incidence and management of dysphagia in a personal series of patients who underwent a laparoscopic fundoplication in a District General Hospital in the United Kingdom.

Patients and Methods

From December 1997 to February 2004, 75 patients who underwent laparoscopic fundoplication under the care of a single consultant surgeon in a district general hospital were included in this study. It became routine practice for LF to be performed by one dedicated surgical team (JMT) who kept a complete prospective list of procedures. This series was complete and the hand written records of all the procedures were used to identify patients undergoing operations for LF with or without reduction and repair of Para-oesophageal hernia during the study period. These records were cross-checked with the theatre logbook, hospital computer system as

well as with the surgeon's own record. This ensured full inclusion in the analysis of patients.

The groups were not randomised and 'all comers' where included in the study. However, Group 1 consisted of the first 20 LF whereas Group 2 included LF (numbers 21-75). Informed consent was obtained in writing prior to surgery. At least a single dose of prophylactic antibiotics (of either a third generation cephalosporin or co-amoxiclav) was administered at induction; all patients received standard thromboprophylaxis (subcutaneous clexane, TEDS, intermittent pneumatic calf compression).

Patients underwent a laparoscopic fundoplication as briefly described below. The patient was placed in the lithotomy position with reversed Trendelberg tilt; a pneumoperitoneum was created and 4 ports inserted. The liver was elevated using a 'Nathanson' liver retractor placed through a 5 mm epigastric incision. Initially the right and left limbs of the right crus are dissected alongside the pancreaticogastric and phrenogastric ligaments. A window is created behind the distal oesophagus. A Penrose drain is passed through the gap. The short gastric vessels are divided using a harmonic scalpel (Ethicon, USA), if required. The crural limbs are approximated using 2, 2-0 ethibond sutures to leave a hiatus 1 cm wider than the oesophagus. A laparoscopic babcock is placed behind the oesophagus and the gastric fundus is brought left to right behind the oesophagus and bought round to meet with the remaining portion of the fundus anteriorly. Two (or rarely three) sutures of 2-0 ethibond were used for the fundoplication. The upper suture included a bite of the anterior hiatal margin to anchor the wrap. Of note, the important feature of the procedure is the creation of a 'floppy' tension free fundoplication. This is hugely aided by good mobilisation of the gastric fundus with its associated ligaments and if required, division of the short gastric vessels. Notably, one must carefully create a window behind the oesophagus and an overlap of no longer than 3 cms length and one must stay high up on the fundus in order to avoid the creation of a '2' compartment stomach syndrome'.

Post-operatively all patients were treated in an identical manner. As soon as tolerated after the operations the patients were allowed the consumption of water; diet and analgesia were made available as soon after surgery as required by individual patients. Complications were noted as they occurred during the follow-up period. Both general and specific complications were documented for at least 6 months. Furthermore, patient demographics, details of operations, all complications and follow-up data were kept. Follow up for the purpose of this audit involved completion of a proforma at a minimum post operative period of one year and a maximum of eight years.

All patients where regularly reviewed daily on the ward whilst they were in-patients and in the outpatients at 4-6 week intervals or sooner should the need arise by the surgical team. Thereafter they were given a "see on request" appointment. Data on patient and procedure related morbidity and acceptability was also collected.

At the time of the study contact was made via the telephone and a questionnaire was completed. A telephone survey asking the patient four questions,

1. Where they happy with the operation
2. Would they reccomend the procedure to a friend
3. Had there symptoms resolved
4. If they had had post op dysphagia had it resolved

The data was reviewed and analysed in conjunction with our department of medical statistics. Analysis was performed using the Mann-U test. Multivariate analysis of the means was performed using the Kruskal-Wallis Test.

Results

Overall the 75 patients who underwent laparoscopic fundoplication consisted of 44 males (59%) and 31 females (41%). The mean age was 47.0 years (range 22-80 years). Group 1, which consisted of the first 20 LF cases included 11 male and 9 females. The mean age was 53.25 years (range 32-80). Group 2, which consisted of the LF cases numbering 21-75 included 33 male and 22 females. The mean age was 44.8 years (range 22-78). Both groups were well matched across the above parameters with no statistical differences (Table A). Only 4 patients were obese (5%), smoker (n=10, 14%), 7 patients suffering with Hypertension (10%) and one with diabetes mellitus (2%) and were equivalently represented in both groups (data not shown).

Presenting features are shown in Table B. Notably, the commonest presenting complaints included regurgitation of acid/ food in 79% (n=59), heartburn in 73% (n=55) and pain and discomfort 53% (n=35). Other complaints included dysphagia 21% (n=16), cough/wheeze 19% (n=14) and excess salivation 18% (n=13).

Table A: Patient Demographics

	Group 1	Group 2	P value
Numbers	20	55	NS
Male: Female	9: 11	22: 33	NS
Age range (mean) yrs	32-80 (53)	22-78 (45)	NS
Operating time (median) mins	120-240 (190)	75-195 (144)	<0.05
Sliding/No sliding	11	44	NS
Type II/Type III hiatus hernia	9	11	NS

Patients underwent pre-operative evaluation with Upper GI endoscopy 88% (n=66), pH manometry 47% (n=35) and barium swallow 32% (n=24). Previous to this procedure all patients (100%) were on or had been during some part of their illness on therapeutic doses of proton pump inhibitors.

Table B: Presenting Features

	No. of cases
Regurgitation (acid/food)	59 (79%)
Heartburn	55 (73%)
Dysphagia	16 (21%)
Cough/wheeze	14 (19%)
Excess Salivation	13 (17%)
Nausea	10 (14%)
Epigastric pain	6 (8%)
TOTAL	173 (100%)

There was a significant difference between the operating times in the two groups. Thus in Group 1 the average operating time was 190 minutes (range120-240 minutes) whereas in Group 2 the average operating time was 144 minutes (range 75-195 minutes, $P < 0.05$).

Table C: Post Op Mild and Moderate Complications

	Cases (n=75)
Dysphagia	40
Regurgitation	7
Nausea	4
Diarrhoea	3
Heartburn	5
Excess Salivation	2
Portsite discomfort	6
Gas Bloat	4
Total	71

One of the major aims of the study was to record post-operative complications. Table C shows all mild and moderate complications which resolved completely with conservative management. Of note Table F shows that dysphagia occurred in up to 40 of our patients. Table F shows the distribution of dysphagia in both groups. In group A (n=20) the are 15 patients who complained with dysphagia (75%) of which 5 settled spontaneously and 10 required further investigation with OGD +/- dilation. in group B (n=55), 25 patients suffered with dysphagia all of which settled with conservative management. Our initial policy was to perform an OGD and dilate prophylactically; however, this was abandoned halfway through the study. It was found that the dysphagia settled in all patients with conservative management. Furthermore, other mild/moderate complications, of note included regurgitation of stomach contents (7/75) and port-site discomfort (6/75), all of which also resolved spontaneously

Table D: Major Complications Groups 1 & 2

	Group 1	Group 2	P value
PE	1 (5%)	0	NS
Pneumonia	1 (5%)	1 (2%)	NS
Oesophageal Perforation	1 (5%)	1 (2%)	NS
Stomach perforation	0	1 (2%)	NS
Pneumothorax	0	1 (2%)	NS
Major desaturation	0	1 (2%)	NS
TOTAL	3 (15%)	5 (9%)	NS

Major complications are shown in Table D. Of note there are three conversions to 'Open' surgery in Group 1 and five in Group 2 (Table E).

Table E: Conversion to Open Surgery

	Group 1(n=20)	**Group 2(n=55)**	**P Value**
Desaturation	0	1 (2%)	**NS**
Perforation viscus	1 (5%)	1 (2%)	**NS**
Pneumothorax	0	1 (2%)	**NS**
Technical (Obese/previous surgery)	2 (10%)	2 (4%)	**NS**
TOTAL	3 (15%)	5 (9%)	**NS**

In detail, four cases (two in each group) were converted early because of poor or very difficult access. They included difficulty in reducing the stomach and omentum from the mediastinum into the abdomen, unable to reach the hiatus despite placing the ports as high as possible, dense adhesions between the liver and stomach and G-O junction thereby leaving no access to the hiatus and simply impossible access to the upper stomach. Further, oesophageal perforation which was caused by intra-operative insertion of a nasogastric bougie (Group 1), this was repaired laparoscopically with no sequelae. Other reasons for conversions included perforation of the greater curve of the stomach due to the fact that there was thickened fatty tissue around the greater curve of the stomach and spleen which produced a perforation while dissecting the stomach free. Also in Group 2 there was one pneumothorax and in another patient there was marked desaturation on creation of the pneumoperitoneum and in both cases it was deemed safer to open the patient.

Table F: Dysphagia Group

	Group 1(n=20)	Group 2 (n=55)	P value
Dysphagia	15	25	NS
Resolved Spontaneously	5	25	<0.05
Investigated (swallow and OGD)	10	0	<0.05

Relaparotomy occurred in three patients; one developed severe pain and clinical shock at 24 hours and it was found on laparotomy to have a perforated oesophagus, the second patient we found disruption of the wrap (requiring re-operation and refashioning the wrap) and a final patient developed small bowel obstruction.

Finally a telephone survey at the conclusion of the study managed to contact 70/75 patients. It was found that overall 68/70 patients were satisfied with their procedure and would recommend the procedure to a relative or friend.

Discussion

Gastro-oesophageal reflux disease (GORD) is the commonest disorder of the Upper GI tract affecting approximately between 10-40% of most western populations and with rising incidence (11). In Australia it has shown to consume around 10% of the national expenditure on prescription drugs. Fortunately the majority of patients settle with simple measures including weight loss and reductions in smoking, caffeine and chocolate consumptions. Furthermore, better timing of meals as well as increasing the number of pillows and raising the head end of the bed can lead to improved symptoms. The advent of H_2-receptor antagonist (H_2RA) and later proton pump inhibitors (PPIs) has led to symptom control in the majority of patients. However, patients on maximum therapy who remain symptomatic or who develop complications (i.e. haemorrhage, oesophagitis, strictures) or those who refuse long term medication are deemed candidates for surgical intervention.

LF has emerged as the procedure of choice for GORD. The present study, which is a personal single surgeon series, shows that laparoscopic fundoplication is a safe and effective procedure with low rates of long-term complications. Importantly, post operatively these patients may develop dysphagia which settles with conservative measures in the vast majority of cases (13).

There is no doubt that for LF a 'learning curve' exists but there is debate about the actual numbers. Most studies suggest that it is around 20 for an individual and around 50 for a department (12), thus in the present study we compared our first 20 (classically thought to be within the learning curve) with the next 55 in order to assess major complications, conversions to open procedure. We found that in Group 1 there were 3 major complications (15%) whereas in the next 55 cases there were five (9%). Indeed only one major complication in Group 1 and two in Group 2 could be considered as technical, they were oesophageal and gastric perforations the rest being post operative pneumonia, PE and major desaturation. There were no deaths in either group. This was in keeping with previously published series (14-16).

Previously published data and our own observations revealed that there were significant post operative rates of dysphagia. In the present series dysphagia was the single commonest complication experienced by 53% of patients (n=40). Initially these were investigated with barium swallow and OGD and treated aggressively with early dilation (Group 1) however this strategy was abandoned after it was found that the vast majority of our patients resolved their dysphagia with conservative treatment. From thereon we adopted a very conservative approach reassuring the patient and keeping within close contact until the dysphagia resolved. We reserved dilatation for only highly resistant dysphagia or patients who where non-compliant with conservative treatment. We found that clear explanations pre-operatively, regular reassurance and assessment was generally all that was required. In Group 2 (21-75) none of the patients required dilation for dysphagia. It is almost universal that patients undergoing LF will have a degree of dysphagia. However what is now accepted and reflected from the experience from the present study is that dysphagia after LF should only cause concern if severe, presenting with severe pain, uncontrolled retching and vomiting requiring immediate surgical revision (17). Most commonly this is due to over-tightening of the hiatus or with poor mobilisation and a 360 degree wrap. This may be related to the learning curve, being more common in the earlier cases in a personal series. In our series 53% of patients (n=40) experienced dysphagia. This is comparable to previous reported data (2,16). Notably, Fontaumard et al reported a dysphagia rate of 78% (40/51). The reason for this post operative dysphagia has been thought to be related to the type of procedure. In our series all patients underwent a Nissen type of repair however evidence is now emerging that the incidence of dysphagia and gas related complications are reduced following anterior partial fundoplication (19,20). This is shown from the data of two recent randomised controlled studies. Baigrie et al (18) in a double-blind, randomized study compared laparoscopic Nissen total fundoplication and anterior partial fundoplication. There were no differences in mean heartburn scores between groups but dysphagia scores for both liquids and solids were lower after anterior fundoplication. Also Ludemann et al (19) compared total fundoplication for gastro-oesophageal reflux disease with an anterior 180 degrees partial fundoplication. Both achieved effective reflux control but the partial wrap was associated with fewer side-effects in the short term than total fundoplication. After 5 years, dysphagia, measured by a visual analogue score for solid food and a composite dysphagia score, was worse at 5 years after total fundoplication.

Our study confirms what has previously been shown with the learning curve for LF and its acceptability. It has also clearly highlighted that post operative dysphagia is common and affects a significant number of patients post operatively. However in our study we found that this was best managed conservatively and the almost all resolved spontaneously. There is no evidence to support early intervention unless the symptoms are very severe and occur very soon after surgery, when the patient should be taken back to theatre for another look. The specific causes of the dysphagia are not known but it is postulated that it is due to increased pressure as the upper part of the wrap augments the pressure of the lower oesophageal sphincter causing it to become over competent. Over time this mechanism relaxes leading to an improvement in dysphagia with simple conservative therapy. Furthermore, there was a hugely positive satisfaction score on a simple telephone survey suggesting symptom control from this procedure.

COMPETING INTERESTS
None Declared

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Original Article

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Comparative Evaluation of Four Hepatitis B vaccines available in Pakistan: Reactogenecity and Immunogenecity

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Abstract

Aim: Main objective of this study was to evaluate the immunogenicity of hepatitis B vaccines commonly available in the Pakistan's market. For this purpose we compared immunogenicity and reactogenicity of four recombinant hepatitis B vaccines in apparently healthy young female volunteers in Karachi.

Introduction: Today most of the world's people recognize the importance of vaccination and more than 80% of the world children are now immunized against diseases covered by EPI (expended program on immunization). The Hepatitis B vaccines have been available since 1982 and more than one billion doses have been used. Approximately 100 countries, consistent with World Health Organization policy, have added HB vaccination to their routine childhood immunization programs. Infect many developing countries have scored astonishing success in controlling communicable diseases through mass vaccination and environmental sanitation.

Materials and Methods: A total of 243 apparently young healthy female students of two Universities of the city were included in this study performed during Jan 2003 to Jan 2006, after receiving written informed consent. Four recombinant yeast derived HB vaccine were used as test regimens i.e. Euvax-B (LG Chemicals Ltd., Korea), Heptis-B (Boryang, Korea), Amvax-B (Amson, Pakistan) and Engerix-B (GS & K, Belgium). Participants were injected with the vaccine of their own choice. Information broachers of the four vaccines were distributed among participants to help them make a choice. anti-HBV antibody titres were recorded using EILSA (IMX-ELISA, Abbott).

Results: A total of 243 HBV and HCV negative individuals came forward with the interest for immunization with the Hepatitis B vaccine of their own choice. Out of total 729 doses administered to 243 individuals during this study (Jan'2003 – Jan'2006)……, 195 were of Engerix-B, 420 were Heptis-B, 75 were Amvax-B, and 39 doses were of Euvax-B. Among these four candidate vaccines Engerix-B came up with the least adverse effects, Euvax-B and Heptis-B showed moderate level of side effects, while Amvax-B showed maximum level of side effects. Although, none of these vaccines showed very sever type of adverse effects like demylination or central nervous system disorders during last 05 years period, except soreness, indurations, swelling, redness, mild pain, granuloma formation, and mild fever at the time of injection or just after injecting the vaccine, which was recovered within couple of hours.

Conclusion: Overall serum protection rate achieved in case of Engerix-B was 95.9%, in case of Euvax-B, it was 95.2%, in case of Heptis-B was 95.0% , and in case of Amvax-B it was 95.1%, which fulfils the WHO requirements for a hepatitis B vaccine (i.e. seroprotection rate of > 95%), P values observed were lesser than 0.05 indicating significance of the vaccines and good safety profile in subjects.

Key Words: Sero protection, Mass Immunization, HBV, Reactogenecity, Immunogenecity

Hepatitis B is one of the world's major health problems [1]. By recent estimates, worldwide more than 2 billion people have been infected with hepatitis B virus (HBV) globally and more than 350 million have chronic (long term) liver infections[2]. The infection is supposed to be causally related to 1 to 2 million deaths per year worldwide [3]. Hepatitis B is a blood borne infection that is transmitted 1) by an infected mother to the newborn, 2) by contact with infected blood through unsafe injection, transfusion, open wounds, and sharing toothbrush or razors, and 3) by unprotected sex. Approximately 90% of newborns infected with HBV develop chronic infection, whereas 30-50% of children under age 5 years, 10% of adolescents aged 15 years, and 2-5% of older individuals develop chronic infection [4,5].

In Pakistan, it is Hepatitis (B & C) not Human immuno deficiency virus (HIV) that is the most common serious viral infection. Number of hepatitis B carriers in Pakistan is estimated at around seven million [4] that is about 5% of the world wide 350 million carriers of hepatitis B [5]. Unlike HIV, there was no large-scale national awareness campaign to educate the public and healthcare professionals in Pakistan about these infections before 2006, but now a comprehensive national strategy that will lead to the elimination and control of hepatitis B is becoming a top public health priority in Pakistan after inclusion of HBV immunization in government's expanded Program for Immunization (EPI). The World Health Organization (WHO) Assembly endorsed the recommendation of its Global Advisory Group that all countries should implement a hepatitis B immunization program [6]. The threat of HBV to the health of the nation is frequently under-recognized by epidemiologists, policy makers and the public because unlike the influenza virus, it is often not the acute infection that makes people sick, but the consequences of chronic HBV infection that occurs after 20-30 years. Fortunately, hepatitis B is a vaccine preventable disease, global eradication is therefore possible if everyone worldwide receives the HBV vaccine before they become infected. Despite advances in antiviral therapy, only a minority of patients with chronic hepatitis B will have a sustained response. Thus, primary prevention by vaccination to

increase herd immunity remains the main thrust in the control of HBV infection.

The development of hepatitis B vaccine is considered to be one of the major achievements of modern medicine. Three different classes of hepatitis B vaccine are available based upon how they are derived (from plasma, yeast, or mammalian cells).The first generation HBV vaccine was prepared by concentrating and purifying plasma from Hepatitis B surface antigen (HbsAg) carriers to produce 22 nm sub viral particles, which contain HBsAg alone. Derivation from plasma has left lingering concerns regarding the potential to transmit blood-borne infections, although this vaccine has excellent efficacy and safety [7]. Yeast-derived recombinant HBV vaccines were first introduced in the mid 1980s. They are produced by cloning of the HBV-S gene in yeast cells. These vaccines contain non-glycosylated HBV small S protein as the envelope antigen which must be released from the yeast during the manufacturing process [8]. These vaccines do not contain antigens of the pre-S regions. The third class of HBV vaccine is the mammalian cell-derived recombinant vaccine. Three vaccines of this class have been developed. In addition to the S antigen, one of these contain antigen from the pre-S2 region while the other two contain antigens from both the pre-S1 and pre-S2 regions [9]

The efficacy of universal immunization has been shown in different countries, with striking reductions of the prevalence of HBV carriage in children, most importantly; the HBV vaccine can be considered the first successful anti-cancer vaccine, as 20 years of mass vaccination has clearly reduced the incidence of hepatocellular carcinoma in children, at least in Taiwan [10]. Currently available hepatitis B vaccine in Pakistan's market are genetically engineered DNA recombinant vaccines and the recommended series of three intramuscular doses of hepatitis B vaccines induces a protective antibody response (anti-HBs > =10 milli-international units {mIU/ml}) in > 90% of healthy adults and in >95% of infants, children and adolescents [7, 11].

A vaccine consists of many parts, only one of which is the antigen by which it is known. Other components of the presentation may include, for instance, an adjuvant, a preservative or other ingredient. There may be components not stated on the information sheet that are classified as proprietary and therefore the manufacturers are not obliged to declare them. Thus, the effect the vaccine has, on an individual may be influenced in various ways by each and all of these components. Preservatives are just one of a number of additives to vaccines that are carefully regulated and which come under special scrutiny from time to time [12]. Several case reports raised concerns that hepatitis B (HB) immunization might be linked to new cases or reactivation of multiple sclerosis, could shift the immune system toward an auto-immune direction, or may cause central nervous system (CNS) demyelinating diseases etc [13, 14, 15, 16]. The present study sought to compare the safety of four hepatitis B vaccine regimens available in Pakistan's market, in apparently healthy young females, and to determine the sero-response (i.e. reactogenicity and immunogenicity) to these vaccine in the same group of volunteers.

MATERIALS AND METHODS:

Study Duration: Jan 2003 to Jan 2006

Study Design: Prevention, Open Label, Dose Comparison, Parallel Assignment, Safety/Efficacy Study.

Subject: A total of 243 apparently young healthy female students of two Universities of the city were included in this study.

Informed Consent: Prior to immunization, all volunteers were requested to give written informed consent to participate in this study. The volunteers were also advised that they are free to withdraw from the study at any time without any obligation to disclose her reason (s) for so doing.

Criteria For Inclusion In The Study: All volunteers after submitting their signed consents were subjected to selection criteria on the basis of health checkups by a medical doctor to record the various factors including:

a) Age: 18 – 30 years, b) History of Jaundice, blood transfusion, exposure to syringe, surgical and dental,

c) Weight: > 45 Kg, d) Body Temperature: 96 – 98°F, e) Hemoglobin: > 10 g/ dl, f) Blood Pressure: Systolic 100 – 180 mm of Hg, Diastolic: 60 – 100 mm of Hg, g) Pulse rate: > 65/min.

After qualifying for inclusion in this study, volunteers were asked to give 10 cc of blood sample for different hematological (CP i.e. complete blood picture and Hb% i.e. hemoglobin percentage by Sysmex blood analyzer & ESR i.e. erythrocyte sedimentation rate by Westergreen method), and Biochemical analysis (Direct Bilirubin, Indirect Bilirubin, ALT, AST and, Alkaline phosphatase by MicroLab- Merck chemistry analyzer), this data was used to keep the record of health status of participants and its comparison with adverse effects if appeared. Screening for HBs antigen, anti HBs antibodies and HBc IgM antibodies by Immunochromatography (ICT, Australia and Abbott, USA) and confirmation by enzyme linked immunosorbent assay (IMX ELISA - Abbott, USA) was also done before first dose of immunization.

Test Vaccines: Four recombinant yeast derived HB vaccine were used as test regimens i.e. Euvax-B (LG Chemicals Ltd., Korea), Heptis-B (Boryang, Korea), Amvax-B (Amson, Pakistan) and Engerix-B (GS & K, Belgium). To avoid complications related to multi dose vials, it was strictly followed that the vaccination dose for each subject should be company packed, individually in a sealed container and, formulated for intra muscular injection. The dosage vial should contain same amount i.e. 20 µgm/ ml of HBs Ag absorbed on to approximately 0.5 µgm / ml adjuvant (aluminum hydroxide) and 100 µgm / ml preservative (Thiomersal/ Thimerosol) in a final volume of 1.1 ml (1 dose/ vial). Storage temperature should maintain as 2°C to 8°C to ensure integrity. Participants

were injected with the vaccine of their own choice. Information broachers of the four vaccines were distributed among participants to help them make a choice. Out of total 729 doses administered to 243 individuals during this study, 195 were of Engerix-B, 420 were Heptis-B, 75 were Amvax-B, and 39 doses were of Euvax-B.

Categories for Determining Severity of an Adverse Effect:

- Local Symptoms: Soreness, indurations, swelling and redness.
- General Symptoms: Fever, headache and dizziness.
- Mild: Adverse events easily tolerated
- Moderate: Adverse event of sufficient discomfort to interfere with daily activity or requiring simple treatment (e.g. Paracetamol, Generic name: Paracip).
- Severe: Adverse event incapacitating and preventing usual activity or which may be life threatening, requiring hospitalization or completed treatment.

The course of an adverse event was described as:

- Spontaneous recovery without discontinuation of vaccination
- Recovery after discontinuation of vaccination
- Continuation of recovery after symptomatic treatment

Eight samples of Peripheral blood (2-3 ml) were taken from all vaccinees before administration of each dose, and at different intervals after completion of immunization as per schedule given below; the sera were collected and stored at - 20°C.

Table 1: Visits Were Scheduled As Follows:

	Vaccination number & sample collection
1.	First sample Before 1st dose of Vaccine (Jan, 2003)
2.	Second sample Before 2nd dose of Vaccine (Feb, 2003)
3.	Third sample Before3rd dose of Vaccine (June, 2003)
4.	Fourth sample After 6 months of 3rd dose (Dec, 2003)
5.	Fifth sample After 15 months of 3rd dose (Sep, 2004)
6.	Sixth sample After 19 months of 3rd dose (Jan, 2005)
7.	Seventh sample After 22 months of 3rd dose (May, 2005)
8.	Eighth sample After 30 months of 3rd dose (Jan, 2006)

Antibody Estimation and Statistics:

Anti-HBs were detected by ELISA using IMX- Abbott and quantitated using appropriate dilution of a positive sample with a known concentration of anti-HBs expressed as IU/L, provided by the manufacturer. The assay determined IgG type of anti-HBs antibody and the protective level of antibody was considered >10 IU/L. *P* values of less than 0.05 were considered significant. On the whole Hepatitis B antibodies titer was determined in participants using five standards i.e. <10 IU/ml, Between 10 – 100IU/ml, Between 100 – 1000 IU/ml, >1000 IU/ml, and no response or no antibody titer for the period of 36 months starting Jan'2003 till Jan' 2006.

RESULTS:

Percentage of Geometric mean titer (GMT) of antibodies below 10 IU/ml was in between 0.0% to 0.22% in case of Engerix-B, 0.0% to 0.20% in case of Euvax B, 0.0% to 0.30% in case of Amvax-B and 0.0% to 0.25% in case of Heptis-B. Percentage of GMT of antibodies between 10 – 100 IU/ml was in between 0.0% to 10% in case of Engerix-B, 0.0% to 9% in case of Euvax B, 0.0% to 8.9% in case of Amvax-B and 0.0% to 9.3% in case of Heptis-B. Percentage of GMT of antibodies between 100 – 1000 IU/ml was in between 0.0% to 35% in case of Engerix-B, 0.0% to 30.1% in case of Euvax B, 0.0% to 39.3% in case of Amvax-B and 0.0% to 40% in case of Heptis-B. While, Percentage of GMT of antibodies above 1000 IU/ml was in between 0.0% to 23% in case of Engerix-B, 0.0% to 25% in case of Euvax B, 0.0% to 26% in case of Amvax-B and 0.0% to 23.7% in case of Heptis-B. When Percentage of GMT of negative response was calculated we found that on the whole Engerix-B showed no response after 6 months of 3rd dose in 0.9% recipients leading towards no response in 31.78% of recipients after 30 months of 3rd dose. Euvax-B showed no response after 6 months of 3rd dose in 7.9% recipients leading towards no response in 35.68% of recipients after 30 months of 3rd dose. Amvax-B showed no response after 6 months of 3rd dose in 11.6% recipients leading towards no response in 25.5% of recipients after 30 months of 3rd dose. While, Heptis-B showed no response after 6 months of 3rd dose in 9.88% recipients leading towards no response in 26.75% of recipients after 30 months of 3rd dose. Period after 6 months of 3rd dose and before 15th month of 3rd dose was the period when highest Percentage of GMT of anti- HBs was observed .

Local and generalized adverse effects observed during and after the immunization of volunteers were recorded separately for each vaccine (Table 2, 3, 4 & 5).

Table 2 Incidence of Local and/or Generalized Symptoms on Vaccination With Engerix-B

Dose	Total	Local Only		General only		Local & General		With symptoms	
	n	n	%	N	%	n	%	n	%
1	65	19	29	5	8	10	15	38	58
2	65	11	17	3	5	7	11	29	45
3	65	8	12	0	0	0	0	18	28
Total	195	38	19	8	4	17	9	85	44

Table 3 Incidence of Local and/or Generalized Symptoms on Vaccination With Euvax-B

Dose	Total	Local Only		General only		Local & General		With symptoms	
	n	n	%	n	%	n	%	n	%
1	13	4	31	2	15	3	23	8	62
2	13	2	15	1	0	2	15	6	46
3	13	2	15	0	0	0	0	0	0
Total	39	8	21	3	8	5	13	14	36

Table 4 Incidence of Local and/or Generalized Symptoms on Vaccination With Heptis-B

Dose	Total	Local Only		General only		Local & General		With symptoms	
	n	n	%	n	%	n	%	n	%
1	140	53	38	10	7	34	24	95	68
2	140	25	18	25	18	27	19	70	50
3	140	22	16	7	5	32	23	84	60
Total	420	100	24	42	10	93	22	249	59

Table 5 Incidence of Local and/or Generalized Symptoms on Vaccination With Amvax-B

Dose	Total	Local Only		General only		Local & General		With symptoms	
	n	n	%	n	%	n	%	n	%
1	25	13	52	8	32	3	56	23	92
2	25	2	8	6	24	4	16	9	36
3	25	14	56	3	12	25	100	12	48
Total	75	29	39	17	27	32	43	44	59

As Shown in Table 6 that one month after the first dose, 180/243 subjects (74.45%) had seroprotection with respect to anti-HBs. One month after the second dose, 189/243 subjects (77.92%) showed seroprotection, four months after second dose, at month 6, 224/243 subjects (92.43%) were seroprotective. After 15 months of 3rd dose 231/243 subjects (95.27%) showed maximum seroprotection level in the immunized women. Later on seroprotection level was determined after 19, 22 and 30 months of 3rd dose. 170/243 subjects (70.08%) subjects were seroprotected even after 30 months of 3rd dose without having any booster dose.

Table 6: Over All Seroprotection Levels and Geometric Mean Titers (GMT) of Anti- HBs Antibodies

	Timing	N	S^+	% of S^+	GMT	Range of Anti HBs Titer
PRE	Before Vaccination (Jan, 03)	243	0	0	0	0
M1	Before 2nd dose (Feb, 03)	243	180	74.45	16	0-50
M2	Before 3rd dose (June, 03)	243	189	77.92	143	1-700
M3	After 6 months of 3rd dose(Dec, 03)	243	224	92.43	18500	45-50000
M4	After 15 months of 3rd dose(Sep, 04)	243	231	95.27	23000	40-50000
M5	After 19 months of 3rd dose(Jan, 05)	243	222	91.57	12100	39-33000
M6	After 22 months of 3rd dose(May, 05)	243	195	80.53	1875	5-17000
M7	After 30 months of 3rd dose(Jan, 06)	243	170	70.08	690	1-1500

Comparative results of serum protection analysis of 04 candidate vaccines determined after 15 months of third dose without giving any booster dose, were found effective in healthy young female volunteers, demonstrating induction of very good immunogenicity. No significant differences were observed in seroprotection level of test vaccines (Table7). Overall serum protection rate achieved in case of Engerix-B was 95.9%, in case of Euvax-B, it was 95.2%, in case of Heptis-B was 95.0% , and in case of Amvax-B it was 95.1%. Calculated P values for all four test vaccines were lesser than 0.05 indicating significance of the used vaccines.

Table 7: Comparative Serum Protection analysis of 04 different Hepatitis-B Vaccines(n= 243; mean age= 21.5+3.7 Years)

Name of Vaccine	Mean Serum Protection Level 10µgm x 3	95% Confidence Level	P Value
Engerix-B (n=65)	95.9%	94.5% - 100%	<0.05
Euvax-B (n=13)	95.2%	94.3% - 100%	<0.05
Heptis-B (n= 140)	95.0%	92% - 99.4%	<0.05
Amvax-B (n= 25)	95.1%	92% - 98%	<0.05

DISCUSSION:

As yet no such immunogenicity trials have been conducted in Pakistan or risk factors indigenous to the region assessed for any of the vaccine being utilized at the population level for such long period. Our study, is one of the longest study, conducted between Jan'2003 and Jan' 2006, which includes total 243 healthy women subjects of child bearing age group. In this study we have demonstrated that there is no significant difference in reactogenicity and serum protection level among all four candidate vaccines we tested here, excellent immunogenicity of vaccines in volunteers recommends their usage for immunization purpose among different communities without having any doubts related to reactogenicity and side effects.

Recombinant hepatitis B vaccines have long been used for protection in the serum of and three doses have been shown to produce Anti HBs in the serum of approximately 95% of people who have not encountered the virus. The antibody response declines with increasing age. Patients older than 30 years have an increased risk of no response to HBV vaccine, as compared with younger persons [17]. Thus, immunization during childhood or adolescence offers the greatest potential for protection [17] and provides lifelong immunity. Ninety percent of healthy adults and 95 percent of infants, children, and adolescents have protective serum anti-HBs antibody concentrations after the vaccine series has been completed [18].

Two kinds of recombinant vaccine are used for active immunization against hepatitis B; one of them contains the PreS1 and PreS2 antigenic domains while the other kind contains S and PreS polypeptide. No important differences between the effectiveness of these two types of vaccine have been detected [19]. In a series of studies it has been demonstrated that 90-99% of healthy neonates, children, adolescents and adults develop protective levels of anti-HBs antibody following a standard vaccination course with hepatitis B vaccine [20, 21, 22, 23, 24, 25].

Efficacy of vaccines in the field have been measured long after the vaccine have been introduced at large scale population levels and only selected countries have record keeping such as the Centers for Disease Control in USA and the National Health Services in UK. Most developing countries do not have infra structure to support these activities and therefore the efficacy and risk indigenous to the population remains unknown.

Procurement and delivery of high-quality vaccine has national and international public health and 'public good' implications far beyond the scope of most products. People immunized with vaccines of inadequate quality can become ill and die from the disease that the vaccine should have prevented. Even more lives are placed at risk if vaccination coverage declines as a result of reduced public confidence in immunization programs. If we look at the outcome of immunization programs in different countries then we will have a good idea that how mass vaccination helped in reduction of disease burden?[26]

Importance of dose size, number of doses and dose response is another important issue related to immunization programs. Published studies regarding the dose-response relationship in terms of immunogenicity and sero-protection are highly varied. Chiaramonte *et al* [27] reported that the sero-protection reached a level of 99.6% within one month after primary immunisation with the recombinant hepatitis B vaccine. The findings of Assateerawatt *et al*[28] and Just *et al* [29] also were the same. Baldy JLS *et al* carried out a comparative study with three recombinant hepatitis B vaccines, one Brazilian *(*Butang, Instituto Butantan) and two Korean vaccines *(*Euvax-B, LG Life Sciences Ltd. and Hepavax-Gene, Green cross Vaccine Corp.), administered intramuscularly to students aged 17to19 years in three doses (corresponding to half the amount of antigen routinely used for adult vaccination) at intervals of one month between the first and second dose, and of four months between the second and third dose. The GMT of anti-HBs induced by the Euvax-Band Engerix-B vaccines were higher than those obtained with the Butang vaccine ($p < 0.05$); this difference was not significant when comparing the other vaccines two-by-two. No spontaneous adverse effects attributable to the application of any dose of the three vaccines were reported [30].

Vaccine efficacy is defined as the reduction in the incidence of a disease among people who have received a vaccine compared to the incidence in unvaccinated people. The efficacy of a vaccine is measured in clinical trials by giving one group of people a vaccine and comparing the incidence of disease in that group to another group of people who do not receive the vaccine. In our study overall efficacy of the vaccines used was satisfactory, without producing sever adverse effects, also there is no report of incidence of disease till now, in those who were vaccinated during this study(Table 2, 3, 4, 5).

Maximum protection level in terms of immunogenicity was observed in Euvax-B, which showed GMAT of 35.68% in test population. Engerix-B showed GMAT of 31.78%, Heptis-B showed GMAT of 26.75% and, Amvax-B showed GMAT of 25.5% after 30 months of 3rd dose of immunization While highest serum protection level was achieved in case of Engerix - B i.e. 95.9%. On the whole, r-hepatitis B vaccines showed high immunogenicity and good safety profile in the test population.

The inclusion of Hepatitis B in the list of compulsory and Extended Program for Immunization (EPI) in Pakistan since 2005 will result in mass vaccination of pediatric population. However, a big chunk of the adult population, especially healthcare workers, also needs to be immunized against Hepatitis B infection. We believe that all of the above mentioned HB vaccines, which are easily available in Pakistan's market can be used for these mass vaccination programs without having any doubts related to Reactogenecity and Immunogenicity.

CONCLUSION:

In conclusion, this prospective study reinforces that the four different recombinant hepatitis B vaccines licensed in Pakistan have a good tolerability and are highly immunogenic among young women. It is also recommended that government should ensure the serosurvey of HBsAg and vaccine coverage at country level in order to reduce the disease burden on country's economy.

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COMPETING INTERESTS
None Declared

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Original Article

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Mental illness and comorbid insomnia: a cross- sectional study of a population of psychiatric in-patients

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Abstract

Aim : To investigate the self-reported quality of sleep in a population of psychiatric in-patients and to explore any associations between sleep quality and clinical and demographic factors.

Method : This was a cross-sectional survey of 46 psychiatric-disordered patients' self-reported quality of sleep on the acute adult wards at a London psychiatric hospital (the Highgate Mental Health Centre) using the Pittsburgh Sleep Quality Index (PSQI). Relevant demographic and clinical parameters were obtained concurrently by review of medical records.

Results: There was a high prevalence (78%) of subjects categorised as "poor sleepers" (defined as a global PSQI score of 5 or more). Subjective good quality sleep was associated with formal detainment in hospital (under Section 3 of the Mental Health Act (1983) (p=0.01). No statistically significant associations were found between other clinical or demographic variables to distinguish between good and poor sleepers. There was a statistically significant difference the two groups for all PSQI component scores and global scores.

Conclusion: This study represents the first attempt to examine the degree of self-reported sleep quality among a population of psychiatric in-patients in a UK hospital. Results indicate that poor subjective sleep quality is a common finding, suggesting the need to improve strategies to manage sleep-related problems on the ward. Further studies are needed to replicate these results and to derive comparisons from a suitable patient population control group.

The significance of disturbed subjective sleep quality in the general population is important because of high prevalence rates (of up to 30%)[1] and the association with decreased quality of life.[2] Poor sleep affects cognitive and physical functioning, and insomnia is associated with a greater risk of falls and accidents,[3] higher rates of absenteeism[4] and increased health care utilization.[4]

Insomnia is commonly encountered in primary and secondary care settings, and can be symptomatic of many medical, neurological, substance abuse or primary sleep disorders.

Epidemiological and clinic-based studies consistently demonstrate high rates of psychiatric comorbidity.[5,6] Sleep disturbance is an important clinical construct in psychiatry. It represents formal diagnostic criterion in mental illnesses such as affective and anxiety disorders.[7,8]

Insomnia is broadly defined as the subjective experience of poor or unrefreshing sleep, with some objective evidence of reduced time asleep or delayed sleep-onset. The *subjective* nature of such complaints remains key, because sleeping is a private event, and there is often no informant history. Furthermore, it is the perceptual aspects of sleep that influence patients' help-seeking behaviour, such as consultation requests, demands for night sedation, and medication and substance use. It is noteworthy that despite the wide-ranging implications and subjectively distressing nature of this phenomenon, it remains arguably one of the least satisfying symptoms to treat. Seeking a better understanding of the extent and nature of patients' sleep perception can help optimise appropriate therapeutic strategies.

This is the first study assessing the subjective sleep quality of a sample of psychiatric disordered in-patients in a UK psychiatric hospital setting, using the Pittsburgh Sleep Quality Index (PSQI).[9] This study is framed in the context of increasing the awareness of the significance of patients' complaints of insomnia and addressing the wider psychosocial issues that this raises.

Method

Design: This was a cross-sectional survey of the self-reported quality of sleep in a population of psychiatric in-patients on the acute adult wards of a London psychiatric hospital.

Participants and Procedure: Participants consisted of psychiatric in-patients (ages 18-65) on all five of the acute adult open psychiatric wards of the Highgate Mental Health Centre, London, currently admitted for the assessment or treatment of mental illness. Financial compensation was not provided for any subject.

Subjects were approached on the ward by a member of nursing staff and asked if they were interested in participating in a study about sleep. The researcher was then introduced to explain further details with the aid of the participant information sheet. After a minimum of 24 hours, patients were approached again by the researcher and asked if they were willing to participate. Recruitment of subjects took place if the patient was agreeable

to take part and did not meet any of the exclusion criteria (listed below). A scheduled time and date was made with participants in order to obtain written informed consent and to administer the questionnaire. Questionnaire data was collected from each subject by the researcher in a private interview room located on the patient's psychiatric ward. Demographic and clinical data required from the patient's medical notes was recorded on the day of sampling. Exclusion criteria were: the presence of severely disturbed behaviour, or having received rapid tranquilisation for such behaviour on the day of sampling; a significant impairment in physical condition (e.g. infection, trauma); a history of a sleep disorder (e.g. obstructive sleep apnoea); the presence of organic illness including dementia; and lack of capacity to give informed consent.

Quality of Sleep: Subjects' quality of sleep was assessed by the administration of the Pittsburgh Sleep Quality Index (PSQI).[9] This is one of the most widely used questionnaires employing standardised measures to assess subjective sleep quality in clinical and research settings. It assesses sleep quality and disturbances over a 1-month time interval. 19 individual items are used to generate 7 component scores (with a range of possible subscale scores from 0 to 3): 1) overall subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) habitual sleep efficiency; 5) sleep disturbances 6) use of hypnotic or sedative medication; 7) daytime dysfunction. Higher scores indicate greater sleep disturbances. The sum of the component scores yields a global score (ranging from 0 to 21), which was used as the primary outcome measure in this study. A global PSQI score cut off score of 5 discriminates between good and bad sleepers and the PSQI gives acceptable measures of internal homogeneity, consistency (test-retest reliability) and validity.[9,10]

Other Variables: Demographic and clinical data recorded concurrently from participant's medical notes included: sex (male/female); age (years); ethnicity (Asian/Black/Mixed//Other); body mass index (BMI) (calculated as the ratio between weight [kilograms] and squared height [metres]); primary psychiatric diagnosis (based on ICD-10 criteria); duration of psychiatric illness (years); past medical history; number of currently prescribed medications; length of admission to date (days); current admission status (informal/detained under Section 2 of the Mental Health Act (MHA) (1983) (this is for a maximum period of 28 days for further assessment)/detained under Section 3 MHA (1983) (this is for a maximum period of 6 months for psychiatric treatment). A further category (detained under another type of section) was dropped as this did not apply to any of the subjects.

Ethics Committee Approval: Ethical and research governance authorisations were granted from Camden and Islington Community Local Research Ethics Committee, and from the North Central London Research Consortium, respectively.

Statistical Analysis: The aim was to compare clinical, demographic and PSQI data between the poor sleepers and good sleepers. The prevalence (%) of poor sleep was determined by the proportion of subjects with global PSQI score of 5 or more. Statistical analyses were predominantly performed using the software package Stata, version 9.2.

Results

Sample Characteristics

77 patients were initially identified as potentially eligible subjects. Of these, 31 (40%) were excluded due to: the presence of disturbed behaviour (n=1); inability to give informed consent (n=9); unwillingness to participate (n=19); absence from ward (either on leave or absent without leave) (n=2).

This left a total of 46 patients who were enrolled in to the study. Subject characteristics are given in Table 1.

Table 1: Demographic and clinical characteristics of study subjects

Sex, *n* (%)	
Male	24 (52)
Female	22 (48)
Ethnicity, *n* (%)	
Asian	1 (2)
Black	9 (20)
Mixed	1 (2)
Other	1 (2)
White	34 (74)
Current Admission Status, *n* (%)	
Detained under Section 3 MHA	22 (48)
Detained under Section 2 MHA	5 (11)
Informal	19 (41)
Age, years: mean (s.d.)	**38 (11.1)**
Range	18-62
Body Mass Index, kg/m²: mean (s.d.)	**25.99 (4.96)**
Range	17.9-41.5
Duration of mental illness, years: mean (s.d.)	**10.51 (7.93)**
Range	0.17-30
Length of admission, days: mean (s.d.)	**42.43 (63.21)**
Range	2-366
Prescribed regular medications, mean (s.d.)	**1.83 (1.05)**
Range	0-5
Medical comorbidities, mean (s.d.)	**0.59 (0.98)**
Range	0-3

s.d.: standard deviation

As defined by ICD-10 criteria, the most common subdivisions of patients' psychiatric diagnoses in descending order were: paranoid schizophrenia, F20.0, (n=16); emotionally unstable personality disorder, F60.3, (n=6); depressive disorder, F32, (n=6); bipolar affective disorder, F31 (n=5). Other subdivisions of subjects' diagnoses included: organic mood disorder, F06.3 (n=1); organic personality disorder, F07, (n=1); residual and late onset psychotic disorder due to alcohol use, F10.7, (n=1); persistent delusional disorder, F22, (n=1); acute and transient

psychotic disorder, F23, (n=1); unspecified non-organic psychosis, F29, (n=1); post traumatic stress disorder, F43.1, (n=1). One patient was undergoing psychiatric evaluation and therefore had no formal diagnosis.

Medications prescribed regularly were: antipsychotics (for 40% of the total sample of patients), mood stabilizers (16%), antidepressants (14%) and benzodiazepines (7%). In terms of regular night time sedation, two patients out of a total of 46 were prescribed zopiclone and diazepam respectively. Zopiclone was prescribed on an "as required" basis for 15 patients (33% of the total sample).

Overall sleep quality evaluated by the PSQI revealed a mean score of 9.74 (standard deviation= 5.11). Poor sleep quality (defined as a global PSQI score of 5 or more) was present in 36 out of the total of 46 subjects (78% of the sample).

Comparison between good and poor sleepers

Comparison of numerical measurements between the two sleep groups is presented in Table 2. For the normally distributed variables the figures reported for each group are the mean (standard deviation) and the p-value from the t-test. For the non-normally distributed variables the figures reported are the median (inter-quartile range) and the p-value from the Mann-Whitney test.

Table 2: Comparison of demographic and clinical data between good and poor sleepers.

Variable	Good sleepers (total PSQI <5) Mean (SD)	Poor sleepers (total PSQI ≥5) Mean (SD)	P-value
Age (years)	41.0 (12.1)	37.2 (10.9)	0.34
BMI (kg/m²)	23.0 (2.5)	26.7 (5.2)	0.15
Duration of psychiatric illness (years) (*)	10 (8, 12)	9.5 (3, 12)	0.70
Duration of admission (days) (*)	44 (13, 111)	15 (5, 41)	0.06
Medications (*)	2 (1, 3)	2 (1, 4)	0.55
Psychiatric medications (*)	1.5 (1, 2)	2 (1, 2)	0.68

(*) Median (Inter-quartile range) reported. Analysis performed using Mann-Whitney test

The results indicate that there was no strong evidence of a statistically significant difference between good and poor sleepers for any of the variables examined. However, there was a possible difference for duration of admission, although this result was only of borderline statistical significance (p=0.06). The results indicate a median duration of admission of 44 days for good sleepers and 15 days for poor sleepers.

The difference between sleep groups for the categorical variables was examined using Fisher's exact test. Results, presented in Table 3, show the number (and percentage) of subjects falling into each category, with the p-value indicating the significance of the results.

Table 3: Comparison of categorical data between good and poor sleepers

Variable	Group	Good sleepers (total PSQI <5) N (%)	Poor sleepers (total PSQI ≥5) N (%)	P-value
Sex	Female	3 (30%)	19 (53%)	0.29
	Male	7 (70%)	17 (47%)	
Admission status	Section 3	9 (90%)	18 (50%)	0.01
	Section 2	0 (0%)	5 (14%)	
	Informal	1 (10%)	13 (36%)	
Physical comorbidities	None	7 (70%)	24 (67%)	1.00
	1+	3 (30%)	12 (33%)	

There was a significant difference between sleep groups with regard to their admission status. Almost all (90%) of the good sleepers were detained under Section 3 MHA (1983), whilst this applied to only half of those in the poor sleepers group. Being detained under Section 2 MHA and informal admission were more commonly found amongst those categorised as poor sleepers.

There was no significant difference between groups in terms of sex or the presence of physical comorbidities.

The final set of analyses compared the differences between groups for the PSQI measures, and the results are summarised in Table 4. The figures reported are the mean (standard deviation) score for each group. For the individual components the Mann-Whitney test was used to compare between groups, and the p-values from this analysis are reported. For the PSQI total score, the unequal variance t-test was used to compare between groups.

Table 4: Comparison of PSQI measures between the good and poor sleepers

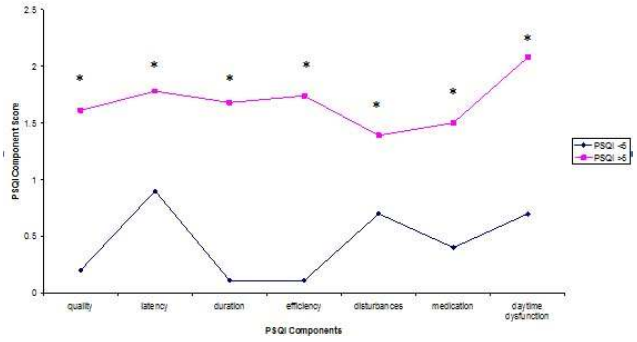
	Good sleepers (total PSQI <5) Mean (SD)	Poor sleepers (total PSQI ≥5) Mean (SD)	P-value
PSQI C1 score (quality) (*)	0.2 (0.84)	1.6 (0.9)	<0.001
PSQI C2 score (latency) (*)	0.9 (1.0)	1.8 (1.0)	0.02
PSQI C3 score (duration) (*)	0.1 (0.3)	1.7 (1.3)	0.002
PSQI C4 score (efficiency) (*)	0.1 (0.3)	1.7 (1.3)	0.001
PSQI C5 score (disturbances) (*)	0.7 (0.5)	1.4 (0.6)	0.003
PSQI C6 score (sedatives) (*)	0.4 (1.0)	1.5 (1.4)	0.04
PSQI C7 score (daytime dysfunction) (*)	0.7 (0.9)	2.1 (0.8)	0.004
PSQI total	3.1 (1.3)	11.6 (4.1)	<0.001

(*) Analysis performed using Mann-Whitney test

There was a statistically significant difference between good and poor sleepers for all PSQI components and for the PSQI total. The PSQI component values and PSQI total scores for poor sleepers were significantly higher than for good sleepers.

A profile of the mean PSQI individual component scores between the two groups (good sleepers versus poor sleepers) is displayed in Figure 1.

Figure 1: Mean component PSQI scores of good and bad sleepers



Profiles of the PSQI represent group differences of individual component scores. Mann-Whitney test, *p<0.05).

Subjective Patient Comments

The PSQI also comprises an open ended question, providing subjects with the opportunity to cite "other" (subjective) reasons for difficult sleep. The most common response was anxiety (n=8). Other examples included: medication alterations (n=3); environmental noise (n=2); "thinking excessively" (n=1); "a desire to be creative" (n=1); hard mattress (n=1); "food eaten" (n=1); "sedentary lifestyle" (n=1); alcohol (n=1); hunger (n=1); asthma (n=1); symptoms of the menopause (n=1); and "voices"(n=1).

Discussion

Main Results

This is the first study to examine the subjective quality of sleep among a population of psychiatric in-patients in the UK. The prevalence of poor sleep, as defined by a cut off PSQI score of 5 or more, was present in 78% of the patients sampled. Patients detained under Section 3 MHA (1983) were more likely to report sleeping well when compared to informal patients or those detained under section 2 MHA (1983). There was some evidence of good subjective sleep quality being related to a longer duration of admission, but this requires further investigation.

There were no significant differences between good and poor sleepers for any of the other demographic and clinical variables studied, including age, body mass index, duration of psychiatric illness, number of prescribed medications, sex, and physical comorbidities.

Individual PSQI component scores and global scores were significantly lower for good sleepers compared to poor sleepers. This would be expected given that higher scores indicate more severe sleep complaints, and this supports the consistency of the PSQI as a research instrument.

Factors Affecting Sleep

In-patients' disturbed sleep may be caused by a variety of exogenous factors such as unfamiliar surroundings, environmental noise, bright lighting and staff interactions or monitoring. Physical and psychological factors, such as the side-effects of medication and substance use, may also have a detrimental effect on sleep quality. In the added presence of a psychiatric disorder, each of these factors may act synergistically on the relationship between mental illness and sleep. Despite substantial research supporting the robust associations between insomnia and comorbid conditions, specific mechanisms linking sleep, medical and psychiatric factors have not been well established.

Sleep complaints may represent early symptoms and risk factors for new episodes of mental illness rather than simply representing phenomena secondary to experience of mental illness. For example, longitudinal studies have found insomnia to be a substantial risk factor for the development of a depressive disorder[5,11,12] and the risk for developing new anxiety disorders and alcohol abuse is also greater for insomniacs.[6]

Stepanski & Rybarczyk[13] present research arguing against the more traditional conceptualisation of insomnia as simply a consequence of another disorder. They propose the need for a revised model to understand insomnia that is *comorbid* with medical and/or psychiatric illness. Abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis may represent the underlying pathophysiological process in many chronic insomnia patients.[14] This may signify a common risk factor for insomnia and depression, thus predisposing the individual to a vulnerability to both conditions.[15]

In this study, detained patients (under Section 3 MHA (1983)) were significantly more likely to be classified as good sleepers. A suggestion for this finding could be that these patients may be less resisting of remaining and sleeping on the ward due to the involuntary nature of their admission. Alternatively these patients may represent the group with the most severe mental illnesses and with the least insight, and therefore less able to accurately recall their (poor) sleeping habits over the previous month.

There was also a potential association between longer admission status and better sleep quality. Explanations for this observation might include: patients' acceptance over time of their admission and the consequent conditioning to, and familiarisation with, the ward environment; achievement of stability in mental state over time; or the adaptation of the

perception of sleep quality to the sleep disturbances that accompany mental illness.

Limitations

This study is based on cross-sectional data and the relationship between the course of mental illness and sleep perception cannot be determined. In order to verify the direction of causality, it is necessary to demonstrate longitudinally that improvement in symptom severity is accompanied by an increase in subjective sleep quality.

This study was not designed to look at the prevalence of poor sleep across the different classes of psychiatric illnesses and dual diagnoses were not considered. It did not measure psychopathology or self-reported psychological distress. Possible confounding factors were not taken in to account, such as concurrent use of caffeine, alcohol, nicotine, illicit substances, hypnotics or other medications known to affect sleep.

The PSQI measures sleep quality averaged over the previous month. In cases where patients had only very recently been admitted to hospital, measurements would have been unlikely to accurately reflect the perspective of an in-patient's experience. The mean length of admission for this population however was longer than one month (42 days).

These results were drawn from a small sample, with a fairly high proportion of excluded patients (40%). This may explain why this study did not identify factors previously found to more frequently affect sleep adversely such as female gender, the elderly and those with chronic medical conditions.[16] In addition the population sample has little ethnic diversity which limits the generalisability of the results.

Implications

This study found that the prevalence of poor sleep quality was more common than previously reported in the general population[17] and more comparable to the higher rates reported in similar patient populations. Two previous studies investigating subjective sleep quality using the PSQI, found prevalence rates of poor sleepers to be 45.5%[18], and 91.22%[19] among a population of schizophrenia patients and psychiatric in-patients respectively.

Complaints of poor sleep are important for diagnostic purposes and also raise the need to address the adequacy of therapeutic strategies, given the consequent adverse impact on patients' mental state, physical health, daytime function and quality of life.

Improving Sleep

Hypnotics such as benzodiazepines and benzodiazepine receptor agonists can be efficacious for the treatment of insomnia.[20,21] However the clinical benefits must be weighed against well known adverse effects, such as daytime sedation, agitation, memory impairment, confusion and ataxia. This, together with the recommendation that hypnotics should only be used for short periods of time because of the risk of drug tolerance and dependence,[22] highlights the need for suitable non-pharmacological alternatives.

Recent reviews support the notion of the effectiveness of Cognitive Behavioural Therapy for insomnia in the treatment of people with psychiatric or medical conditions.[13,23] Modified, lower cost education initiatives to promote good sleep could be employed by utilising the skills of the mental health professionals caring for patients on the ward, supplemented by the provision of clear written material.

Environmental variables to consider include adherence to regular ward routines including bedtime and awakening times, attention to ward layout and design (including the provision individual bedrooms), lighting, ambient noise, temperature, and the provision of comfortable mattresses and appropriate bed linen. Medication scheduling times, regular medication reviews, and avoidance of non-prescribed substances such as caffeine, alcohol and illicit substances are also important. Physical health problems, pain and psychological distress should be optimally managed. Moderate intensity exercise programs have also been found to bring about significant improvements in self-rated sleep quality.[24] Finally, increased staff awareness and sensitivity to the sleep problems on the ward, supplemented with objective recording of such disturbances, would be informative in gaining a further understanding of patients' insomnia experiences.

Future Directions for Research

The PSQI is simple and inexpensive to perform. Results could be followed longitudinally in order to examine the course of sleep problems throughout an episode of acute mental illness, or to examine the effects of specific therapeutic interventions for sleep disorders. Sleep diaries have been shown to provide reliable estimates of subjective sleep parameters[25] and could be used as an adjunct to the PSQI. Ideally, concomitant objective measures such as polysomnography or wrist actigraphy (which detects physical motion), as well as cognitive and behavioural measures could be used to provide additional data.

This study represents the first attempt to examine the degree of self-reported poor sleep quality in a UK-based population of psychiatric in-patients and results suggest unsatisfactory sleep is a common finding. Large prospective longitudinal studies of sleep quality with control for confounding factors are needed to confirm the high prevalence rates in psychiatric in-patients. Studies comparing psychiatric patients with healthy controls, and also with insomniacs without psychiatric comorbidity, would further clarify the role of psychopathology in sleep disturbance.

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Original Article

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Demographic, socio-economic and psychological determinants of HIV treatment: A community out-patient experience

Subhasish Bose, Ajay Varanasi and Gyi Mo

Abstract

Objective: To find out basic understanding of HIV infection, degree of awareness regarding the ongoing treatment and reasons behind irregular follow-up visits of our HIV patients in the out-patient clinic.

Participants and Methods: 75 patients of our inner city community hospital HIV clinic (J.E. Wood Clinic of Pennsylvania Hospital, Philadelphia) were given an anonymous, survey questionnaire. 68 of them were sufficiently completed to be evaluated for the study. We collected information related to patients' demographic and social status, knowledge about their HIV disease and compliance with follow-up appointments. Completed questionnaires were evaluated and comparative data was tallied using Microsoft excel sheet. We also reviewed relevant literature to understand our findings in the light of previous related studies.

Results: Patients who had completed high school education or equivalent were 2.5 times more likely to remember the names of their HIV medications(95 % confidence interval CI=1.42 to 4.98) and 1.75 times more likely to remember their last CD4 count(95 % confidence interval CI=1.12 to 4.38). Women patients in our practice were 2.0 times more likely to practice use of protective measures during sexual activity (95 % confidence interval CI=1.22 to 4.67). 7 patients mentioned significant psychological problems in their daily life as the reason for non-adherence to medication or follow-up appointments.

Conclusion: Identifying socio-economic, behavioral and psychological variables that intervene treatment of HIV patient is important as it can help us to provide patient specific support and guidance to improve treatment compliance.

ABBREVIATIONS: AIDS = Acquired Immunodeficiency Syndrome; CD4 = Cluster of Differentiation antigen 4; CI = Confidence Interval; HIV = Human Immunodeficiency Virus; HAART = Highly Active Anti Retroviral Therapy; WHO = World Health Organization.

The acquired immunodeficiency syndrome (AIDS) was first recognized among homosexual men in the United States in 1981[1,2]. While initially limited, infection with the human immunodeficiency virus (HIV) has immensely increased over the past two decades to become the biggest epidemic of the twentieth century. However, we have witnessed dramatic improvement in prevention of disease progression and long-term survival in the era of Highly Active Anti Retroviral Therapy (HAART).

Apart from biological factors associated with the virus and host which play a role in the transmission and progression of HIV infection, several demographic and social variables have been studied and described in different studies worldwide. Understanding the variety of non-biological factors and behavioral patterns which can affect care and prognosis of HIV patients gives us the opportunity to design non-pharmacological interventions and where possible, to facilitate better care for our HIV positive population.

BACKGROUND:

J.E. Wood clinic of Pennsylvania Hospital in Philadelphia is a teaching outpatient care facility where Internal Medicine residents of Pennsylvania Hospital acquire their ambulatory care experience under supervision of teaching attendings. We have once a week clinic sessions dedicated to the care and follow-up of HIV/AIDS patients under close supervision of Infectious Disease specialists. Our patients have diverse socio-economic, educational and stages of HIV infection.

OBJECTIVE:

We aimed at finding out basic understanding of HIV infection, degree of awareness regarding the ongoing treatment and reasons behind irregular follow-up visits of our HIV patients who attend J.E. Wood outpatient clinic of Pennsylvania Hospital, Philadelphia for treatment of HIV/AIDS.

PARTICIPANTS AND METHODS:

In order to collect relevant information from our patients, a two paged, anonymous, study questionnaire was given to all patients who attended the clinic during January 2007 to December 2007. The questionnaire looked into three different areas of patient related factors which can influence the disease outcome: demographic and social information (Age, Sex, level of education), patients' knowledge about their HIV disease (source of the infection, duration of HAART, individual recent CD4 count, names of current medications, duration of therapy, medication side-effects) and their behavior (sexual precautions, reasons for medication and follow-up non-compliance). Out of the 75 patients who were given the questionnaire, 7 questionnaires were rejected from the study because of the information received was incomplete, illegible or not related to the questions. 68 completed questionnaires were evaluated and comparative data was tallied using Microsoft excel sheet. We

also reviewed relevant literature in pubmed to understand our findings in the light of previous studies related to demographic, socio-economic and psychological aspects of HIV treatment.

RESULTS:

We analyzed the information which was obtained from 68 patients by means of the questionnaire. Our patients consisted of 35 male, 33 female (Table 1). We had a wide range of patients regarding distribution of their age as shown in Table 2 below. Significant numbers of our patients (36%) were diagnosed with HIV for >10 years ago and more than 60% had the diagnosis at least for 5 years (Table 3).

Table 1: Socio-demographic characteristics of patients (n=68)

Variables	Percentage
Gender	
Male	51.5%
Female	48.5%
Education	
<High school	34%
High school graduate	50%
>High school	16%

Table 2: Age distribution of patients (n=68)

Age group	Percentage
Upto 30 years	19%
31 to 40 years	22%
41 to 50 years	37%
51 to 60 years	18%
61 years and above	4%

Table 3: Duration of diagnosis (in years)

Duration of diagnosis (years)	Percentage of total patients (n=68)
Unknown	3%
< 5	36%
>5 to 10	25%
>10	36%

Half of our patients (n= 68) completed high school education or equivalent. About 34% quit education before attaining high school diploma. Roughly, 10% of our patients went to college for further education and 6% acquired some vocational training after high school.

We tried to establish the level of our patients' participation in their treatment by gathering information through the questionnaire whether they could recall the names of their HIV medicines and the last CD4 count. We found that 74% of our patients, who are on HIV medicines, could recall the names of their medicines but only about 45% of our patients remembered their last CD4 count. Our patients who had completed high school education or equivalent were 2.5 times more likely to remember the names of their HIV medications(95 % confidence interval CI=1.42 to 4.98) and 1.75 times more likely to remember their last CD4 count(95 % confidence interval CI=1.12 to 4.38).

We asked our patients whether they knew that HIV medications need to be taken life long and we also enquired about their knowledge about their safe sexual practices. Only 48% patients of our study group knew that HIV medicines are for life. About 50% of all our patients mentioned that they ensure use of condom during sexual activity and another 40% claimed they practice sexual abstinence. Women patients in our practice were 2.0 times more likely to practice use protective measures during sexual activity (95 % confidence interval CI=1.22 to 4.67).

In our study, only 32 patients (47%) attempted to answer the question where we asked about reason behind not turning up for their follow up appointments as scheduled. Eight patients could not specify a cause, 7 mentioned transport related problems and 2 had insurance issues. Five patients thought their appointments were too often whereas 3 just forget to keep the appointment. Although we did not specifically ask questions on psychological state of our patients, 7 out of the 32 patients mentioned significant psychological problems in their daily life as the reason for non-adherence to medication or follow-up appointments. The responses included responses like "still dealing with the diagnosis mentally", "feel lack of energy in life", "life seems to have too many problems", "been drinking heavy lately" etc.

DISCUSSION:

Interestingly, our small patient cohort roughly reflects the sex ratio of HIV patients globally in 2007 as published by World Health Organization (WHO). In our study the ratio was Male : Female = 51.5% : 48.5% and in the WHO worldwide survey it was 50% : 50%; At the end of 2007, estimated total global HIV positive adults = 33 million (30million – 36 million) [3].

Rates of progression of HIV disease appear to be similar by sex and race category if adjusted for the quality of care [4, 5]. Multiple studies on chronic disease management showed that patients' level of education and health literacy has direct influence on the treatment compliance. Moreover, limited health literacy is thought to be a strong contributing factor to racial disparities in health care. A study was published in 2007 which examined the mediating effect of limited health literacy on the relationship between race and HIV-medication adherence. For the study, a total of 204 patients infected with HIV were recruited and structured in-person interviews were conducted to obtain information. In an adjusted analysis that excluded literacy, African Americans were 2.40 times more likely to be non-adherent to their HIV-medication regimen than whites (95% confidence interval [CI]=1.14-5.08). When literacy was included in the final model, the effect estimates of race diminished from 25% to insignificant level. Therefore, health care providers need to consider the potential utility of

responding to literacy and communication barriers in health care as part of interventions to reduce racial disparities [6]. In our study, we found that patients who had completed high school education or equivalent were more conscientious regarding their HIV care as demonstrated by the fact that they were more likely to remember their last CD4 count and current HIV medications.

Multiple studies have demonstrated that increasing age at the time of HIV infection is associated with more rapid progression to AIDS in the absence of antiretroviral therapy. In one series, for example, the median time from seroconversion to AIDS without therapy was 15 years for patients aged 16 to 24 years at seroconversion, compared to 6 years for those 35 years or older at seroconversion [7]. In our study, it is notable that 36% of patients were diagnosed with HIV >10 years ago and more than 60% had the diagnosis at least for 5 years. The reason behind the high survival rate is clearly attributable to HAART. Fifty-four patients out of the 68 are currently on HAART and 25 of them are on it for more than last 5 years.

Patients' knowledge of their HIV condition and its treatment has been recognized as a factor that influences adherence to antiretroviral therapy. Patients' knowledge & perception of the disease and participation in the treatment can be improved through targeted educational programs and support groups. One study done in Nigeria found that individuals living with HIV/AIDS who belonged to a support group and had availed themselves of relevant literature were more knowledgeable and positive about their illness than those who did not belong to support groups. The study concluded that HIV/AIDS support group membership is an important component of psycho-social care in HIV/AIDS patients [8]. Another study done in France showed that an educational intervention improves adherence to antiretroviral regimens and health status and suggests that it should be initiated early in therapy [9]. Communicating with patients about adherence issues is important issue, although this may not have an immediate impact on patients' behaviors. Health care professionals should play a pro-active role in this regard. The use of multi-disciplinary adherence teams to ensure that each HIV-positive patient receives the optimal amount of information and support for adherence is a practical approach. Health literacy should be provided in the context of different ethnicity, culturally sensitivity and individual needs associated with HIV, like any other chronic diseases. Epidemiological researches have shown that injection drug abusers and younger patients tend to have worse compliance, as well as subjects with depression and lack of self-perceived social support [10]. Therefore, special care should be taken by health care providers to ensure treatment compliance and health literacy in these patients. In our J.E. Wood clinic, we have dedicated psychologist and social worker to for care of our HIV patients.

Psychological impact associated with treatment of any chronic illness is often neglected in clinical practice but indeed carries a huge significance in terms of long-term treatment compliance and outcome. We identified 7 of our patients who clearly expressed psychological issues related to their HIV infection and it was evident enough that those psychological problems were adversely affecting their treatment compliance. Formal and regular counseling sessions should be arranged for HIV/AIDS patients to promptly identify and manage any psychological or psychiatric disturbance that HIV patients might suffer from. We know that presence of a preexisting psychiatric disorder can increase the risk of HIV acquisition and can also complicate HIV treatment. Moreover, HIV infection can produce a number of psychiatric conditions and exacerbate many others; there is an intense co-morbidity and linkage between HIV and various types of psychiatric conditions. Personality disorders are more prevalent among HIV-infected (19 to 36 percent) and HIV at-risk (15 to 20 percent) individuals [11, 12] than the general population (10 percent). Antisocial personality disorder (ASPD) is the most common personality disorder among HIV infected individuals, and has been shown to significantly increase risk of HIV infection [13]. Successful treatment can be achieved with even the most difficult patients by applying a comprehensive diagnostic formulation that includes psychiatric disease syndromes such as major depression, personality vulnerabilities, behavioral disorders such as addiction, and problems of life experiences such as trauma. With regards to anti-retroviral treatment of HIV positive or AIDS patients, nearly perfect compliance seems to be indispensable to obtain the maximum benefit from HAART. There is a clear relation between high adherence levels and virologic success. We reviewed relevant published literatures to understand the adverse effects and possible interventions of psychological problems in HIV patients. A prospective, randomized, two-arm controlled study was published in 2000 which included 116 patients starting their first-or second-line HAART who were randomized to receive psychoeducative intervention to implement adherence (experimental group [EG]) or a usual medical follow-up (control group [CG]). The study showed that specific and maintained psychoeducative interventions based on excellence on clinical practice are useful to keep high levels of adherence and therefore, high levels of viral suppression [14].

CONCLUSION:

Human Immunodeficiency Virus infection is one of the most serious disease entities in our modern time. We have witnessed dramatic improvement of long-term survival rate of HIV positive patients due to use of HAART in clinical practice. By identifying the demographic, socio-economic, behavioral and psychological variables which significantly influence patients' adherence to treatment and understanding of the disease process, we can further improve treatment compliance and the long term prognosis of our HIV patients. These factors may not have very significant role individually, but collectively can dictate the course of success of HAART treatment in patients. Increasing awareness of these factors by practitioners caring for HIV-infected persons, recognizing and potentially treating

some of them, should indirectly improve the effectiveness of antiretroviral therapy.

COMPETING INTERESTS
None Declared

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Case Report

BJMP 2009:2(2) 46-47

Blocked percutaneous endoscopic gastrostomy tube - an unusual cause

Vijay Joshi and Ashis Banerjee

Case report

An 82 year old lady, who had suffered multiple strokes in the past and was currently on long term percutaneous endoscopic gastrostomy(PEG) feeding, was admitted as an emergency from a nursing home with a two week history of productive cough and fever. She had been on PEG feeding since her first stroke six years previously. The first PEG tube (placed in 2001) subsequently fell out of position, and a second tube (15 French Frecka PEG tube) was inserted in 2003.

On admission, she was pyrexial, dehydrated, and hypoxic on room air. Chest examination revealed bilateral crackles and neurological examination revealed expressive dysphasia, and spastic weakness in both lower limbs. Abdominal examination revealed an inflamed PEG site with purulent discharge. Blood tests revealed raised inflammatory markers with neutrophilia (WBC 20 x 10^9/L with a neutrophil count of 12 x 10^9/L) and a raised C-reactive protein at 193 mg/L.

She was managed with intravenous fluids and antimicrobial therapy (tazocin and metronidazole) for possible aspiration pneumonia. Vancomycin was subsequently commenced as methicillin resistant staphylococcus aureus (MRSA) was isolated from the PEG site. As she remained stable, PEG feeding was recommenced.

A week following her admission she became unwell with an episode of vomiting and choking following PEG feeding. This was associated with difficulty in infusing feeds and medications through the PEG tube. Multiple flushes through the tube were unsuccessful. The tube was found to be persistently blocked and lacked free mobility within the tract.

Urgent upper gastro intestinal endoscopy revealed a buried bumper as the cause of blockage of the PEG tube. This necessitated insertion of a new PEG tube (9 French Frecka) for enteral feeding. The old PEG tube was removed surgically under local anaesthesia in due course. As the removal of the buried bumper was found to be very difficult endoscopically, and surgical intervention was deemed to be inadvisable in view of co morbidities, the bumper was left in situ. Feeding was recommenced through a new tube. In view of persistent discharge through the PEG site, abdominal ultrasound examination was performed, revealing a possible gastro-cutaneous fistula. No local collection was seen around the PEG wound.

As the patient remained clinically stable, she was discharged home with necessary instructions to her carers for regular flushing of the PEG tube with water, before and after each feed, to prevent further blockages.

Fig 1: Buried bumper (stomach-lower body)

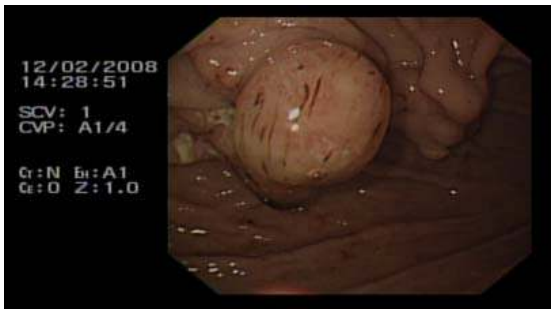
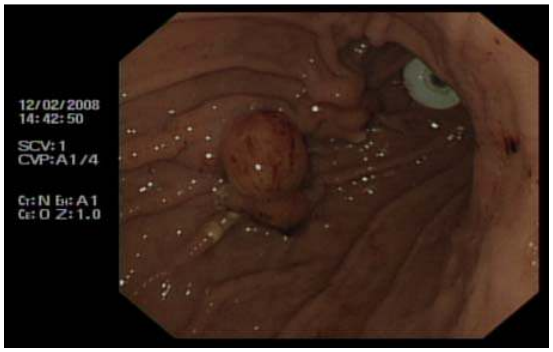


Fig 2: New peg and buried bumper



Discussion

PEG is primarily used for long term (longer than 6 weeks) enteral alimentation for patients with impaired swallowing (e.g. from stroke, degenerative neurological disease, head injury, and oropharyngeal malignancy). However numerous complications have been reported since its introduction in 1980.

Buried bumper syndrome (BBS) is an uncommon but well documented complication of PEG insertion, first described in 1988 [1]. It is usually a late complication occurring up to 3 years

post PEG insertion and reported to occur in 0.3-2.4 % of patients[2].

The internal bumper of the PEG tube should normally sit snugly against the anterior gastric wall, and this is confirmed endoscopically at the time of initial placement. BBS develops when there is migration of the internal bumper/flange through or into the anterior abdominal wall. This probably occurs as a result of excessive tension between the internal and external bumpers, from over-tightening of the external flange, leading to gastric wall erosion. During migration it becomes lodged along the gastrostomy tube tract between the gastric and abdominal walls. Once epithelialisation occurs the bumper gets covered with gastric mucosa[3].

The diagnosis of BBS should be suspected if localised abdominal pain, peri-tubal leakage or inability to infuse feed occurs. Initial measures to deal with a blocked tube include flushing with warmed water, and occasionally passage of a flexible wire through the lumen, in order to unblock any obstruction. Tube obstruction is usually related to the administration of protein-enriched formulae or medications, especially if the tube size is 9 French. Fungal colonisation may also lead to tube blockage, requiring specific solutions for flushing the tube[4]. Tube exchange should only be considered if the gastrocutaneous tract is mature (6 weeks or longer after placement of the tube).

Endoscopy is confirmatory in cases of BBS. The internal bumper is not seen, and the site of the PEG is indicated by an elevated area of submucosa with a central depression. Failure to recognise BBS can result in gastric perforation and gastrointestinal haemorrhage or intra abdominal sepsis, peritonitis and even death[5].

Ideally, the buried bumper should be removed even if the patient is asymptomatic, to avoid potential complications from continued tube migration until it is completely impacted in the abdominal wall. The literature describes various methods of dealing with this complication. Endoscopic ultrasound of the gastric wall with a catheter US probe can facilitate the localisation of the bumper and also provides information regarding feasibility of surgical or endoscopic removal of PEG tube[6].

Regular and optimal PEG care has been vital in identifying and prevention of this complication. During daily cleaning of the external PEG site, the PEG should be pushed in approximately 1 cm and rotated prior to repositioning of the external bumper. The length of the tube outside the abdominal wall should be examined at regular intervals so that migration can be recognised[5].

This report reinforces the fact that physicians should be aware of this recognised risk of PEG feeding and prompt referral for endoscopy is necessary to avoid serious consequences including gastro-intestinal bleeding, peritonitis and death. Similarly specific instructions should be given to carers for prevention of BBS.

COMPETING INTERESTS
None Declared

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Case Report

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Omental herniaton through umbilicus following lower segment caesarean section in a post caesarean pregnancy

Chandana Das and Snehamay Chaudhuri

Introduction

The incidence of caesarean section is rising[1] and there is evidence that women who have a caesarean section may be at increased risk of complications in a subsequent pregnancy[2]. Compared with vaginal delivery in the first pregnancy, caesarean section has been found to be associated with significantly increased rates of: uterine rupture in labour;[3] placenta previa and placental abruption;[4] placenta previa leading to peri-partum hysterectomy;[5] stillbirth;[6] and perinatal death[7]. Sometimes some unusual complication develops with which, we are not familiar. Here an uncommon complication following caesarean section in a post caesarean pregnancy has been reported.

Case report

A 25 years old lady P $_{1+4}$ presented at the emergency department of NRS Medical College & Hospital, Kolkata as an unbooked sixth gravida with the complaint of leaking per vagina for last 4 hours and the period of amenorrhoea was 38weeks. Her past obstetric history revealed that she had caesarean section 4 years earlier (indication of caesarean section was not known to the patient) and 4 successive M.T.Ps, the last being done 1 year back. The baby was alive. The couple wanted ligation operation.

On examination, she was mildly anaemic. Pulse was 88/min and BP was 126/80 mm Hg. She was free of any medical or surgical complications like morbid obesity, COPD and umbilical hernia. Per abdominal finding revealed a term size uterus with cephalic presentation and average liquor. FHS was 144/min and regular. Her previous caesarean section scar was low transverse and there was no scar tenderness.

Per speculum examination showed dribbling of clear liquor. Vaginal examination revealed cervix was 1.5 cm dilated, tubular, station was high up (-3) and membranes were absent.

An emergency L.S.C.S. was performed under spinal anesthesia. The skin incision was Pfannenstiel with excision of the previous scar. On opening the abdomen, uterus was found to be adherent with anterior abdominal wall from which uterus was separated for delivery of the baby (a living male baby of 2.75 Kg) and bilateral tubectomy operation. Bladder was also pulled high up which was dissected and pushed down before opening the uterus. Parietal peritoneum was not closed and rectus sheath was repaired with no 1 chromic catgut. Duration of operation was one hour which was longer than usual operation time of 35 minutes.

Figure I showing omentum like structure protruding through umbilicus

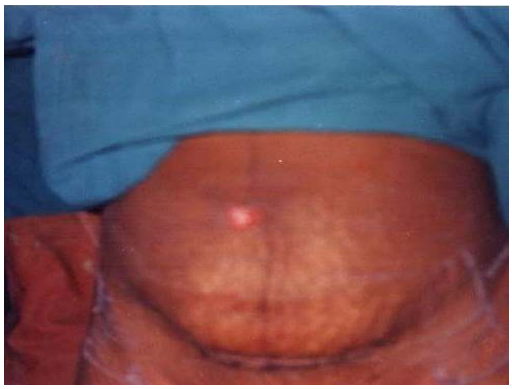
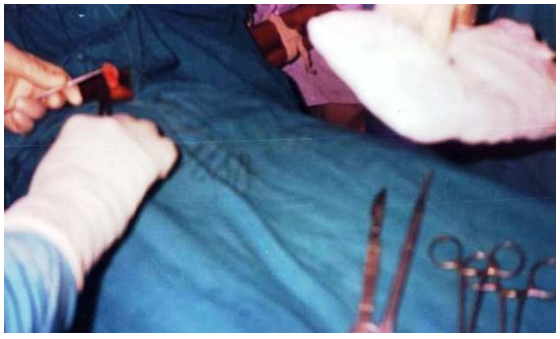


Figure II showing omental tag held during herniorrhaphy operation



First two post operative days were uneventful. On the 3rd day there was a small amount of serosanguinous discharge from the umbilicus. The caesarean section wound, which was located much below the umbilicus, was healthy. Methylene blue dye was introduced into the bladder to rule out any communication with umbilicus, through which no dye came out. On 4th post operative day a mass was seen protruding through the umbilicus and on gentle prodding it seemed to be omentum like structure

(Fig-I) A provisional diagnosis of omental hernia through umbilicus was made.

On the 5th post operative day, she underwent herniorrhaphy operation under general anesthesia. A tag of omentum was seen to herniate through anterior rectus sheath and skin (Fig-II). The protruding tag of omentum (sent for histopathological examination and confirmed) was excised and a double breasting of rectus sheath was done, keeping a drain which was removed after 48 hours. Her subsequent recovery was uneventful. She came for check up after 6 weeks, when no abnormality was detected.

Discussion

A review of literature has failed to demonstrate the type of complication mentioned above . Intra operative complication like dense intra abdominal adhesion resulting in injury to the bladder and the bowel is not uncommon[8]. Probably this case report presents an unusual complication for the first time. Probable explanation is that during too much dissection of anterior rectus sheath (to get access to the fallopian tubes) which was firmly adherent with uterus, there was inadvertent injury to the anterior rectus sheath and skin through which omentum had protruded.

COMPETING INTERESTS
None Declared

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View Point

BJMP 2009:2(2) 50-54

The right to consent: Is it absolute?

Christian P Selinger

Abstract

Informed consent is required for all medical investigations and procedures and is considered a corner stone of modern medicine. This review article examines the question whether the right to consent is absolute by looking at the philosophical, ethical and legal principles underlying consent. There are several legal exceptions to the right of consent in the United Kingdom concerning minors, incapacitated patients, patients with mental illness and patients suffering from communicable diseases. Furthermore the practical implications of consent and shortcomings of informed consent are discussed as well as the concept of advanced directives and lasting powers of attorneys. While a patient has a right to refuse treatment (all exceptions are discussed), there is no legal right to demand treatment in the United Kingdom.

The patient's right to autonomy should always be respected and steps shall be taken to make consent truly informed. There is, however, no absolute right to consent on the basis of philosophical, ethical, legal and practical considerations.

Introduction

Consent to investigations and treatment is considered a cornerstone in the doctor-patient relationship.[1] The Oxford Dictionary (1998) defines consent as "permission for something to happen or agreement to do something".[2] This definition does not entail understanding of the action agreed to and for medical purposes the term "informed consent" meaning "permission granted in the knowledge of possible consequences" has been developed.[2] General Medical Council (GMC) guidance requires the ability to comprehend and weigh up information as well the ability to communicate for informed consent.[3]

Most authors describe consent as a principle relatively new to medicine.[4-6] This is however incorrect as even Plato and Hippocrates used consent in their medical practice.[7]

This review addresses the issue whether the right to consent is an absolute right by exploring the ethical and legal framework of consent or more specifically informed consent. Whereas most of the ethical issues are universally applicable, the legal aspects and guidance by the regulatory authorities apply only to the United Kingdom (UK). Where law differs between Scotland and the rest of the UK, I have focused on the laws for the latter.

Ethical principles around consent

The four main principles of medical ethics are justice, non-malificence, autonomy and beneficence.[8] Autonomy is the main ethical consideration underlying informed consent. The patients' right to determine what investigations and treatment to undergo must be respected by all doctors.[3] For consent to be informed patients rely on the information provided by their doctor. Honesty and truthfulness are required to make the process of consent valid.[3] The ethical principle of justice needs to be applied when deciding what treatments are offered to or withheld from patients. This touches the process of informed consent and is further explored when the right to demand certain treatments is discussed.

Philosophical aspects

The debate whether a right or a principle is absolute not only involves ethical and legal aspects. It also touches on the philosophical argument of absoluteness. Freedom as an example can't exist as an absolute principle because granting one individual absolute freedom will infringe the freedom of a second individual considerably. Person A's freedom to take any good will influence the freedom of person B to have property. When applying these principles to autonomy the same problem arises: Total autonomy of one individual has a negative effect on autonomy of other individuals. The modern democratic society has designed rules and laws to create a fair way of living. On the one hand this restricts autonomy, while on the other hand this same restricted autonomy guarantees the same amount of it to all members of this society.

I argue therefore that on a philosophical basis the principle of total autonomy contradicts itself when applied to society. As autonomy is the main ethical principle for informed consent an absolute right to consent cannot exist.

Requirements of informed consent

The basic difference between consent and informed consent is the patients' knowledge behind the consent decision. Informed

consent requires the patient to understand the diagnosis and uncertainties about it as well as the different treatment options (including doing nothing) and their advantages, disadvantages and achievable outcomes.[3] The amount of information required to make consent informed may vary depending on complexity and risks of treatment as well as the patient's wishes.[3] Furthermore individual patients will have different intellectual capabilities and understanding of their illness. It is therefore mandatory to tailor information provided to the individual patient and the current situation. An emergency like acute myocardial infarction for example will allow less time to discuss diagnosis and treatment than an elective endoscopy.

To judge whether a patient has really understood the information provided can be difficult and often little of the information is retained (see practical aspects chapter). This leaves physicians in doubt whether their patient's consent is truly informed. Consent based on partial information may be invalid but this may go unnoticed by patient and treating physician.

The principal of an absolute right to consent could be easily undermined by partial information. It is highly dependant on the willingness to provide full information and the patient's capability to understand it and weigh up the options.

Legal framework

A medical intervention without valid informed consent is a criminal offence and the physician can be charged with battery. Examples of such situations include treatment against the patient's will, different treatment than the one consented for and treatment after consenting deliberately with wrong information.[9]

Guidance for consent has been set up by the regulatory body (GMC). While no one can consent for a competent adult UK laws are regulating consent for minors, patients with acutely or permanent incapacity and patients suffering form severe mental illness.

Minors

At the age of 16 persons are to be considered as adults and can therefore be presumed to have capacity. Children younger than 16 years may have capacity depending on their understanding. When a competent child refuses treatment persons with parental responsibility may authorise this or a court may overrule the child's decision.[3] Incompetent children will be treated with consent from a person with parental responsibility.

Acute and permanent incapacity

The presumption that every adult patient has capacity applies unless the opposite can be clearly demonstrated.[3, 10] Patients lacking capacity due to an acute (i.e loss of consciousness after an accident or patients on mechanical ventilation) or chronic illness (i.e dementia) cannot make decisions about their treatments themselves. In those situations it is the doctor's duty to act in the "best interest of the patient". Views about the patient's preferences may be sourced from a third party (relatives for example). This third party can however not consent or object to treatment.[3] If a patient has clearly given an advance directive while still competent, the treating physician is bound to respect this (see advance directive).

To give informed consent a patient needs to have mental capacity and the ability to communicate.[11] The physician needs to establish the patient's "ability to understand, retain, believe, evaluate, weigh and use information that is relevant to a medical intervention or its withdrawal".[11] This test of capacity has been supported by several court rulings[10, 12, 13] and is embedded in the Mental Capacity Act (2005).[14]

Making an irrational choice does by no means constitute lack of capacity and a competent patient's irrational decision has to be accepted even if this leads to an adverse outcome (including death).[3]

Mentally ill patients

The Mental Health Act (1983) regulates the treatment and hospital admission of mentally ill patients not volunteering to undergo assessment and/or treatment.[15] These patients can only be admitted to hospital if due to their mental illness they pose a threat to themselves or others. Patients can be detained against their wishes to conduct an assessment and if their condition is deemed treatable they can be detained to receive such treatment. While this allows treatment for psychiatric conditions, the treatment of physical conditions not related to mental illness cannot be undertaken against the patient's wishes. If needed, a court can decide on treatment of non-psychiatric illnesses in those patients.

This aspect of the law can leave physicians in difficult situations. If a depressed patient takes an overdose of an anti-inflammatory drug he can be detained in hospital using section 5.2 of the Mental Health Act. A resulting medical complication like severe gastrointestinal bleeding is however not covered by the mental health act. The patient therefore still remains competent to refuse a life-saving endoscopy or blood transfusion.

Protecting the public: infectious diseases, infection control and confidentiality

In order to protect the public form contagious infectious diseases the Public Health (Control of Disease) Act (1984) regulates notification of diseases and mandatory treatment of conditions like tuberculosis (TB).[16] The individual's right to consent is severely restricted in two areas: Firstly information about the patient's diagnosis has to be given to the relevant authorities. The patient should be informed about this step. Section 11 regulates the disclosure of information. It is

mandatory for a medical practitioner to disclose personal details of the patient and the diagnosis to the relevant authorities even if the patient does not agree to this. The list of notify-able diseases ranges from food poisoning and viral hepatitis to tuberculosis.

Secondly patients suffering from communicable diseases can be forced to take their medication by supervised administration or involuntary inpatient treatment. Sections 37 and 38 of the Public Health (Control of Disease) Act have recently been used to detain a man for inpatient treatment of TB against his will at North Manchester General Hospital.[17] The act was used to prevent the spread of TB to the wider public by forcing treatment onto an individual, who was not compliant.

While above regulations are clearly set out by law, a physician might encounter situations in which no clear guidance is given. If a patient confesses a crime or a planned crime to a doctor, it is left to him to decide whether to pass on this information to the police. This decision requires careful weighing up whether the right to consent on passing on information is more important than the right of the public to be protected. GMC guidance (Confidentiality: Protecting and Providing Information, 2004) gives general advice on disclosure, but leaves the ultimate decision with the medical practitioner.[18]

The legislative has given clear laws stating when a right to consent does not apply to a patient. Incompetent minors, adults lacking capacity and some mentally ill patients do not have an absolute right to consent. Furthermore patients suffering from some infectious diseases have limited right to consent and can be detained and treated against their will. Using the principles of capacity and justice towards other individuals the right to autonomy has been cut in a few well-defined circumstances.

Advance directives

When an adult becomes incompetent he loses the right to decide on his medical care. To allow patients to express their ideas and wishes before they become incapacitated the Mental Capacity Act was introduced in 2005.[19] Patients can give an advance directive or "living will" to outline the treatments they wish or wish not to receive. A physician is required to act within this advanced directive unless there is evidence that the patient revoked the will when still competent. A "living will" does not necessarily apply to all situations and it has to be checked whether the patient's current condition is covered by his will.

Practical application of advance directives can be difficult: Unclear wording like "no life-prolonging treatment" leaves room for interpretation and the same intervention might have different outcomes depending on underlying conditions. A healthy patient might set up an advance directive to not receive mechanical ventilation without discussing the merits of this intervention with a health care professional. This generally prohibits any doctor from administering such treatment in any situation. While this might be the patient's wish should he suffer a devastating stroke (very little chance of recovery), it could be argued that his view would be different if the merits of ventilation after major emergency surgery (reasonably good chance of full recovery) would have been explained to him.

Furthermore the act established the lasting power of attorney (LPA) concept. This enables the patient to grant rights of consent and refusal to a LPA while still competent. The LPA then takes over these powers when the patient loses capacity.

Research without consent

While consent should always be sought for including patients in clinical research, there are conditions that do not allow a delay: Unconscious patients, patients in shock and studies with short therapeutic windows. While including those patients without consent infringes their right to autonomy society as a whole benefits from such research. The European Union (EU) allows such studies to recruit patients without their consent under strict regulation.[20]

The right to refuse or demand treatment

British law clearly gives competent patients the right to refuse any treatment (the very few exceptions have been outlined in the chapter legal framework). In contrast, however, no patient has a right to demand certain treatments. GMC regulation (2008) states that if a patient wishes treatment that in the doctor's view is clinically not indicated there is no ethical or legal obligation to provide such treatment.[21]

Burke, who suffers from a chronic and progressing neurological illness, challenged this guidance. He wishes to receive artificial nutrition and hydration (ANH) when he loses his ability to swallow and he does not want doctors to make decisions on his behalf. Arguing that the relevant GMC guidance infringes his human rights he took the case to court achieving a favourable ruling initially. Mr Justice Munby ruled in Burke[22] that the Human Rights Act (1998)[23] entitles a person to demand life-prolonging treatments such as ANH. He based his decision on article 2, 3 and 8 arguing that a competent person's right to life and autonomy constitute an entitlement to ANH.[11]

The Court of Appeal overturned this ruling although the right-based analysis of Munby's decision was acknowledged. Two lines of argument were used to justify the decision. Firstly the case of Bland[24] (Airedale NHS Trust 1993), an advance directive to withdraw treatment in a case of persistent vegetative state must be respected, does not automatically lead to a reverse decision in opposite cases.[11]

Secondly an advanced directive demanding life-prolongueing treatment would not be in consistence with the Mental Capacity Act, which requires the doctor to take the incompetent patient's best interest into consideration.[11]

Another aspect of demanding treatment is the effect on the wider community. Graber and Tansey argue that demanding certain (more expensive, equally effective) treatments leads to injustice.[25] While doctors may feel pressured to please their patient's wishes, financial and organisational constraints in society (and a public health care system) will mean that other patients might not get treatments they require.

Currently there is no legal right in the UK to demand treatment. Furthermore such demands infringe justice by prohibiting resources to be allocated by need.

Practical aspects of consent: understanding and retention of information provided

Informed consent requires the ability to understand and weigh up information. Several studies have addressed the issue of understanding and retention of information provided. Even in a research setting where rigorous measures for consent are applied severe defiencies have been identified: in a randomized drug trial 44% of participants did not know that they were assigned to treatment or placebo by chance.[26] A capsule endoscopy study recruited healthy volunteers, of whom 90% had university education and 60% were medical students. Still vital information (drugs used, potential risks) given during the consent was only completely recalled by around 20%.[27] These examples show that most patients or research participants do not have a good understanding and/or recall of the information provided by standard consent procedures. Despite that treating doctors and researcher had treated or included patients based on this "informed" consent.

Methods like enhanced consent forms and multimedia interventions during informed consent have shown mixed results, while only additional time spent in one-on-one interviews significantly improved understanding and recall of information.[28]

Discussion

Informed consent is required for any investigation or treatment proposed to a patient. Understanding of the nature of procedure, benefits and risks are the cornerstones of informed consent. While autonomy is one of the four main ethical principles, I argue that there is no absolute right to autonomy or consent.

On a philosophical basis an absolute right to autonomy and consent contradicts itself.

Several restrictions in the right to consent are set by the legal framework in the United Kingdom (or England). The main statuary instruments concerned are: Mental Health Act, Mental Capacity Act and Public Health Act. UK Law regulates the right to consent for minors, mentally ill patients, patients with incapacity and patients with communicable diseases. Their rights to consent are restricted and in special circumstances not granted. Disclosure of information without consent is mandatory in infectious diseases cases and legal in cases where the doctor believes that non-disclosure will leave the public in danger. Furthermore patients can be recruited to studies of emergency medical treatment without consent under strict EU regulation. On a legal basis there is no absolute right to consent therefore.

Patients with anticipated incapacity can set advance directives to guide their future treatment while still competent or a LPA can be given the right to decide on treatment on the patient's behalf. While this increases the right of consent and improves patient autonomy to refuse treatment, there is no right to demand treatment if this is considered medically inappropriate (futile for example) by the treating medical practitioner.

Looking at the practical aspects of consent shows that the information provided is often poorly understood and retained. Patients giving consent are doing so without being truly informed. In other words they can't give informed consent due to their lack of understanding. As shown in the chapter practical aspects this will often not be noticed by the treating doctor or researcher. It is difficult to conceive an absolute right to consent in practice, when the effort to supply information required for informed consent fails so often.

In summary the patient's right to autonomy should always be respected and step shall be taken to make consent truly informed. On the basis of philosophical, ethical, legal and practical considerations, however, there is no absolute right to consent.

COMPETING INTERESTS
None Declared

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Medicine in Pictures

BJMP 2009:2(2) 55-56

Pictorial essay: central venous catheters on chest radiographs

Krishnan Melarkode and M Y Latoo

Chest radiographs are one of the most common radiological procedures performed in medical practice. The chest radiograph should ideally include views of the heart, lungs, trachea, mediastinum, bones of the chest and upper part of the abdomen. Chest radiographs are normally taken in the posterior-anterior (PA) view with the patient in upright / standing position but for patients admitted in the intensive care unit (ICU) or other emergency situations, this is not possible and so they are taken in the supine (anterior-posterior views) or semi-erect position.

Chest radiographs are done not only for diagnostic reasons to look for abnormalities in the lungs, soft tissues and bones but also to check the position of various invasive lines and tubes. In this article, we aim to discuss and compare the normal and abnormal positions of central venous catheter (CVC) on chest radiographs.

Indications for Central Venous Catheter (Internal Jugular Vein Cannulation)

There are many indications for central venous cannulation [1]. These include:

- Central venous pressure (CVP) monitoring
- Pulmonary artery catheterisation and monitoring
- Transvenous cardiac pacing
- Administration of drugs (vasoactive drugs, chemotherapy etc)
- Aspiration of air emboli
- Administration of fluids (in case of difficult peripheral venous access)

Confirming the position of the central venous catheter tip:

For accurate CVP measurement, the tip of the central venous catheter (CVC) should lie within the superior vein cava (SVC), above its junction with the right atrium and parallel to the vessel walls 1. After insertion of a CVC, the position of the catheter tip must be confirmed radiologically, as catheter tips located within the heart can cause cardiac perforation and tamponade [1]. Hence, optimum positioning of the CVC tip is required to prevent complications.

If the CVC tip is situated high up (above the pericardial reflection), this can cause vessel wall erosion and if they are very low (in the right atrium), they can cause arrhythmias, placement in the coronary sinus and damage to the tricuspid valve [2].

The carina is a useful radiological landmark for CVC tip position. In this edition of pictorial essay, we aim to discuss the optimum position of both the right and left sided IJV cannula on chest radiographs.

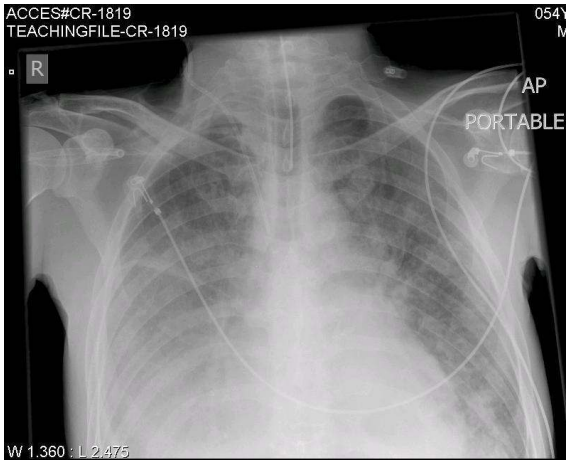

Fig: 1 (CR-1819) shows the normal position of a right sided IJV catheter. The tip of the right sided IJV cannula should ideally lie just above the level of the carina 2. This is the junction of the left and right innominate veins with the superior vena cava (SVC).

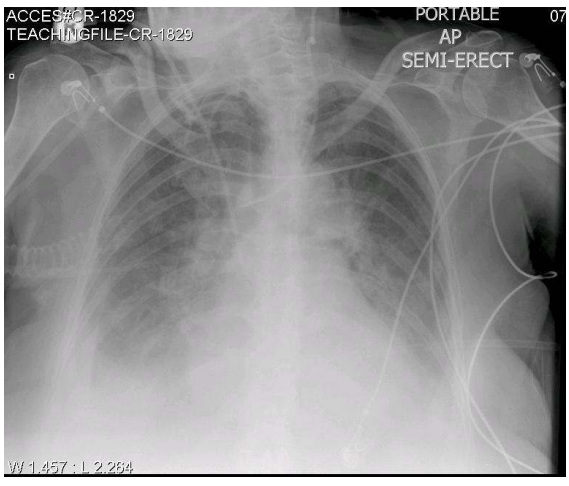

Fig: 2 (CR-1829): The optimum position of the left sided IJV cannula is at or just below the level of the carina 2. This radiograph shows the comparison between the right and left sided IJV cannula in the same patient.

The right sided IJV cannula is too low (below the level of the carina) and is probably in the right atrium while the tip of the left sided IJV cannula is optimally placed.

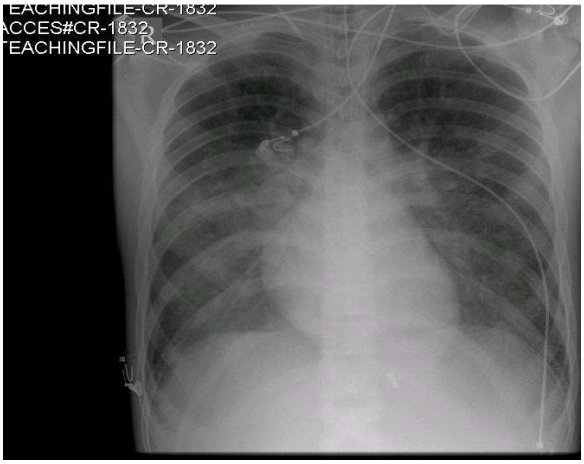

Fig: 3 (CR-1832): In this radiograph, the right sided IJV cannula is too high in the neck. This will not give an accurate CVP measurement. Besides, there is also a risk that the CVC might get dislodged and lead to extravasation of administered fluids and drugs.

Seldinger technique for CVC insertions:

The CVC's are usually inserted using the Seldinger technique. The IJV can be located by using anatomical landmarks or under direct vision with the help of an ultrasound machine. In the Seldinger technique, after puncture of the IJV, a thin J-shaped guide wire is introduced through the puncture needle. The needle is then slowly withdrawn leaving the J-shaped guide wire in place. A dilator is then introduced over the guide wire to dilate the skin and the subcutaneous tissue. Next, the dilator is removed and the CVC is introduced over the guide wire. Finally, it is important that the guide wire is removed and the CVC is secured.

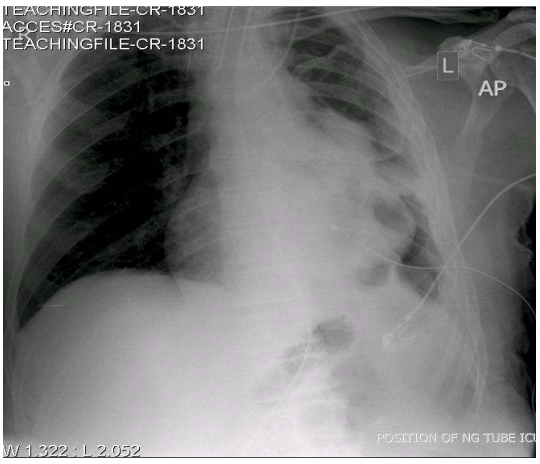

Fig: 4 (CR-1831). This chest radiograph shows an unusual complication where the guide wire has been left accidentally in situ on the right side. (Note the presence of the J-shaped guide wire on the right side of the neck). This can result in serious complications if the guide wire migrates distally.

Conclusion:

In this article, we have highlighted the optimum placement of central venous catheters on chest radiographs. It is imperative that after every CVC insertion (via the IJV or subclavian vein), the position of the tip be confirmed radiologically and if any re-positioning is required, it must be done. The above discussion is true for even CVC's inserted through the subclavian veins.

Self Assessment

MCQ:

The tip of the right sided IJV cannula should be located
a. below the level of the carina
b. at the level of the clavicle
c. just above the level of the carina
d. in the right atrium

Answer: c

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COMPETING INTERESTS
None Declared

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Internal Medicine
July 15-17, 2009 United Kingdom / London

BRITAIN PACIFIC MEDICAL AND LEGAL CONFERENCE
Contact: Lorenzo Boccalbella Tel: 011-61-07-3254-3331 Fax: 011-61-07-3254-3332 Email: info@educationcpe.com Website: www.conferences21.com
Legal/Ethics
July 17-24, 2009 United Kingdom / Oxford
BRITAIN PACIFIC MEDICAL & LEGAL CONFERENCE
Contact: Continuing Professional Education Pty Ltd. Tel: 011-61-7-3254-3331 Fax: 011-61-7-3254-3332 Email: info@conferences21.com Website: www.conferences21.com
Legal/Ethics
July 17-24, 2009 United Kingdom / Stratford-upon-Avon

BASIC SCIENCE: CELL SIGNALLING AND THE GUT
Contact: United European Gastroenterology Federation Secretariat Tel: 011-43-1-997-1639 Fax: 011-43-1-997-1639 ext. 10 Email: office@uegf.org Website: www.uegf.org
Gastroenterology
July 19-21, 2009 United Kingdom / Cambridge

MRCOG PART 2 REVISION COURSE
Contact: Royal College of Obstetricians & Gynaecologists Tel: 011-44-20-7772-6245 Fax: 011-44-20-7772-6388 Email: conference@rcog.org.uk Website: www.rcog.org.uk/events
Obstetrics/Gynecology
July 20-22, 2009 United Kingdom / London

FRCS (PLAST) AESTHETIC STUDY DAY
Contact: Royal College of Surgeons of England Tel: 011-44-20-7869-6336 Email: aesthetic@rcseng.ac.uk Website: www.rcseng.ac.uk/education/courses/course_list.html
Plastic Surgery
July 21, 2009 United Kingdom / London
2009 BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY (BAP) SUMMER MEETING
Contact: Lynne Harmer, BAP Tel: 011-44-1223-358-421 Email: lynne@bap.org.uk Website: www.bap.org.uk
Clinical Pharmacology / Psychiatry
July 26-29, 2009 United Kingdom / Oxford

BASIC PRACTICAL SKILLS IN OBSTETRICS & GYNAECOLOGY
Contact: Royal College of Obstetricians & Gynecologists Tel: 011-44-20-7772-6245 Fax: 011-44-20-7772-6388 Email: conference@rcog.org.uk Website: www.rcog.org.uk/events
Obstetrics/Gynecology
July 27-29, 2009 United Kingdom / London

CORE SKILLS IN LAPAROSCOPIC SURGERY
Contact: Julie Bradley Tel: 011-44-121-424-1488 Email: julie.bradley@heartofengland.nhs.uk Website: www.rcseng.ac.uk/education/courses/course_list.html
Surgery
August 19-21, 2009 United Kingdom / Birmingham

11TH NATIONAL CONFERENCE: PARKINSONS DISEASE
Contact: Mark Allen Group Tel: 011-44-20-7501-6762 Fax: 011-44-20-7733-8174 Email: conferences@markallengroup.co.uk Website: www.mahealthcareevents.co.uk
Neurology
August 25, 2009 United Kingdom / London