PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

VOLUME 14 No:1 NOVEMBER 2006

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PROCEEDINGS

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EDITORIAL

Dr John O'Neill MD, FRACP

Consultant Neurologist

Editor, Proceedings

This is the 18th Issue of Proceedings. Unfortunately, because of a last minute cancellation by the lecturer, it does not include the usual Annual Sandra David Memorial Lecture.

The Issue incorporates seven diverse medical articles, the first of great import to all Australians, an excellent review by Dr Warren Hargreaves on the epidemiology, diagnosis and current management of melanoma, the third most common cancer affecting men and women in NSW.

Next follows a review by Dr Romesh Markus, Director of the Stroke Unit of St Vincent's Hospital, on the use of intravenous thrombolysis in the first three hours after an acute ischaemic stroke. Stroke is the third leading cause of death and a major cause of disability in Australia. Thrombolytic therapy is the first major advance in management for the acute stroke situation, international trials showing that treated patients have a 30 per cent increase of excellent outcomes (independence with all activities).

Dr Robert Feller, gastroenterologist, has produced a thorough review of the technologically advanced non-invasive technique of Capsule Endoscopy for detection of pathologies involving the small intestine, a five metre length of bowel that has hitherto proven very hard to image for various suspected disease states. His review incorporates the St Vincent's experience, over 200 studies having been undertaken at the time of the article.

Female readers would be particularly interested in Dr David Eizenberg's article on the modern medical and surgical options for management of heavy menstrual bleeding. It has been rewarding to have gynaecological topics presented in this and the last two Issues.

Associate Professor Anne Keogh, Cardiologist of the Heart and Lung Transplant Unit, has written a scholarly article on pulmonary arterial hypertension, a condition often not considered and diagnosed until late in its development. The article increases the readers' awareness of the manifestations of this condition and the importance of early diagnosis at a stage where new effective agents offer a real chance of cure.

Dr Simon Tan and Associate Professor Michael Neil, two dynamic orthopaedic surgeons, have combined to write about the function of cartilage, the effect of its damage at the knee and the pros and cons of two cutting edge surgical approaches to treatment of cartilaginous injuries to the knee.

Finally Dr Richard Parkinson, a relatively new neurosurgical appointee to St Vincent's Campus with a special interest in vascular neurosurgery, describes his experience in another cutting edge device, Orbit DCS Detachable CoiI, in the management of intracranial aneurysms.

On page 13 of this Issue is the list of St Vincent's Clinic Foundation Grants awarded during 2006. These totalled $390,000, the major grant (to Dr Romesh Markus – see his article on Page10) being The Ladies' Committee Sister Mary Bernice Research Grant ($100,000), the name recognising the great work of fundraising undertaken each year by The Ladies' Committee of St Vincent's Private Hospital and St Vincent's Clinic. This year, the St Vincent's Clinic Foundation has established two Travelling Scholarships, each for $10,000. If you would like to make a donation to the St Vincent's Clinic Foundation, a form is present on Page 23.

Cutaneous Melanoma

Dr Warren Hargreaves

Introduction

Skin cancer is the most common cancer in Australia and melanoma is the most significant form with the greatest potential morbidity and mortality. Traditionally, the public perception of melanoma treatment was of radical excision and skin grafting and limbs swollen by lymphoedema secondary to lymph node removal. However, rigorous examination of treatment techniques and results has allowed less radical surgery without compromising outcome. Public health campaigns may have had an even more significant impact on melanoma treatment by virtue of raised community awareness and earlier detection.

Early detection and improved surgical methods have been significant advances in melanoma management, however, the treatment of disease that is no longer confined to the primary site is still unsatisfactory and remains the subject of intense investigation and hopefully further improvement.

Epidemiology

Melanoma is a malignant tumour of melanocytes, the cells that produce pigment. The pigments (eumelanin and pheomelanin) produced by melanocytes are packaged into melanosomes which enter neighbouring keratinocytes in the skin and hair. As well as providing skin and hair colour the pigments are key factors protecting our skin from damage by ultraviolet radiation. However, melanocyte damage by UV radiation may lead to the formation of melanoma. This relationship between melanocytes and the sun underpins the significance of melanoma in Australia.

Figures from cancer registries show Australia has the highest rate of melanoma in the world. Crude rates per 100,000 population are approximately 46 in New South Wales versus 21 in the USA and 10 in the UK. This translates to a lifetime risk of melanoma of one in 18 for men and one in 25 for women in NSW.

Figures from the New South Wales Central Cancer Registry (latest 2003) show that the incidence has increased steadily since 1972.

In New South Wales melanoma is the third most common cancer overall after prostate and breast cancers. When men and women are considered separately melanoma is the second most common cancer.

However, although the incidence continues to increase and the death rate may have plateaued over the past decade (Figure 1) melanoma remains the number two cause of lost productive years of life.

The Cancer Institute of NSW predicts the incidence of melanoma will continue to increase and expects a further 12 per cent rise over the next five years.[1]

Dr Warren S. Hargreaves
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Risk Factors

Writing in the Medical Journal of Australia in 1957, Lancaster and Nelson noted the relationship between fair skin, sun exposure and development of melanoma.[2] Since then, a significant body of evidence has been accumulated confirming that solar radiation causes cutaneous melanoma and non-melanoma skin cancer. It is estimated that in our population approximately 95 per cent of melanoma can be attributed to sun exposure.

However, the relationship between sun exposure and the development of melanoma is not a case of simple dose:response. Host factors as well as environmental factors are involved. The most susceptible are those with fair skin, red hair, light-coloured eyes and who have a tendency to burn rather than tan. The genetic basis of this phenotype has recently been elucidated with the discovery of the MC1R gene. This gene controls the production of eumelanin and pheomelanin by melanocytes and people with certain genetic variants are also at increased risk of developing melanoma.

Patterns of sun exposure are also important and information from population and migration studies shows that high UV exposure in childhood and adolescence may be more significant than exposure in adult life. This clearly has public health implications and has in part led to the "No hat – No play" policy now implemented in many schools.

The importance of the relationship between age and sun exposure is highlighted by the fact that migrants who arrive before 10 years of age will have the same melanoma risk as those born here, whereas arrival after 15 years of age results in a risk one quarter of the local population.

A small number of people are at increased risk of melanoma due to inherited or acquired genetic mutations. Xeroderma pigmentosum (Figure 2), a rare disease with a mutation in the genes responsible for repairing the DNA damage induced by UV radiation, carries an increased risk of melanoma 2000 times the general population. Other syndromes associated with increased melanoma risk include hereditary retinoblastoma, Li Fraumeni Syndrome and the Atypical Mole Syndrome. This latter condition, also known as the Dysplastic Naevus Syndrome, is defined by the presence of 50 or more atypical naevi. These are usually greater than 6mm in diameter and have irregular pigmentation and borders. Patients with this syndrome have a risk of developing melanoma in a naevus or clinically normal skin at a rate ten times the general population.

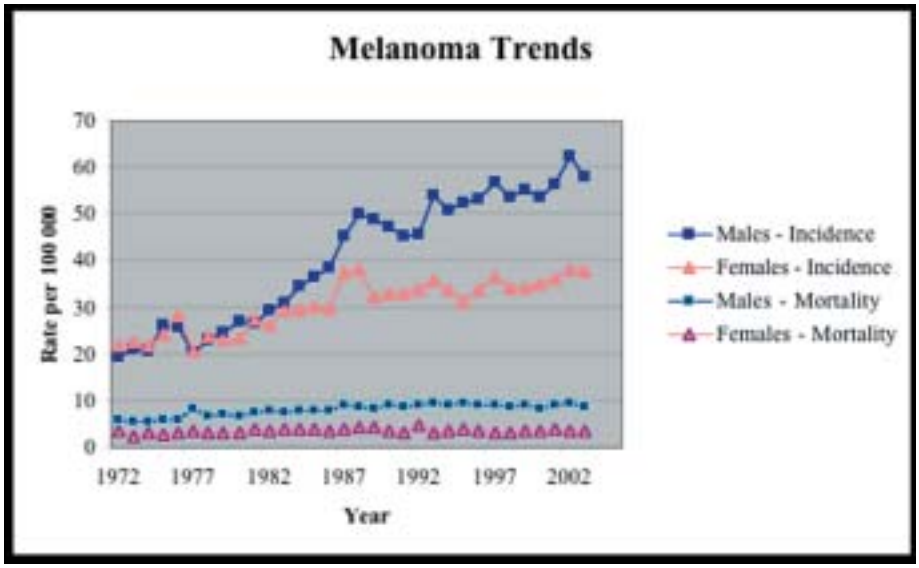

Figure 1. *NSW Central Cancer Registry data 1972-2003.*[1]

Other families with hereditary melanoma have been shown to carry a mutation in the gene CDKN2A. One product of this gene is a protein known as p16INK4A or "p16". Abnormalities in this gene and its products may lead to a loss of cell cycle control and subsequently the development of tumours. The lifetime risk of developing melanoma for patients carrying this mutation is between 60 per cent and 90 per cent. Studies carried out in Queensland have estimated that abnormalities in this gene may occur in up to 0.2 per cent of the population.[3]

Diagnosis

The histological diagnosis of melanoma can be difficult to make as benign pigmented lesions share many common histological features with melanoma. The final diagnosis is then a clinicopathologic one, taking into consideration both macro and microscopic appearances. The macroscopic appearances have been conveniently described in a system that allows ready assessment and surveillance of pigmented skin lesions. The "ABCD" system has been in use for over 20 years and has recently been revised and

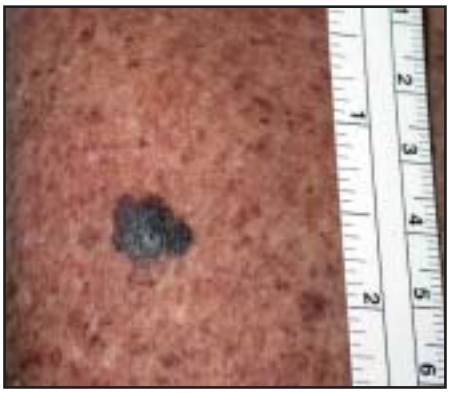

Figure 2. *Melanoma in a patient with Xeroderma Pigmentosum*

modified.[4] The Cancer Council of NSW has recently produced posters displaying how the system demonstrates the characteristic clinical features of melanoma.[5]

A – Asymmetry. Melanomas are likely to be asymmetrical

B – Border. Melanomas are likely to have an irregular, "coastline" border

C – Colour. This refers to the often variegated colour of melanomas.

D – Diameter. Be suspicious of lesions larger than 6mm diameter.

E – Evolution. Melanomas change in size, shape, surface and symptoms over time.

Patients with lesions considered suspicious based on these criteria should be referred for specialist opinion prior to biopsy. Biopsy can usually be performed under local anaesthetic and will generally be an excision of the lesion with a 2mm lateral margin.[6] Expert examination of the specimen is required for diagnosis and subsequent treatment planning.

Pathology

Pathological examination of the excised lesion aims to determine the nature and location of abnormal melanocytes. Two patterns of melanocyte proliferation are recognised histologically. Proliferation within the epidermis is termed the "radial growth phase" and leads to melanoma in situ. The "vertical growth phase" is present when the cells enter and proliferate in the dermis. Histologic assessment of the location of abnormal melanocytes has allowed the development of standardised nomenclature for classifying melanoma. The Clark level refers to the maximum depth of penetration of melanocytes with respect to the various anatomical levels in the skin while the Breslow thickness refers to the absolute distance (as measured with an ocular micrometer) from the granular cell layer to the deepest abnormal melanocyte. Breslow's thickness is the more useful measure, with a higher rate of reproducibility by different pathologists. Clark's level is still important in sites where the skin is thin, such as eyelid and ear, where absolute measurement of depth may underestimate the prognostic significance. Another important pathological feature is the presence of ulceration as this has been shown to be an independent indicator of poorer prognosis.

The combination of clinical and pathological findings allow cutaneous melanoma to be classified into one of four main types:

- Superficial spreading melanoma
- Nodular melanoma
- Acral lentiginous melanoma
- Lentigo maligna melanoma (arising in lentigo maligna)

Superficial Spreading Melanoma (Figure 3) makes up approximately 70 per cent of melanomas. It is usually found on the head, neck and trunk in males and on the limbs in females. It appears as a flat, irregularly-shaped lesion, often quite variegated in colour.

Nodular melanoma (Figure 4) accounts for about 10 per cent of melanomas. It arises on any skin site but particularly on the chest of males. The colour is often uniform and the surface commonly ulcerates. Up to five per cent of these are amelanotic.

Acral lentiginous melanoma makes up only five per cent of melanomas in white people but is the most common type in dark-skinned individuals. They occur on the palms, soles and beneath nails (Figure 5).

Lentigo maligna melanoma is the type of melanoma that arises from a precursor known as lentigo maligna or Hutchinson's melanotic freckle (HMF). It is most often found on the middle-aged and elderly, particularly on areas of high sun exposure on the head, neck and upper trunk (Figure 6). The precursor lesions may be several centimetres in diameter have often been present for many years. Lentigo maligna may be considered melanoma in-situ and only around five per cent will develop an invasive melanoma.

Although several clinicopathologic subtypes are recognised (and useful guides to clinical diagnosis), the treatment is the same for each and is based on the Breslow thickness.

Along with tumour thickness, details of the presence and number of lymph node and distant metastases are used to formulate a staging system that provides prognostic information, comparison and assessment of treatment modalities and the development of clinical guidelines. The current staging system (Table 1) is that developed by the American Joint Committee on Cancer (AJCC) in 2002 and adopted by the International Union Against Cancer (UICC) TNM Committee.[7] The system is used internationally by all major research and treatment bodies.

Primary Melanoma

After histological confirmation of the diagnosis treatment of primary melanoma is surgical.

It was clear to 19th century surgeons that survival from melanoma relied on the timely removal of the primary. However, how radical that surgery should be was the subject of debate right up to the end of the twentieth century. Several randomised trials have demonstrated that the thickness of the primary tumour should determine the excision margin.[8-11] These trials have also shown that increasing the width of excision beyond one centimetre does not improve survival but does decrease the risk of local recurrence. Therefore, the

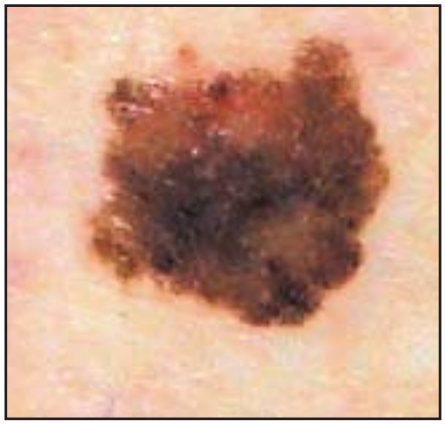

Figure 3. *Superficial spreading melanoma on the ankle*

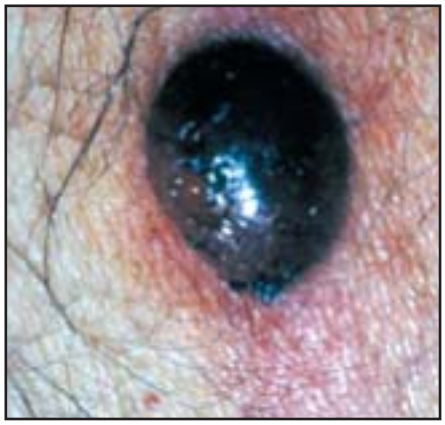

Figure 4. *Nodular melanoma on the chest*

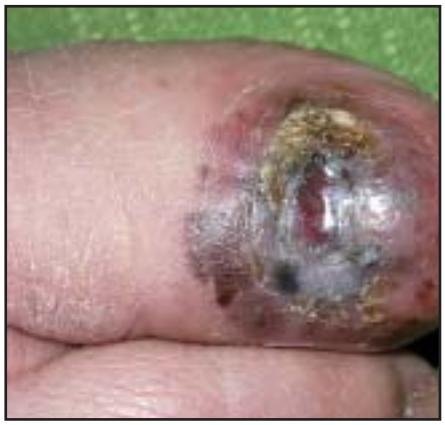

Figure 5. *Subungual melanoma of the great toe*

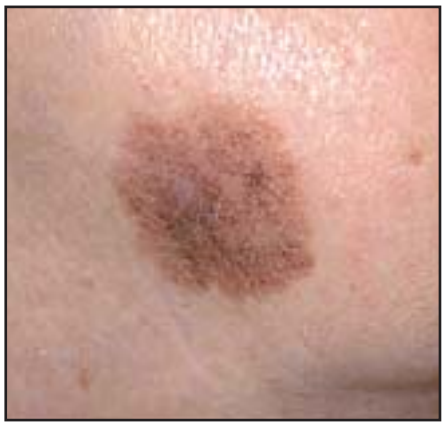

Figure 6. *Lentigo maligna melanoma on the cheek*

T Classification	Thickness	Ulceration
Tis	Melanoma in situ	
T1	≤ 1.0mm	a: without ulceration and Level II/III
		b: with ulceration or Level IV/V
T2	1.01-2.0mm	a: without ulceration
		b: with ulceration
T3	2.01-4.0mm	a: without ulceration
		b: with ulceration
T4	>4.0mm	a: without ulceration
		b: with ulceration
N Classification	**No. of Metastatic Nodes**	**Nodal Metastatic Mass**
N1	1 node	a: micrometastasis*
		b: macrometastasis†
N2	2-3 node	a: micrometastasis*
		b: macrometastasis†
		c: in-transit/satellites without metastatic nodes
N3	4 or more nodes or matted nodes or in-transit/satellites with metastatic nodes	
M Classification	**Site**	**Serum LDH**
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other viscereal metastases	Normal
	Any distant metastasis	Elevated
*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.		
†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic gross extracapsular extension		

Table 1. *AJCC/UICC Melanoma Staging System, 2002*

majority of patients will now be able to have excision and primary closure rather than the skin grafts that were often required with "radical" excision. Table 2 illustrates a reasonable approach to excision margins based on current knowledge.

While a two centimetre margin for intermediate and thick melanomas aims to decrease the risk of local recurrence lesser excisions may be performed if the cosmetic or surgical morbidity is considered too high.

Cosmesis is also relevant to the treatment of the pre-invasive lentigo maligna as it commonly occurs on the face and may cover several square centimetres. Although surgery is the current standard treatment a number of alternatives are currently under consideration. Cryotherapy and radiotherapy have recurrence rates of up to 50 per cent and 15 per cent respectively but topical immunotherapy with imiquimod is showing promise and is currently the subject of a clinical trial.

Excision of the primary tumour with the recommended margin results in an approximately one per cent recurrence rate for thin tumours. However, local recurrence rates may be up to 20 per cent after excision of thick (>4mm) tumours.

In an attempt to reduce this risk of local recurrence radiotherapy has been proposed but trials have not as yet been able to demonstrate a benefit.

Lymph Node Disease

Cutaneous melanoma metastasises with a frequency dependent on the thickness of the primary lesion. The first

Tumour Breslow Thickness	TNM Classification	Excision Margin	Five year survival (per cent)
In situ	Tis	5mm	95-100
<1.0mm	T1	1cm	95-100
1.01-2mm	T2	1-2cm	80-96
2.01-4mm	T3	1-2cm	60-75
>4.01mm	T4	2-3cm	40-50

Table 2. *Excision Margins for Primary Melanoma*

site of metastasis is the regional lymph nodes in approximately 80 per cent of those who recur. Patients with thin melanoma (<1mm) have a low risk of lymph node metastases but the risk of nodal metastasis in patients with tumours 1-4mm thick approaches 20 per cent.[12] In these patients the lymph nodes are frequently the only site of metastatic disease. Unfortunately, the majority of lymph node metastases are not detectable by clinical examination. This then presents clinicians with the problem of identifying patients with "positive" lymph nodes whilst avoiding unnecessary procedures in those with "negative" nodes. Put another way, performing lymph node dissection on all at-risk patients (melanoma greater than 1mm thick) would be unnecessary in 80 per cent and would expose them only to the complications of the operation.[13,14,15] With this in mind the procedure of sentinel lymph node biopsy (SLNB) was applied to patients with intermediate thickness melanoma in an attempt to identify the group of patients that would benefit from full ("completion") lymphadenectomy.[16] The Multicenter Selective Lymphadenectomy Trial (MSLT-1) was designed to test the role of SLNB and completed recruitment of patients in 2001. The final results of the trial are not yet available but interim analysis has confirmed the safety of the procedure and suggested its usefulness in the management of nodal metastases.[17]

Patients who have clinically detectable lymph node metastases undergo therapeutic lymph node dissection without the need for SLNB. Lymph node dissection for melanoma involves the complete resection of all node-bearing tissue in the area of interest and may be associated with significant post-operative morbidity. The most common early complications are related to difficulties with wound healing, in particular wound infection and skin flap necrosis. Late complications are due to alterations in lymphatic fluid movement and include seroma formation and lymphoedema.

Following surgery for involved lymph nodes long-term survival rates of around 50 per cent can be achieved. However, despite undergoing surgery to remove all nodal disease, patients with lymph node metastases have a significant (45-70 per cent) risk of developing recurrent disease.

Distant Metastases

Although early stage (localised) disease is curable there is no current treatment that reliably alters the course of metastatic disease.[18]

The presence of distant metastases confers a median survival of approximately 8 months and an overall five year survival of ~5-8 per cent.

However, there is a clinically significant difference in survival that depends on the site of metastatic disease. This is recognised in the AJCC/UICC classification where metastases are recorded as being in the skin or subcutaneous tissues, the lungs, or other visceral sites (see Table 1).

Skin and subcutaneous metastases, often referred to as "satellite" or "in transit" metastases, can vary in presentation from single to hundreds of nodules. Occasionally, skin metastases may develop into large fungating, often foul-smelling, tumours that pose significant management problems. If disease is "low volume" in size and number it is usually treated by excision. Scalpel or carbon dioxide laser excision may be used depending on the location and number of lesions. Laser excision is particularly useful if there are many small lesions as the wounds are generally comfortable and require only simple dressings for two weeks.

When disease is "high volume", that is, large tumours or many hundreds of small tumours, surgical removal is not usually possible. If such disease is confined to a limb then regional chemotherapy in the form of either isolated limb infusion (ILI) or perfusion (ILP) may be possible. Both these techniques involve circulation of chemotherapeutic agents within a limb that has been "isolated" from the systemic circulation with the aid of a pneumatic tourniquet. This allows the administration of drugs in concentrations up to 25 times the systemic dose but without systemic side effects.[19] Response rates may be as high as 95 per cent with a complete response in over 65 per cent of patients (see Figures 7a and 7b). A recent series has reported a mean time to disease progression of eleven months and an overall five year survival of 33 per cent.[20]

Pulmonary metastases are found in 70 per cent of post-mortem examinations of melanoma patients yet only a quarter of patients with lung metastases will develop symptoms of their disease. Approximately five per cent of patients will develop a single pulmonary tumour as their only site of metastatic disease. Without treatment the median survival is in the order of 8-10 months but if amenable to surgical resection then five year survival can be as high as 20 per cent.[21]

Gastrointestinal tract (GIT) metastases are found at autopsy in 50 per cent of patients who die of melanoma but only between 1-10 per cent are detected during life. Patients may present with overt or occult blood loss, bowel obstruction or abdominal discomfort. Surgery is able to palliate symptoms in up to 97 per cent of patients and if complete resection of GIT metastases is possible then five-year survival following this may be as high as 40 per cent.[22]

Brain metastases occur in up to three-quarters of patients with metastatic melanoma and may be single or multiple. Cerebral melanoma metastases are particularly prone to haemorrhage and thus result in the death of approximately half of these patients. Surgical excision may be performed for solitary, symptomatic metastases but is only able to prolong median survival for three months over whole brain radiotherapy.[23,24]

Adjuvant Therapy

As the thickness of the primary melanoma increases so does the risk of recurrence, both local and distant. Patients with melanoma >4mm thick have a 50 per cent risk of developing a detectable recurrence. So, the aim of adjuvant treatment is to decrease this risk while the tumour is still apparently localised. Unfortunately, despite extensive trials no agent has been shown to be effective in the adjuvant setting. Agents subjected to clinical trials include

1. Cytotoxic chemotherapy
2. Radiotherapy
3. Biological therapies.

Dacarbazine, also known as DTIC, has been the mainstay of "standard" cytotoxic chemotherapy for the past forty years. Unfortunately, less than a quarter of patients respond to this treatment with less than five per cent showing a complete clinical response. Most responses are short-lived and the median is around 5-6 months. Trials using combinations of other cytotoxic agents with DTIC have shown only minor benefit so, given that DTIC is generally well-tolerated, it remains the major agent in clinical use.[25]

Due to difficulties in determining the appropriate dosing schedule melanoma has traditionally been regarded as a radioresistant tumour. More recently, rigorous laboratory and clinical trials have shown several uses for radiotherapy in melanoma management and demonstrated response rates of up to 70 per cent. It is particularly useful in the management of cerebral metastases and provides good palliation of painful bone metastases.[26] It may also relieve tracheobronchial obstruction caused by enlarged mediastinal lymph nodes. The place of radiotherapy in managing primary disease (unresectable or "high-risk" resected disease) is less certain. The Trans-Tasman Radiation Oncology Group is currently evaluating the use of radiotherapy following lymph node dissection.

The clinical observations that melanoma may spontaneously regress in association with lymphocyte infiltration and that immunosuppression may hasten melanoma growth have led to the development of therapies aimed at modulating the immune response. Several biological agents have been trialled and the most promising therapy to date is Interferon a-2b (IFNa-2b). Experimental evidence suggests that IFNa acts by increasing the immunogenicity of melanoma cells and facilitates their destruction by T-lymphocytes. Unfortunately, clinical trials have provided conflicting results for efficacy and highlighted toxicity as a significant limiting factor.[27] Up to 20 per cent of patients are unable to tolerate IFNa due to its side effects, thus limiting its therapeutic use. In clinical practice IFN is rarely used and is only usually offered to patients under 60 years.

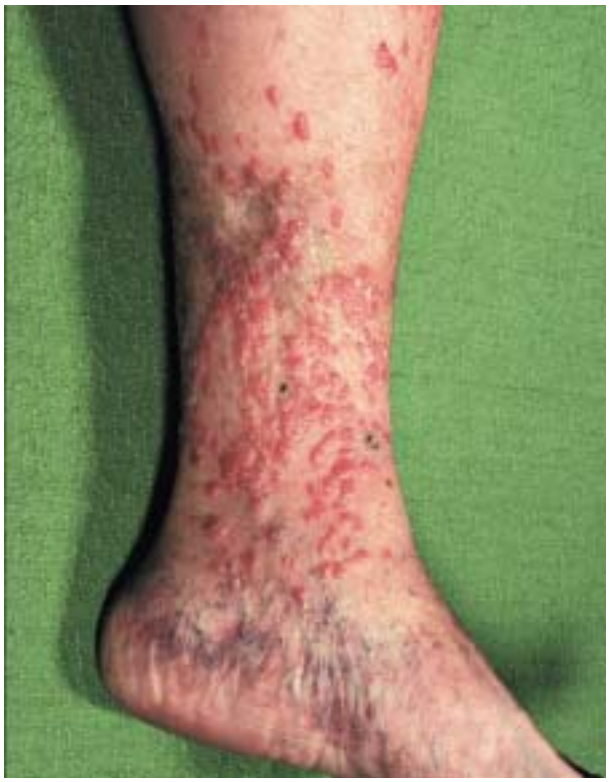

Figure 7a. *Extensive In-transit metastases*

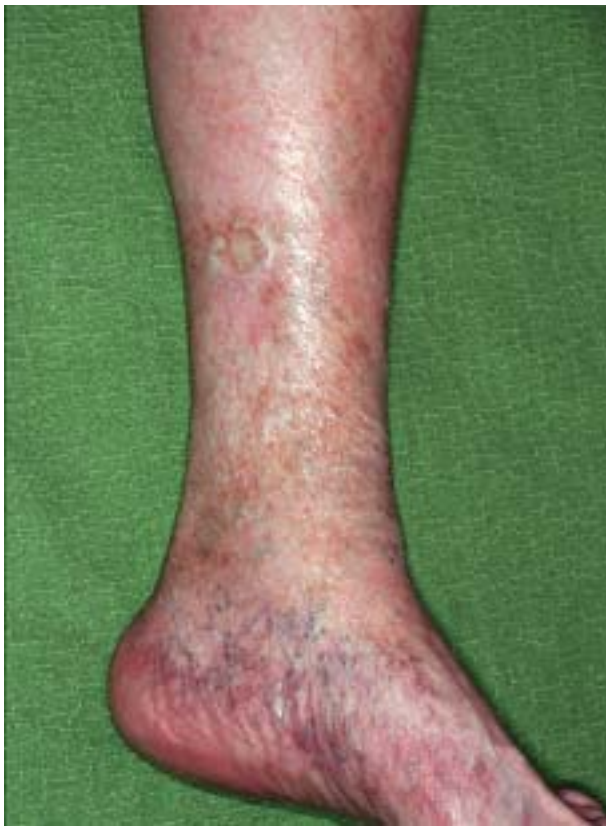

Figure 7b. *Nine months after ILP*

Another biological therapy undergoing clinical trials is Interleukin-2 (IL-2). This cytokine acts by inducing lymphocyte-mediated killing of tumour cells.[28] Due to its promise shown in trials IL-2 is currently the only FDA-approved systemic biologic therapy for metastatic melanoma.[29] However, its clinical use is significantly limited by toxicity due to activation of other pro-inflammatory cytokines.

Vaccines to various melanoma antigens have also been used in attempt to control metastatic disease without causing systemic toxicity.[30] However, despite being able to demonstrate the production of antibodies in treated

patients, the clinical results have been poor. Trials are still being conducted as new targets are identified.

The most recently investigated agents are those targeting cellular growth factors. Already used in the treatment of metastatic colorectal cancer, the Vascular Endothelial Growth Factor (VEGF) inhibitor bevacizumab is currently under investigation following the identification of target molecules on the surface of melanoma cells.[31] Another novel agent, sorafenib, acts by inhibiting cell growth signal transduction pathways and is the current subject of clinical trials in combination with cytotoxic chemotherapy.[32]

Unfortunately, despite intensive research into new therapies, survival in the presence of metastatic disease has barely altered over the past 20 years.

Conclusions

Long-term follow-up consistently shows that as the thickness of the primary tumour increases survival decreases. It is also clear that treatment of advanced disease is difficult and associated with significant morbidity. With this in mind there can be several approaches to improving outcomes for patients with melanoma.

Firstly, it is sensible to consider mechanisms of prevention and early detection. Public health strategies such as the "Sun Smart" campaign and use of the "ABCDE" system for evaluating skin lesions are clearly key components.[5]

Secondly, continued basic research into tumorigenesis and mechanisms of tumour spread will hopefully lead to less toxic and more effective systemic therapies. Understanding the molecular pathways that regulate melanocyte growth (e.g. the RAS/RAF pathway) has allowed the development of agents to specifically target melanoma cells. Monoclonal antibodies such as sorafenib and anti-CTLA-4 act to modify tumour growth and improve T-lymphocyte mediated tumour killing respectively.

Finally, surgical trials such as the Multicenter Selective Lymphadenectomy Trials I and II will hopefully provide information that will refine surgical treatment and improve patient follow-up after treatment of primary disease.

Ultimately, these collaborative efforts between medical researchers, public health physicians and clinicians will lead to further advances in the management of cutaneous melanoma.

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Dr Romesh Markus

Intravenous Thrombolysis for Acute Ischaemic Stroke

Introduction

Acute ischaemic stroke is a medical emergency. Untreated, the consequences are devastating for the patients and their carers. Stroke is the third leading cause of death and the leading cause of disability in Australia.

Although studies showing that thrombolysis improved clinical outcome in acute ischemic stroke were published 10 years ago its adoption into routine clinical practice has been dogged by controversy over its practicality and safety. Worldwide only a small proportion of eligible stroke patients receive this biologically potent therapy. In Australia, the proportion treated is even smaller. In this article the rationale for stroke thrombolysis and the results of its use at St Vincent's Hospital are reviewed.

Pathophysiology Of Acute Ischaemic Stroke

The viability of brain tissue is dependant on constant provision of energy substrates (glucose and oxygen) via the circulation. In acute stroke, abrupt interruption of focal cerebral blood flow results in reduced delivery of oxygen and glucose and the consequent energy failure induces a time dependent cascade of functional and metabolic changes in the hypoperfused brain. Infarction occurs initially in the region with the most severe reduction of blood flow. Surrounding the infarct core is a hypoperfused, functionally impaired brain region that is threatened by necrosis (Figure 1). This region, termed the ischemic penumbra retains sufficient metabolism to maintain cellular viability for a period of time and is potentially salvageable. Unless early reperfusion occurs the ischemic penumbra progressively evolves towards infarction. Survival of the penumbra is one of the main determinants of clinical recovery.[1]

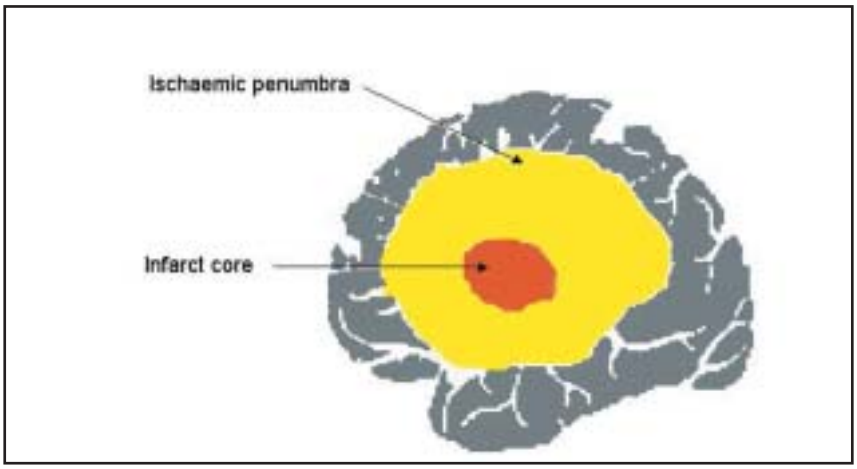

Figure 1: *Following occlusion of a cerebral artery, infarction occurs initially in the most severely hypoperfused region (infarct core). The hypoperfused, non-functional brain that is potentially viable and surrounds the infarct core is termed the ischaemic penumbra. Thrombolysis in acute ischemic stroke is aimed at rescuing the ischaemic penumbra thereby limiting infarct size to improve neurological and functional outcome. In the absence of timely reperfusion, the infarct core expands at the expense of the penumbra.*

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This concept of an ischemic penumbra has three important clinical implications. Firstly, it is potentially salvageable and hence the target of reperfusion with thrombolysis and other acute stroke interventions on the assumption that limiting infarct size will result in improved neurological and functional outcome. Second, it is a dynamic region that undergoes evolution into infarction progressively in time and space. Hence, the time window for thrombolysis (within three hours of onset) and the importance of delivering this therapy without delay ('Time lost is Brain lost'). Third, since infarct core and functionally impaired penumbral tissues both contribute to the neurological deficit their relative effects cannot be distinguished by clinical examination alone.

Thrombolysis for acute ischaemic stroke – trial results

Efficacy of intravenous alteplase (r-TPA), a tissue plasminogen activator produced by recombinant DNA technology, given within three hours of onset of ischemic stroke was shown by the pivotal NINDS study.[2] Subsequently, a pooled analysis of all trials with alteplase in ischemic stroke confirmed the improved clinical outcomes and also showed that benefit was greatest when treatment was started earlier.[3]

In general, these studies showed that there was a 30 per cent increase of excellent outcomes (independence with all activities) in patients treated with intravenous alteplase compared with placebo. The number needed to treat to obtain a clinical benefit is as few as three patients establishing it as one of the most effective therapies in medicine.

The major complication with intravenous thrombolysis is symptomatic intracerebral haemorrhage (ICH) that was observed in six per cent of patients treated with alteplase compared with one per cent of placebo treated patients.

Thrombolysis for acute ischaemic stroke – Clinical practice

Successful implementation of thrombolysis clearly requires efficient structured systems to deal with acute stroke as a medical emergency. This includes rapid recognition and response to stroke symptoms by the patient, paramedics and the treating physician and hospital. In international centers with experience in acute stroke management at present only 5-10 per cent of stroke patients receive thrombolytic therapy, primarily because of delayed presentation. In clinical practice, adherence to strict protocols for patient selection is crucial as deviations from the protocol have been associated with higher rates of adverse events, principally intracerebral haemorrhage.

Thrombolysis For Acute Ischaemic Stroke – St Vincent's Experience

Acute Stroke Protocol

At St Vincent's we established a 24 hour seven days a week comprehensive protocol for the management of acute stroke patients in December 2004. All patients presenting within three hours of stroke onset are triaged as category 2 and undergo rapid assessment (within 10 minutes of arrival) by a senior Emergency Physician. Monitoring of vital signs, intravenous cannulation and investigations including blood tests and urgent computed tomography (CT) scan of the brain is initiated according to a standing order. The decision to treat with thrombolytics is made by the attending neurologist after reviewing the patient, CT and documenting the severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS). Patients who fulfill strict thrombolysis inclusion criteria are treated with intravenous tPA (0.9mg/kg) in the Emergency Department with 10 per cent of the dose given as an initial bolus over one minute followed by a one-hour infusion. The patient and/or their next of kin are informed about the risks and benefits of thrombolysis prior to initiation of therapy.

All patients receiving thrombolytic therapy are entered into the Safe Implementation of Thrombolysis in Stroke (SITS) International Registry (http://www.acutestroke.org), an internet based, data entry monitoring system designed for auditing the efficacy and safety of routine thrombolytic therapy in acute ischemic stroke.

Results

Between December 2004 and August 2005, 25 patients were treated with IV thrombolysis. 95 per cent of patients with ischemic stroke presenting within three hours of stroke onset who fulfilled eligibility criteria received thrombolytic therapy. This represents six per cent of all stroke admissions during this period which is comparable to the proportion treated in international stroke centres.

The severity of the ischaemic stroke according to NIHSS grading was similar to the population in the large

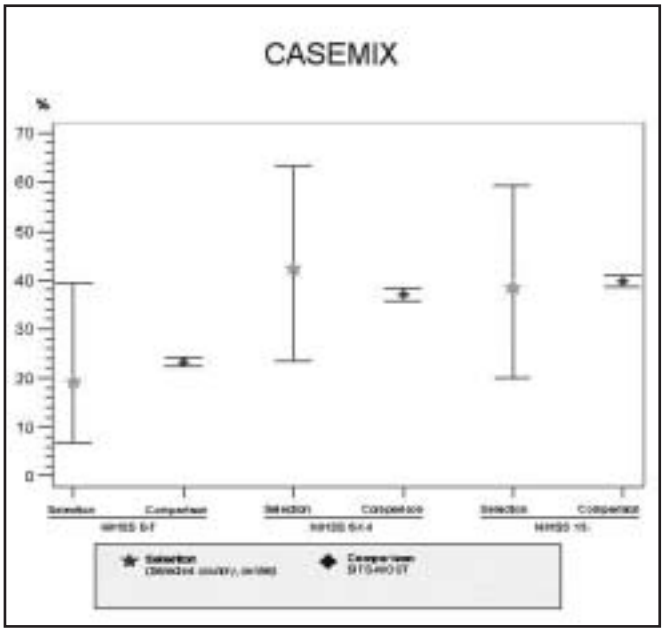

Figure 2. *Stroke Severity graded by the National Institute of Health Stroke Scale in patients treated with thrombolysis. The proportions of patients with mild (NIHSS <7), moderate (NIHSS 8-14) and sever (NIHSS >15) are similar at St Vincent's Hospital (SVH) compared with the Safe Implementation of Thrombolysis in Stroke (SITS) International Registry. Mean values with 95 per cent confidence intervals are shown.*

international registry (Figure 2). Over 80 per cent of treated patients had moderate to severe neurological deficit prior to treatment.

Significant neurological improvement was documented in just over 50 per cent of treated patients and 63 per cent of patients were completely independent at three months. Treatment efficacy was similar to that observed in the NINDS trial and comparable to results in the international registry (Figure 3). To date we have not observed symptomatic intracerebral haemorrhage in our treatment cohort.

Discussion

The comprehensive acute stroke management protocol established at St Vincent's Hospital enables delivery of safe and effective thrombolysis for eligible patients. One of the major reasons that only a limited number of stroke patients receive this treatment is delayed presentation to hospital. Interventions that are necessary to improve rates of thrombolysis in ischaemic stroke include public education to recognize stroke symptoms and optimizing paramedic response and transport times to minimize delays in hospital presentation.

The translation of the basic research understanding of the pathophysiology of acute ischaemic stroke into clinical practice with effective thrombolysis heralds a new era in acute stroke management. Parallel developments in imaging technology with CT (Figure 4) and MRI based perfusion imaging techniques that allow imaging of the ischemic penumbra may allow extension of the time window with targeted therapy for individual patients. [4]

The combination of reperfusion and neuroprotection may improve recovery after reperfusion. It is now possible to deliver lysis intra-arterially and remove clots mechanically and the role of these interventions is being clarified in trials. Furthermore newer thrombolytic agents that are more fibrin specific are being studied.

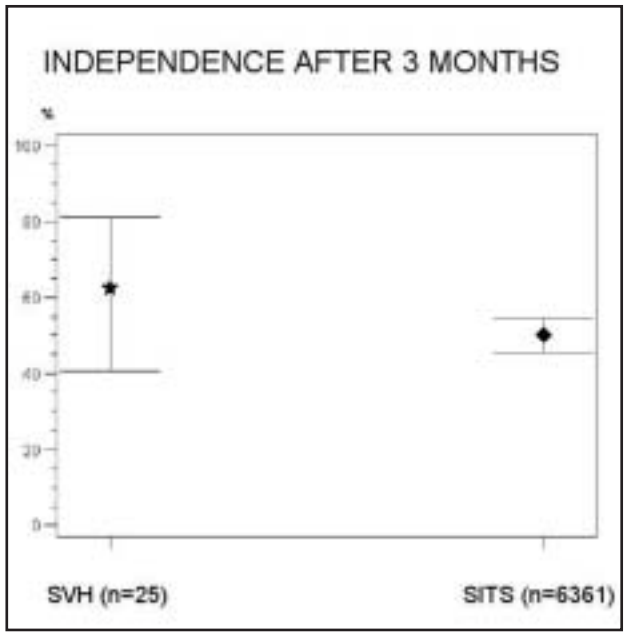

Figure 3. *The proportion of patients with ischaemic stroke treated with thrombolysis that regain independence at 3 months. The figures from St Vincent's (SVH) are compared with those from the Safe Implementation of Thrombolysis in Stroke (SITS) International Registry. Mean values with 95 per cent confidence intervals are shown.*

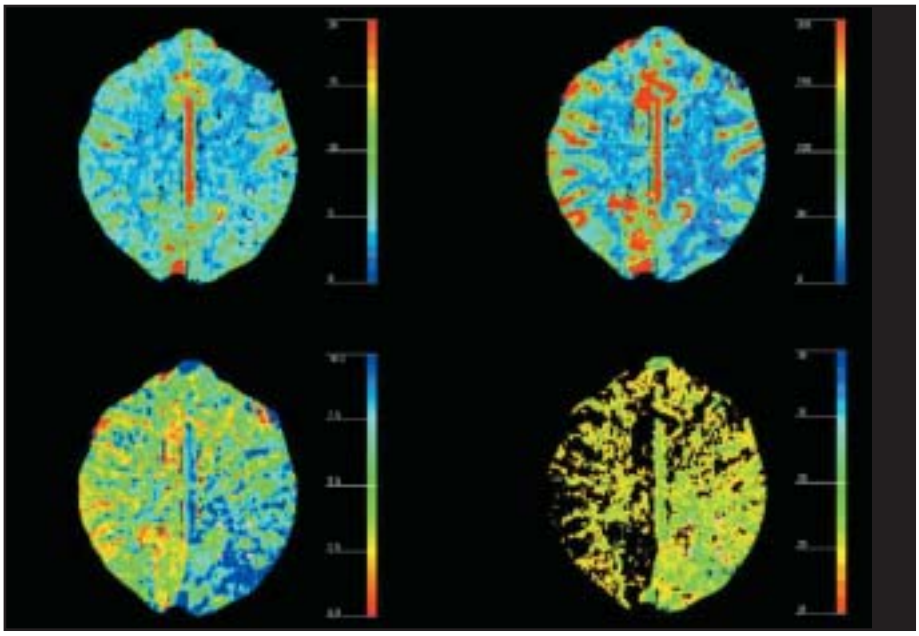

Figure 4: *CT Perfusion maps of a 60 year old female performed 2 hours after onset of sudden right hemiparesis, neglect and hemianopia. Bolus tracking CT perfusion studies generate maps of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP) of contrast enhancement. This patient has reduced CBF with prolonged MTT and TTP indicating hypoperfusion of the posterior left MCA territory. The relatively preserved CBV in this region reflects preserved metabolism. The patient received intravenous thrombolysis and made a complete neurological recovery with no infarction on follow up MRI. The hypoperfused brain region (reduced CBF with prolonged MTT and TTP) that has preserved CBV can be considered penumbral tissue. In this patient the penumbra contributed to the neurological deficit and its salvage by reperfusion was accompanied by complete clinical recovery.*

Acknowledgements

The study of CT perfusion in acute stroke is supported by The Ladies' Committee Sr Mary Bernice Research Grant (St Vincent's Clinic Foundation).

The support of the staff of the Emergency Department, Intensive Care Unit and Acute Stroke Unit at St Vincent's Hospital is gratefully acknowledged.

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2006 St Vincent's Clinic Foundation Grants

The Ladies' Committee Sr Mary Bernice Research Grant – $100 000
St Vincent's Hospital
Dr Romesh Markus – *"Acute ischaemic stroke: imaging viable brain tissue with dynamic perfusion computed tomography".*

The Tancred Research Grant – $50 000
Garvan Institute of Medical Research
Dr Ian Sutton – *"An investigation into the temporal gene expression profiles of microglia and macrophages in relation to the development of axonal injury in experimental allergic encephalitis"*

The K & A Collins Cancer Research Grant – $50 000
St Vincent's Hospital
Dr Reginald Lord – *"HER-2, EGFR and prognosis for oesophageal adenocarcinoma"*

The Di Boyd Cancer Research Grant – $20 000
St Vincent's Hospital
Dr Ian Cole – *"Molecular markers and mechanism of response to radiotherapy and EGFR directed therapies (IRESSA) in head and neck squamous cell carcinoma (HNSCC)"*

The Froulop Vascular Research Grant – $20 000
St Vincent's Hospital
Dr David Robinson – *"Correlation of carotid plaque histopathology with multidetector CT angiography"*

Annual Awards – $20 000 per project
Garvan Institute of Medical research
Dr Bryce Vissel – *"Viral mediated gene delivery in the nervous system: establishing an approach with utility for studying pathology and potential treatment for central nervous system diseases"*

St Vincent's Hospital
Dr Joanne Joseph – *"Investigating the mechanism of platelet glycoprotein lib/IIIa activation and microparticle formation in patients with platelet bleeding disorders"*

Victor Chang Cardiac Research Institute
A/Prof Diane Fatkin: *"Genetics studies in families with atrial fibrillation"*

St Vincent's Hospital
A/Prof Anne Keogh – *"Treatment of symptomatic advanced left ventricular failure with sildenafil – a single centre, investigator driven proof-of-concept, pilot study"*

St Vincent's Clinic
Dr Douglas Fenton-Lee – *"The St Vincent's Minimally Invasive Surgical (MIS) Training Centre"*
Dr Simon Tan – *"Computerised arthroscopy simulator for knee and shoulder arthroscopy"*

Travelling Scholarship – $10 000
The Committee recommended that 2 Travelling Scholarships be awarded:

Dr Devandra Segara – *To undertake further clinical experience and training in breast cancer diagnosis and surgery ay the Brigham and Women's Hospital in Boston, Massachusetts, USA*

Dr Steve Austin – *To study the mechanisms of thrombosis, reactivity of the autoantibodies and contributory factors of these conditions at University College London Hospital.*

Capsule Endoscopy

Dr Robert Feller

Background

Capsule endoscopy (CE) has established a new paradigm in GI investigation by providing a non-invasive method of entire small intestine (SI) imaging that has proven superior to all previous non-operative assessment. The complex looped configuration of the SI has previously made endoscopic examination difficult. Push enteroscopy (PE) may reach up to a maximum of 150cm beyond the duodenojejunal flexure in a total SI length of up to five metres and radiological methods are insensitive for subtle mucosal lesions.[1] Intraoperative enteroscopy (IOE) is usually associated with a prolonged ileus and occasionally more serious problems such as serosal tears and avulsion of mesenteric vasculature. The recent addition of "double balloon" enteroscopy (DBE) has created a complementary pathway with CE of improved SI access.

The history of CE development is dominated by two scientists, Dr Gavriel Iddan (optical engineer, Israel) and Professor Paul Swain (gastroenterologist, UK) who were working independently and, indeed, without knowledge of each other's research until joining forces in 1997 and producing the first prototype in 1999 ("M2A"™, [now "PillCam"™] GIVEN Imaging, Israel). The importance of this discovery was recognized by the publication of an article in *Nature* in 20001 which had only once previously published work in endoscopy. CE was given FDA approval in the USA in 2000, has been available in Australia since 2001 and at St Vincent's Hospital since December 2003.

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CE Examination

CE is performed chiefly as an outpatient examination after liquid diet and an overnight fast with currently variable inclusion of bowel preparation and prokinetic agents. The capsule (Figure 1) is 26mm by 11 mm, weighs 3.7g and emits a radiofrequency signal whilst taking two frames per second. A sensor array consisting of eight discs in adhesive sleeves is applied to the abdomen and connected to a data recorder that is worn in a belt. The patient is able to drink at two hours and eat four hours after capsule ingestion. The patient is encouraged to ambulate during the day and returns after eight hours. The equipment is removed and the patient goes home. The capsule passes through the bowel via normal peristalsis (Figure 2) and, much to the patient's relief (!), does not need to be retrieved. The data recorder is connected to the dedicated computer workstation, the study downloaded and converted to a video for reporting. Frames of interest can be recorded and the entire study stored on CD or DVD.

Contraindications

These include known SI strictures, swallowing disorders and permanent pacemakers (PPM). However, many patients with PPMs (including two at St Vincent's) have now had CE studies under close monitoring with no reports of adverse events. Swallowing difficulties may be overcome if necessary by endoscopic placement of the capsule.

Figure 1 *capsule endoscope*

Difficulties/Complications

Variation in visibility is an issue and the ideal bowel preparation remains controversial and a focus of ongoing trials. Similarly, the use of prokinetic agents such as metoclopramide to ensure passage to the caecum (particularly by improving gastric emptying) varies between centres. Failure to reach the caecum during the study period has been reported to occur in 10-20 per cent of studies but may not significantly affect diagnostic yield. The risk of capsule retention (defined now as non-passage after two weeks)[3] is approximately 1.9 per cent. In many of these cases, the retention has occurred at the site of previously obscure pathology and provided the diagnosis. Interestingly, one patient has refused surgery for a retained capsule and has remained asymptomatic for three years reflecting long-term integrity of the capsule itself.

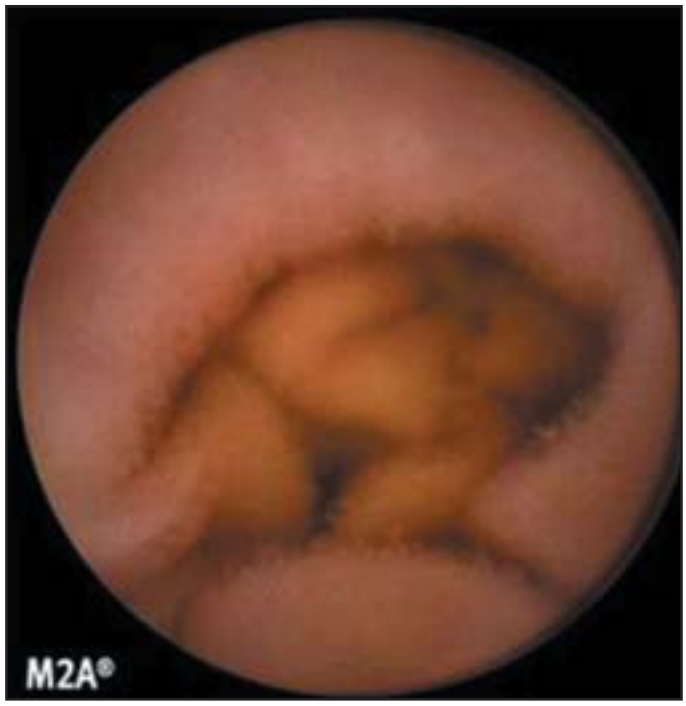

Figure 2 *normal jejunum*

CE vs Other Modalities Of SI Imaging

The most common routine assessment of the SI remains barium follow-through (SBFT) which relies on changes in distensibility and mucosal pattern but which is the least sensitive and compares poorly to CE in the investigation of obscure GI bleeding. CE has proven to be superior in yield in this setting to enteroclysis, CT, MRI and push enteroscopy and the equivalent of the "gold standard" IOE1.[4] Early comparisons with "double-balloon" enteroscopy (DBE) suggest at least equivalent yield.[5] DBE has the advantage of potential therapeutic intervention but requires sedation, often two sessions of 1-2 hours without necessarily achieving complete SI intubation and a relatively low but higher risk of SI injury.

CE – Clinical Applications

CE has been employed in the investigation of obscure GI bleeding, suspected Crohn's disease, non-steroidal anti-inflammatory drug SI injury, SI tumours, complicated coeliac disease, polyposis syndromes and radiation enteritis. The yield in the assessment of unexplained abdominal pain, particularly without peripheral evidence of an inflammatory or other disorder, is low.

CE in the Investigation of Obscure GI Bleeding (OGIB)

OGIB constitutes approximately five per cent of all GI bleeding presentations and a SI source is present in 45-70 per cent of these patients. Causes may include angiodysplasia(=angioectasia) (most common), ulcers, tumours, diverticula and varices.

Investigation of OGIB (manifesting as overt bleeding or iron deficiency anaemia with positive faecal occult blood testing and when panendoscopy and colonoscopy are negative) is currently the major indication for CE and the only one for which there is a Medicare rebate in Australia. Previously, repeated endoscopic assessment, SI radiology, angiography, nuclear medicine imaging and IOE have all been required with variable success and considerable cost to the patient and the healthcare system.

A variable yield of CE in OGIB of 40-83 per cent has been reported.[6] A recent meta-analysis of 21 prospective studies comparing yield of CE to other diagnostic modalities[7] expressed results as incremental yield (ie yield CE minus yield other modality) and found CE vs : all SI imaging(+61 per cent), CT(+63 per cent), MRI(+50 per cent), push enteroscopy (+33 per cent) and IOE(0 per cent). These results suggest that CE is markedly superior to SI radiology and importantly the equivalent of IOE for the entire SI. The most common findings were angioectasia followed by ulcers/inflammatory lesions and tumours.

It is important to know whether this increased diagnostic yield leads to positive outcomes. Pennazio et al[8] demonstrated complete resolution of bleeding and definitive treatment (endoscopy or surgery) in 41- 86 per cent of 100 patients depending on the type (overt/occult, ongoing/previous) of bleeding. The highest diagnostic yield (92 per cent) and the highest definitive intervention (86 per cent) occurred in those patients with ongoing overt bleeding. Other studies have not been able to identify reliable clinical predictive factors for a positive study. It is worth noting that CE has identified caecal bleeding sources not found at colonoscopy.

The following brief case histories from the St Vincent's Gastroenterology Unit illustrate the role of CE in identification and potential resolution of OGIB:

Case 1

A 71-year-old man suffered recurrent iron deficiency anaemia. He was taking

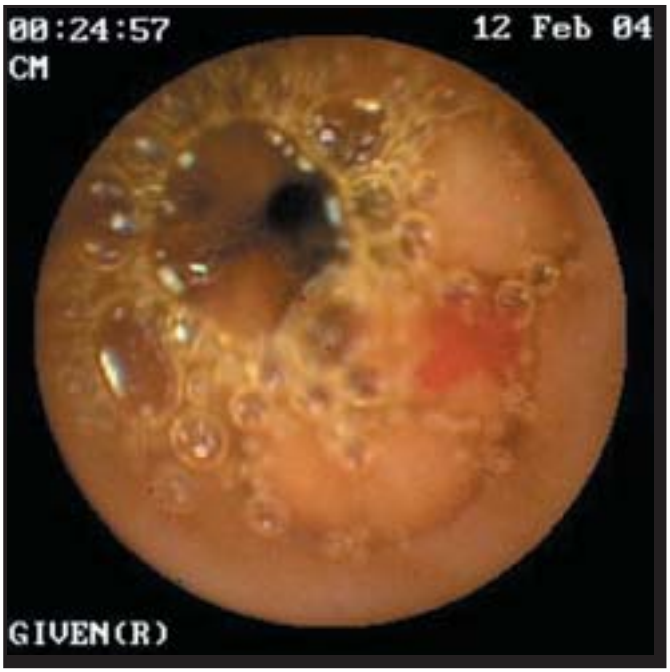

Figure 3 *angioectasia jejunum*

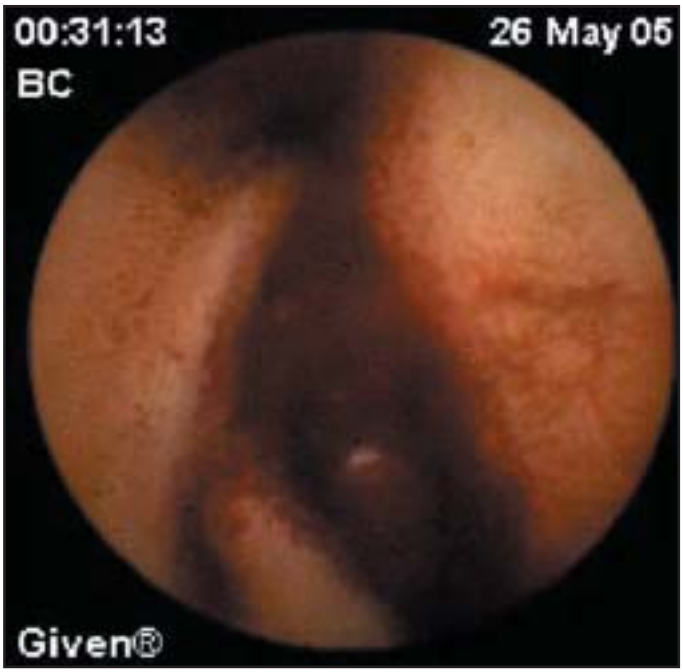

Figure 4 *bleeding vascular lesion jejunum*

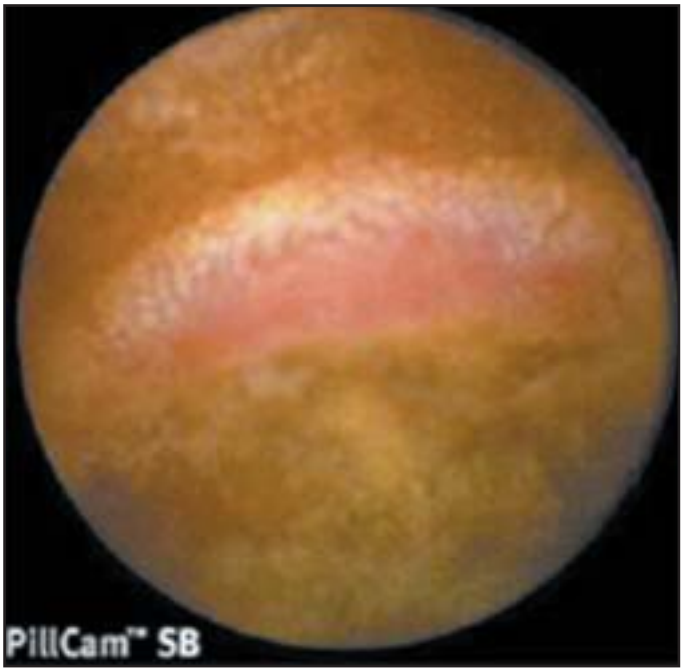

Figure 5a *denuded area jejunum*

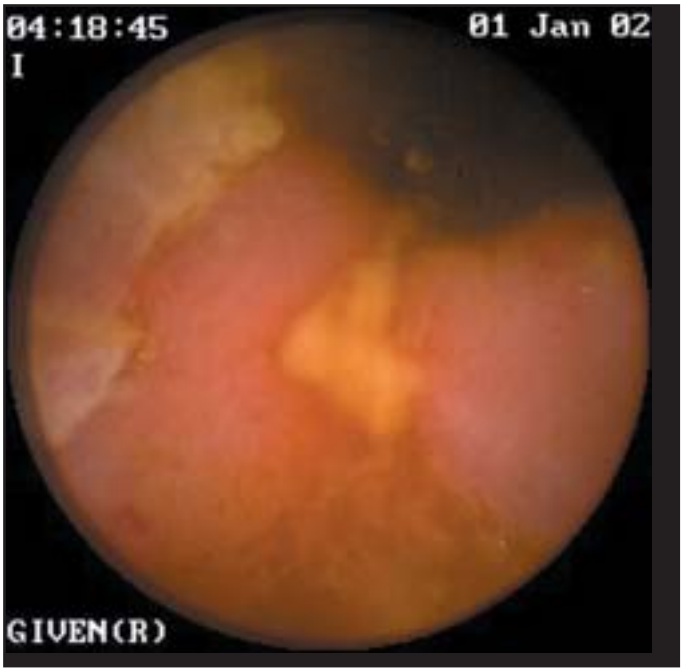

Figure 5b *ulcer in ileal Crohn's disease*

clopidogrel for coronary artery disease and had severe Chronic Airways Limitation. He had been admitted on four occasions for transfusion and had undergone two endoscopies and colonoscopies and a barium SBFT with no lesion identified. CE was performed and identified an angioectatic lesion in the proximal jejunum (Figure 3) that was ablated by argon plasma coagulation (APC). No further transfusion has been required.

Case 2

A 79-year-old man was transferred to St Vincent's from a country centre with ongoing melaena. Over the previous three months, he had suffered recurrent occult bleeding, undergone five endoscopies and colonoscopies and received a total of 11U packed cells. CE was performed and identified an actively bleeding vascular lesion in the jejunum (Figure 4). An initial push enteroscopy was able to access the lesion and place Endoclips to achieve haemostasis; a second PE was performed after further bleeding and APC applied with resolution.

CE and Crohn's Disease

CE may have a role in diagnosis of suspected SI Crohn's disease (CD), SI involvement in ileo-colonic CD and differentiation of indeterminate colitis. CD may involve the SI alone in 25-35 per cent of cases. Definitive diagnosis may be difficult particularly in proximal SI disease. Diagnostic yields of up to 60-70 per cent have been reported and positive findings range from denuded villi (Figure 5a) to gross ulceration[9] (Figure5b). A recent meta-analysis of nine studies comparing CE to other imaging modalities[10] found CE significantly superior to SBFT, CT, MRI, PE and colonoscopy with ileoscopy. Further analysis suggested that the benefit was chiefly in those patients with already established non-stricturing CD being evaluated for SI recurrence

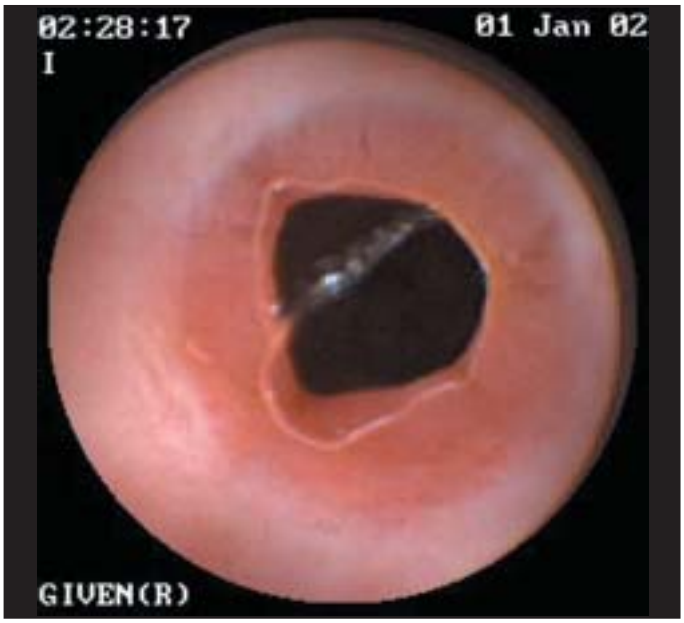

Figure 6 *typical "diaphragm" stricture from NSAID injury*

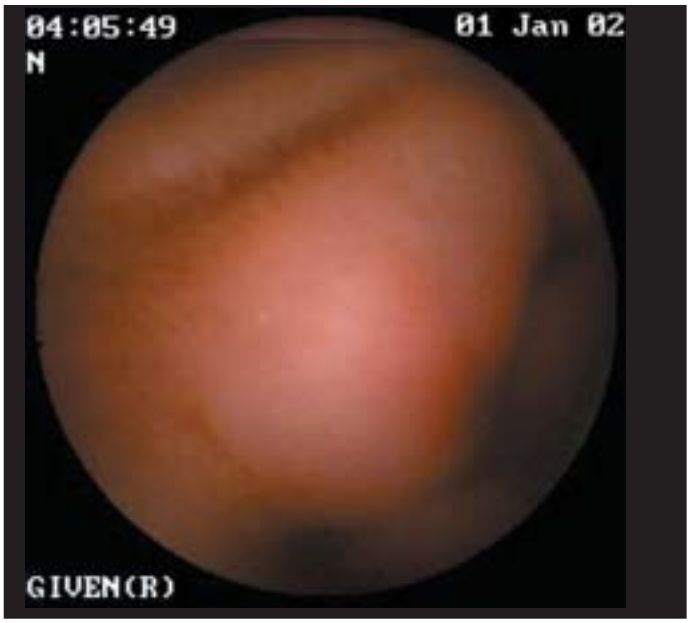

Figure 7 *carcinoid tumour seen as submucosal mass*

although there was a trend to significance for CE compared to SBFT and CT in suspected initial presentation of CD. Adoption of International Conference on Capsule Endoscopy (ICCE) working party guidelines on the definition of suspected CD may improve the CE yield. At least two of the following should be present: pain or diarrhoea, elevated inflammatory markers, iron deficiency anaemia, hypoalbuminaemia, positive serologies, family history IBD and extra-intestinal manifestations. It remains routine for a SBFT examination to be performed prior to CE to exclude strictures although it is relatively insensitive. If strictures are suspected, a radio-opaque, dissolvable Patency capsule(tm) can be employed to assess retention risk. CE has been shown to alter management in patients with both documented and suspected CD usually by demonstrating inflammatory disease not detectable by other methods.[11] It may now form part of the diagnostic algorithm after endoscopy, colonoscopy and SBFT have been performed.

CE and NSAID Enteropathy

Non-steroidal anti-inflammatory drugs (NSAID) are reported to cause GI injury in 10-30 per cent of those on regular treatment. Peptic ulceration is well recognized but SI injury may also occur and range from mucosal breaks to ulcers and perforation. The "diaphragm" stricture (Figure 6) that is well demonstrated by CE may be pathognomonic for NSAID injury. CE was instrumental in establishing the lower GI injury rate of Cox-II vs Cox-I inhibitors.[12]

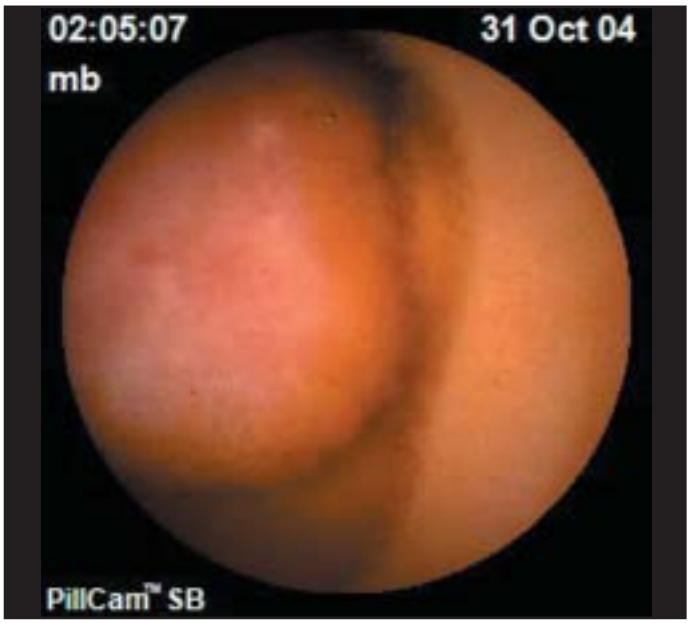

Figure 8 *jejunal polyp of Peutz-Jegher's syndrome*

CE and SI Neoplasms

The SI is the site of 1-2 per cent of all GI tumours and may include adenocarcinoma , carcinoid (Figure 7), lymphoma and gastrointestinal stromal tumours. A prevalence of SI tumours of 6-9 per cent was found in two large series (n= 416, n=562)[13,14] of consecutive patients undergoing CE, most of whom had obscure GI bleeding. CE may have a role in surveillance in hereditary polyposis syndromes particularly Peutz-Jegher's syndrome (PJS) (Figure 8) in which SI polyps distal to the reach of conventional endoscopy may progressively increase in size, cause obstruction, bleed and undergo malignant change. In familial adenomatous polyposis (FAP) patients, duodenal polyps accessible by conventional endoscopy are most common but small series of CE in these patients have demonstrated bleeding polyps distal to duodenoscopy.[15]

Other Applications

CE may have a role in investigation of refractory coeliac disease when findings may include ulcerative jejunoileitis, lymphoma and adenocarcinoma. Other potential applications include HIV, graft vs host disease and sub-acute SI obstruction. CE is being employed increasingly in paediatric medicine.

CE at St Vincent's Hospital, Sydney

The GE Unit has now performed just over 200 studies. We presented data on the first 75 consecutive studies at Australian Gastroenterology Week in 2005. The overall positive yield was 50 per cent (including angioectasia, erosive changes suggesting Crohn's disease, jejunal polyps). A yield of 91 per cent (9/11 patients) was obtained in those with ongoing, overt bleeding. Of these 11 patients, five underwent definitive treatment (argon plasma coagulation or heater probe for angioectasia, resection of jejunal polyp) and all remained clinically stable after a mean follow-up of eight months. Our data further supported an early role for CE in investigation of obscure GI bleeding particularly in those with active bleeding. A trial is planned to employ CE immediately after a negative upper endoscopy in patients presenting with melaena to further improve yield, assist early intervention and avoid unnecessary investigation.

Future

Software upgrades will allow shorter reading times and "real-time" viewing. Further prospective trials with standardized nomenclature and outcome assessment are underway. An oesophageal capsule has been developed that may be useful in screening for Barrett's mucosa in patients with chronic oesophageal reflux and for varices in cirrhotics. A prototype capsule for the colon has also been developed and is undergoing clinical trials. It is hoped that the capsule's functions will eventually include luminal content assessment and biopsy.

Summary

CE is a novel technology that allows direct visualization of the SI by a non-invasive, ambulatory, physiological study that has proven superior to other standard modes of SI imaging and the equivalent of more invasive methods such as IOE. The advent of DBE has provided a means of complementary therapeutic access if required after CE assessment. The role of CE in investigation of OGIB is now established. There is increasing data for other applications. It is a safe procedure that can reduce the need for repeat or more invasive investigation and thus reduce patient morbidity and health care costs.

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Modern Management of Menorrhagia

Dr David Eizenberg

Introduction

Menorrhagia is a very common symptom in women in the third and fourth decade. It has been estimated that, during a normal period, some 20 – 80mls of blood is lost. Defining menorrhagia is difficult to reconcile objectively and is often dependant on a woman's own perception. It is defined as blood >80ml lost per menstrual cycle. Some may complain of menorrhagia but, when questioned, the bleeding is often within normal limits.

The incidence of menorrhagia is unknown. However, approximately 10 per cent of women will complain of increasing heavy periods as they get older. If periods are interfering with a woman's lifestyle, treatment is recommended. Menorrhagia is the main cause of iron deficiency anaemia in women of reproductive age.

Aetiology

Fibroids – About 25 to 30 per cent of women will experience fibroid enlargement of the uterus at some stage in their lives. Evidence from post-mortem examinations shows that many of these are asymptomatic and often not even diagnosed on clinical examination. However, the effect, as far as symptoms are concerned, is not dependent upon size or number.

The fibroids can be any size, are often multiple and the author has personally seen a uterus with literally hundreds of pea-sized fibroids much like a bean bag. Single fibroids can be quite significant in size weighing up to 2kgs or more. As well as causing menorrhagia, they can also distort the shape of the uterus so that it presses on other organs in the vicinity, particularly bladder and bowel.

Adenomyosis – Sometimes called internal endometriosis, the aetiology is still obscure but it is probably a variation of endometriosis. The uterus can be clinically enlarged without any obvious lesions on ultrasound. However, adenomas can grow in size so that they resemble fibroids. The disease is estimated to occur in as many as 50 per cent of women with menorrhagia and is often accompanied by significant dysmenorrhoea. The latter is usually worse on the heaviest day of bleeding. It can be positively diagnosed by pathological examination of the hysterectomy specimen.

Endometriosis – Grade III or Grade IV endometriosis can cause heavy periods. However, this is often associated with significant pain as a feature of the condition. The dysmenorrhoea typically occurs up to 7 – 10 days prior to the onset of menses.

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Polycystic Ovary Syndrome – Usually this condition will produce oligo – or amenorrhoea but occasionally, in the older age groups, menorrhagia can be a problem.

Dysfunctional Uterine Bleeding – Dysfunctional uterine bleeding is a term used when no active pathology is obvious in the presence of significant menorrhagia and a normal size uterus. The cause of this condition is unknown.

Endometrial hyperplasia and carcinoma of the endometrium – This is a rare cause of menorrhagia. Most commonly, this will present with acyclical bleeding but, in women with menorrhagia, it needs to be excluded particularly if intermenstrual bleeding is an additional symptom.

History

It is important to take a detailed menstrual history in women with heavy periods. The patient may state that the bleeding is heavier than it used to be but, on close questioning, is still within normal limits.

Enquiry into the amount of sanitary pads needed during a period will often give an indication of the degree of bleeding. For instance, if a sanitary towel and a tampon are required together and/or changed every hour or so, this is abnormal. Women will sometimes complain of leaving puddles on the bed sheet at night and reveal that their social activities are severely curtailed during period time.

It is also important to ascertain whether dysmenorrhoea is a feature, to ask whether the pain precedes the bleeding and, if so, for how long and which day is the worst for pain. Treatment modalities should also be enquired into such as the use of non-steroidal anti-inflammatory agents (NSAIDs) for pain and their effectiveness. The passage of clots merely indicates that the bleeding is significantly heavy. Other related gynaecological symptoms should be noted.

Dyspareunia may be superficial or deep in nature. If the latter, it may indicate the presence of endometriosis.

Always check for urinary difficulty especially frequency, nocturia, incontinence (stress or otherwise, empty or full bladder) poor stream, dysuria and incomplete emptying.

Obviously, a detailed general medical history is required specifically looking for conditions which can increase the risk of bleeding.

Examination

General physical examination looks particularly for abdominal masses arising from the pelvis which could indicate fibroid enlargement. Pelvic examination measures the size, shape and mobility of the uterus as well as tenderness. Adnexal masses should be noted and a papsmear performed as required.

Investigations

Full blood examination looks for evidence of anaemia and, if necessary, arrange iron studies.

Detailed pelvic ultrasound. The ultrasound should include measurement of the uterus looking for fibroid enlargement and position. Adenomyosis often shows as heterogeneous flecks in the myometrium. The formula: length x width x depth(in cms) x 0.54 will give the approximate uterine volume, normally between 60 – 90ml. It is higher in women who are multigravida. Ovarian and adnexal masses are assessed to see if the disease process is confined to the uterus.

The following are required if the history indicates: thrombophilia screening tests, haemoglobinopathy screen, coagulation studies, hormone studies (FSH, LH, oestradiol, testosterone, SHBG, DHEAS and free androgen index) and thyroid function tests.

A hysteroscope and curette is performed to exclude local lesions if the ultrasound reveals intrauterine pathology and is mandatory in the presence of intermenstrual or acyclical bleeding.

Medical Management

NSAIDS

Mefenamic acid (Ponstan), 500mgs q.i.d. for 3 – 4 days, given as soon as the period commences will often reduce blood flow in women with minimal symptomatology. Other NSAIDs are not quite as effective but may be tried if Ponstan is unsuccessful.

Hormone combinations.

The oral contraceptive pill was the mainstay of medical treatment in the past. This will still give some women good cycle control but, unfortunately, the higher dose progesterone pills are required to control bleeding and side effects such as mood swings and mastalgia are common.

Progestogens such as medroxy-progesterone acetate (Provera) and norethisterone (Primolut N) can be used as an alternate treatment but high doses are often required. The drugs are best given cyclically, medroxyprogesterone acetate, 10 to 30mgs daily and norethisterone, five to 10mgs daily for 7 – 14 days prior to periods. The unwanted side effects of moodiness, depression, bloatedness and breakthrough bleeding will inhibit treatment. Recent controlled clinical studies have noted limited success compared with placebo.

Tranexamic acid (Cyklokapron).

Women with heavy menstrual bleeding have higher levels of plasminogen activators in the endometrium compared with those with normal menstrual loss. Antifibrinolytic agents (plasminogen activator inhibitors) such as tranexamic acid, competitively inhibit the conversion of plasminogen to plasmin and counteract the fibrinolytic activity within the endometrium.

Recent studies have shown that this is now the drug of choice for dysfunctional uterine bleeding. The dose is 1gm q.i.d. taken at the start of the first sign of bleeding. The drug is used for three to four days each menstrual cycle and is usually well tolerated by most women. However, the manufacturers do not recommend that the drug be used for

longer than six months and its use should be reassessed.

There are no controlled clinical trials which detail effectiveness over longer periods. However, some women, if they use the "wonder pill" are happy to take the risk in regard to safety. It is contraindicated in women with a history of thrombosis or are high risk (e.g. thrombophilia).

The Royal College of Obstetricians and Gynaecologists recommends tranexamic acid and mefenamic acid as first-line drugs for women with menorrhagia who either do not require contraception or prefer non-hormonal treatment.

Anti-oestrogens.

Danazol (Danocrine) in a dose of 100 – 200mgs, can be used for control of menorrhagia. However, because of debilitating side effects, the drug is rarely used nowadays. Its use should be limited to women who cannot tolerate other forms of medical management and are reluctant to undergo surgery. It suppresses the pituitary-ovarian axis.

GNRH agonists.

Goserelin acetate (Zoladex) will induce a menopausal pattern in women. It is listed on the Pharmaceutical Benefits Scheme for the treatment of endometriosis. However, Zoladex will certainly reduce the volume of the fibroid uterus by up to 50 per cent. Two or three doses at monthly intervals will shrink fibroids, produce amenorrhoea and allow an abdominal procedure, i.e. hysterectomy, to be converted to a vaginal approach. Alternatively, it can be given to suppress menstruation in women who are anaemic prior to undertaking surgery. It will often obviate the need for transfusion. The maximum dose of six months should not be exceeded because of the risk of bone demineralisation.

Levonorgestrel intrauterine system; LNG-IUS (Mirena).

This is a progesterone device inserted into the uterus for up to five years. In 80 per cent of women, it will significantly reduce menstrual blood flow (mean reduction 75 – 95 per cent) and, in 30 per cent, amenorrhoea will be induced after one to two years. The device releases 20 micrograms of the progesterone, levonorgestrel, every 24 hours to inhibit the endometrium. There is sometimes a trade-off in that menses, whilst significantly less, may be erratic and unpredictable. However, most women are able to tolerate the device and, worldwide, the current number of users exceeds 4 million. It does require a normal size uterine cavity and the results in women with significant fibroid enlargement of the uterus are unpredictable. The device is listed as a pharmaceutical benefit for contraception and, as it is an IUD, it is obviously contraceptive.

The device can easily be inserted in the consulting room in the majority of women, preferably at the end of a period. It can also be inserted at the time of a diagnostic hysteroscopy.

Recent studies have shown that small amounts of levonorgestrel enter the blood stream and may cause side effects of mastalgia and mood changes in susceptible women.

Surgical Management

Endometrial resection (ablation).

Endometrial resection involves destroying the endometrium by surgically removing it or destroying by electrocautery. This is a hysteroscopic technique using a cutting device or a roller ball. The technique has been used for 15 years.

Initially, it was thought that the operation would reduce the incidence of hysterectomy but this has not occurred. The endometrial ablation seems to be an additive medical technology rather than a substitute for hysterectomy.

The operation requires extensive expertise and does have significant complications such as haemorrhage, infection, perforation of the uterus, damage to adjacent organs and fluid overload. The success rate, after five years, i.e. women requiring no further surgery, is 75 per cent and only about 15 per cent of women will experience longterm amenorrhoea.

Second generation devices have been developed to reduce the complication rates of perforation and haemorrhage. Various techniques are used including thermo-ablation (Thermachoice, Cavaterm), microwave (Microsulis), radio-frequency (Nova Sure) and cryoablation. These use computer-controlled systems to destroy the endometrial lining by heat.

Amenorrhoea is produced in about 10 – 20 per cent, reduction in periods in 50 – 70 per cent and no change in 10 – 15 per cent depending on method used. Long term followup, >5years, has revealed a failure rate of 25 – 30 per cent i.e. women requiring further treatment, usually hysterectomy.

The technique is not suitable for use in women with a significantly enlarged uterus (more than 150ml). Recent studies have compared ablation to the LNG-IUS and the latter has equal efficacy with less complications.

Uterine artery embolisation.

Microscopic beads of silicon are inserted in a bolus (through the femoral artery) into the uterine vessels. The idea is to embolise the uterine artery to reduce the blood supply to the uterus. It has been used in the treatment of fibroids where it will reduce the volume by approximately 50 per cent. However, there have been quite significant serious side effects and the technique should be classified as experimental.

Hysterectomy.

Hysterectomy is still the treatment of choice for menorrhagia particularly associated with significant fibroid enlargement or adenomyosis. However, recently, the emphasis has changed from utilising abdominal hysterectomy as mainstream management to vaginal surgery.

Recent studies have shown that simple vaginal hysterectomy (i.e. not associated with prolapse repair) is the surgery of choice as it has the lowest morbidity, complications, shortest operating time and return to normal activities. It is also the cheapest, does not require expensive equipment or extensive training and expertise.

If hysterectomy is being considered as optimum management, the vaginal approach is always considered initially, not as previously where it was only used in conjunction with a repair operation.

Previous absolute contraindications are now considered only relative.

These are:-

a) Nulliparity or no previous vaginal deliveries. If the uterosacral ligaments can be isolated vaginally and there is good vaginal vault access, surgery is feasible. There is almost always uterine descent into the vagina unless endometriosis is present.

b) Previous pelvic surgery (including caesarean section). If the disease is confined to the uterus then a vaginal approach can be countenanced. If necessary, a peri-operative laparoscopy can exclude pelvic adhesions, ovarian disease or endometriosis. In women who have had caesarean sections one has to be careful to isolate the uterovesical pouch and not damage the bladder.

c) A large uterus. If the uterine volume is less than 280 – 300ml (approximately 12 week gestational size), surgery by the vaginal route is optimal management. Techniques such as intraoperative uterine bisection, myomectomy or coring can be used to "debulk" the uterus to allow vaginal removal. Large uterine fibroids can also be reduced in size by two or three months of Zoladex therapy (about 50 per cent reduction in volume). Uterine sizes up to 800ml or more can be dealt with successfully and safely in expert hands.

d) Oopherectomy. In the majority of hysterectomies performed for benign conditions, the ovaries do not have to be removed. However, if required, they can be removed vaginally in up to 90 per cent of women.

Laparoscopically assisted (or subtotal) hysterectomy will only add the complications of laparoscopy to hysterectomy. If the ovaries must be removed or the disease process is outside the uterus, the technique can be justified.

Abdominal hysterectomy should be reserved for very large fibroid disease, extensive endometriosis or genital tract carcinoma (cervix, uterine, ovarian.)

The percentage of hysterectomies that can be performed vaginally is therefore in the order of 80 per cent to 90 per cent.

Summary

Hormone (progesterone or oral contraceptive pill) treatment can still offer help to some women. However, the effects may be only temporary and the longterm benefits of limited value. Danazol and Zoladex are usually reserved for women awaiting surgery.

Tranexamic acid is the drug of choice for short-term management and some women are willing to continue treatment indefinitely. Mefenamic acid is not as effective, but if it works, can be used indefinitely.

The LNG – IUS (Mirena) device is now the choice for medical management of menorrhagia particularly for dysfunctional uterine bleeding. It is safer and just as effective as endometrial resection. It is also reversible.

Vaginal hysterectomy is the surgery of choice for a moderate size (100 to 300ml) fibroid uterus or presumed adenomyosis particularly in women with severe dysmenorrhoea. The operation can be performed under regional anaesthesia and requires only one to three days hospitalisation.

Improved quality of life means no pain, periods, pregnancy, pads or papsmears. One often hears the statement "I wish I had had it done years ago."

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Assoc Prof Anne Keogh

Pulmonary Arterial Hypertension

Introduction

Pulmonary arterial hypertension (PAH) is technically defined in Table 1. It is generally considered a rare and lethal condition with poor prognosis and few or no treatment options. However, PAH is a generic term that includes elevated pulmonary vascular resistance due to a wide range of causes and is not in fact uncommon (Table 2). PAH is often not detected until the late and highly symptomatic stage and when survival is already very limited. In the past, there were no treatment options in Australia apart from heart lung transplantation. With multiple new drugs now demonstrating efficacy in PAH, early diagnosis is very important.

Pathophysiology

Underlying all forms of PAH is an increase in vasoconstrictor substances (thromboxane, endothelin-I) and a reduction in vasodilatory substances (nitric oxide and prostacyclin) with smooth muscle cell proliferation and in situ thrombosis and structural reduction in pulmonary arterial lumen size (Figure 1). The right ventricle ultimately fails to be able to cope with the persistent elevation in pulmonary resistance and right heart failure ensues.

Medical therapies for PAH consist of agents which modify one or more of these pathogenetic mechanisms (Table 3).

Symptoms

Symptoms of mild-to-moderate PAH may be insidious. In the early stages, breathlessness, palpitations, fatigue and a pounding heart may be dismissed as lack of fitness. As PAH progresses, right-sided congestion, elevated jugular venous pressure, ascites, hepatomegaly and peripheral oedema occur. Exertional

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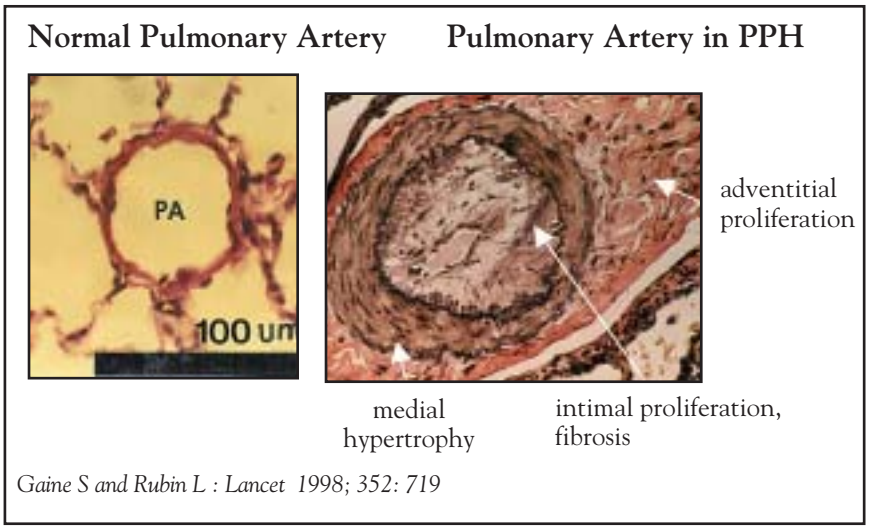

Figure 1: *Pathology of PAH – PAH is a disease of Pulmonary Vascular Resistance. It s a disease of Cell Proliferation, Hypertrophy, Fibrosis and Vasoconstriction*

Table 1

Definition

Resting mean PA pressure >25mmHg, or exercise mean PAP >35mmHg. Pulmonary capillary wedge <15mmHg and pulmonary vascular resistance >3 Wood Units

PVR=$\frac{\text{MPA-PCWP}}{\text{CO}}$ Wood Units

(to convert to dynes/cm/sec, multiply by 80)

Definitive diagnosis of PAH is only possible on right heart catheter.

Table 2

2: Classification of pulmonary arterial hypertension*

Primary pulmonary arterial hypertension:
- Idiopathic
- Familial (up to 25 per cent)

Pulmonary arterial hypertension related to:
- Connective tissue disease (CREST syndrome, scleroderma, mixed connective tissue disease)
- HIV
- Congenital heart disease, Eisenmenger's syndrome
- Portopulmonary hypertension
- Anorexigens (fenfluramine, dexfenfluramine)
- Primary pulmonary hypertension of the newborn
- Pulmonary veno-occlusive disease

2. Pulmonary venous hypertension
- Left heart diseases, left ventricular dysfunction and left sided valvular disease

3. Disorders of the respiratory system
- Chronic obstructive pulmonary disease
- Interstitial lung diseases
- Sleep disordered breathing

4. Chronic thromboembolic pulmonary hypertension

5. Miscellaneous eg sarcoidosis, tumour, fibrosing mediastinitis

*** Adapted from the WHO Classification of pulmonary arterial hypertension, Venice 2003 update (Simmoneau)**

syncope may occur. Unless the diagnosis is considered and actively sought, it will often be missed.

Diagnosis

The most useful initial investigations are echocardiography and respiratory function tests. The echocardiogram may show a hypertrophied, dilated or hypokinetic right ventricle, tricuspid regurgitation and elevated pulmonary arterial pressure. The left ventricle usually contracts normally, but may eventually be encroached upon by the enlarged right ventricle. In the absence of a tricuspid regurgitation jet, pulmonary arterial pressure can be determined on echocardiography. Sometimes, it is not possible to exclude PAH on echo alone. Respiratory function tests show a disproportionate reduction in carbon monoxide diffusion in the lung (DLCO – around 50 per cent of predicted in moderate PAH), with at most a mild-to-moderate restrictive lung defect. The reduction in DLCO in PAH is greater than that seen with comparably symptomatic left failure.

The only definitive test for PAH is right heart catheterisation, providing a direct measure of pulmonary pressures, wedge pressure and cardiac output. This is most easily done as an outpatient procedure, via the right internal jugular vein under local anaesthetic. Anticoagulation does not need to be ceased and fasting is not required. Repetitive straight leg raising to increase cardiac demand may uncover early cases in which PAH is only present during exercise. The six-minute walk test is informative and safe in assessing response to treatment and has a strong independent association with mortality. Once PAH has been detected, a comprehensive search for causes should be undertaken (Table 4).

Screening

Patients with family history of primary PAH have a genetic predisposition to PAH, although the predictive value of the BMPR2 gene, which has been associated with the disease, is not yet well defined. Up to 15 per cent of patients with scleroderma (especially limited scleroderma) ultimately develop PAH, and annual screening with DLCO measurement and echocardiography is advisable.

Survival

Without PAH specific agents, 50 per cent of symptomatic patients die within two years. With monotherapy with new drugs eg bosentan, sildenafil or treprostinil, survival is around 85 per cent at two years.

It is anticipated that double or even triple drug combination therapy will confer even better results.

Table 3

Medical therapies for pulmonary arterial hypertension

Drug class: trial results	Generic Drug	Brand name	PAH Group	Trialled in Administration and dosage	Availability and comments in Australia
Anticoagulants: Associated with improved survival in primary pulmonary hypertension in responders and nonresponders to calcium-channel blockers	Warfarin		idiopathic	To keep international normalised ratio (INR 2.5-4.0	
Calcium channel-blockers: Improved survival and with reduced symptoms in 10% of primary PAH patients	Diltiazem, Amlodipine Nifedipine		idiopathic	Oral: high dose, eg diltiazem 900mg daily	Restricted to patients with preserved right ventricular function. Only 1/20 remain responsive long term
Prostacyclin analogues: Increased survival, reduced symptoms, improved functional class, haemodynamics and walk distance, reduced pulmonary vascular resistance	Prostacyclin	Flolan	idiopathic congenital conn. tissue dis thromboembolic	Continuous intravenous infusion (4-30ng/kg/min)	Reimbursed fr 1/8/06 Continuous IV access needed
	Iloprost	Ventavis	idiopathic Conn. tissue dis CTEPH	Inhaled: 5mgm 5-12 times per day	Reimbursed
	Beraprost		thromboembolic idiopathic	Oral; 40mgm 5-12 times per day	Not available
	Treprostinil	Remodulin	idiopathic conn. tissue dis Eisenmenger's	Subcutaneous infusion; >14ng/kg/min	Injection site pain, Not reimbursed
Endothelin receptor antagonists: Improved walk distance and haemodynamics, delayed clinical worsening, improved echo parameters, improved survival	Bosentan	Tracleer	idiopathic conn. tissue dis CTEPH	Oral; initial, 62.5mg twice daily; for 1 month then, 125mg twice daily	Reimbursed Elevated serum transaminase levels in 3-5% of patients necessitates cessation
Phosphodiesterase 5 inhibitors: Improved functional class and walk distance, reduced pulmonary arterial pressure, improved cardiac output	Sildenafil	Revatio	idiopathic conn. tissue dis thromboembolic	Oral; 20mg three times per day	Not reimbursed Private script viagra,
	Tadalafil	Cialis			
	Vardenafil	Levitra			
Medical foods: Acute reduction in pulmonary vascular resistance	l-arginine			Oral (powder, capsules): 6g/day	GIT side effects, efficacy in some patients

TREATMENT

There is an increasingly wide selection of vasodilator and remodelling agents becoming available, which improve symptoms, exercise tolerance, right ventricular function and survival. Bosentan (oral), iloprost (inhaled) and prostacyclin (IVI) are reimbursed on PBS for patients who fulfil criteria. Other drugs may become available by the end of 2006 (Table).

Where patients fail monotherapy, combinations of drugs with differing mechanisms of action may be extremely effective. This is being actively explored here at St Vincent's Hospital.

British, European, American and International guidelines for the diagnosis and treatment of PAH have been published. Treatment algorithms need frequent updating with the steady stream of new agents and new data available worldwide. Apart from drug therapy, PAH can occasionally be treated specifically (eg pulmonary thrombo-endarterectomy for chronic thrombo-embolic pulmonary hyper-tension – CTEPH). PAH secondary to sleep apnoea may respond to continuous positive airway pressure.

Table 4

3: Investigating the cause of pulmonary arterial hypertension

- Echocardiogram
- Respiratory function tests: lung volumes, CO diffusion capacity
- Chest x-ray
- Ventilation perfusion scan
- High resolution CT scan of the lungs
- CT pulmonary angiogram
- Connective tissue disease screen (antinuclear antibodies, anti dsDNA antibodies, anti-neutrophil cytoplasmic antibodies ± antitopoisomerase (SCL-70) ± antifibrillarin (anti-RNP))
- Thrombophilia screen (anticardiolipin antibody, lupus inhibitor, protein C, protein S, factor V leiden, methyl tetrahydrofolate reductase mutation)
- Sleep study
- ± coronary angiogram (consider if >40 years old)
- Right heart catheterisation for definitive diagnosis.

Cost of Treatment

PAH specific therapies are in general, very expensive to the PBS. Their correct usage is mandated by the HIC via a continuous review process, with documentation of efficacy required before each PBS subsidised script is renewed.

Concomitant

Other Therapies

- Anticoagulation (to prevent in situ thrombosis or thromboembolism; eg warfarin, prostacyclin analogues);
- Vasodilators (eg, calcium channel antagonists reduce PA pressures in 10 per cent of patients and diuretics (to decongest the right side of the heart) and spironolactone (diuretic and possible right ventricular remodelling).

Atrial Septostomy

For patients refractory to vasodilator therapy, atrial septostomy may be considered. The aim is to decompress right-sided pressures into the left side of the heart and augment systemic cardiac output. Experience with this procedure in Australia is limited to St Vincent's Hospital. Its value has been shown in a number of small studies in other countries.

Heart Lung Transplantation

Heart-Lung transplantation for primary pulmonary hypertension was first performed at St Vincent's Hospital, in 1986. This was the first "curative" therapy for this condition, but is now appropriate only for a tiny minority of patients with advanced disease for whom medical therapy has failed.

Future Therapies

Future possible strategies includes imatinibe (platelet derived growth factor inhibitor), fluoxetine (serotonin transport inhibitor), gene therapy and biological peptides.

Referral

It is important that patients are referred to centres such as St Vincent's Hospital, which can offer all diagnostic and therapeutic interventions and also access to most clinical agents via international trials.

Assessing dose response, monitoring outcomes, switching agents and applying combination therapy requires considerable experience and interest.

Conclusion

Since 1999, St Vincent's Hospital has treated hundreds of patients with PAH with a wide range of treatments largely through clinical trials. Presently three drugs (oral bosentan, inhaled iloprost and intravenous prostacyclin) are available via HIC but many other agents are available by trial (ambrisentan, sitaxsentan, VIP, oral treprostinil and combination therapy).

With the availability of new, effective agents, patients can be offered positive and reliable treatments with the very real chance of cure in some. As with most cardiovascular diseases, earlier detection and intervention is likely to be rewarded with better outcomes.

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Cartilage Injury and Modern Pre-Prosthetic Surgical Treatments

Dr Simon Tan and Assoc Prof Michael Neil

Dr Simon Tan

Assoc Prof Michael Neil

Part A: Cartilage Injury And Background

Normal articular cartilage is characterized by a smooth surface with very low friction and the ability to withstand repeated high loads. Loss of this smooth surface leads to pain, loss of motion, swelling and eventually deformity. This will ultimately result in degenerative osteoarthritis.[1,2]

Articular cartilage lesions are difficult to treat in part due to the distinctive structure and remarkable function of hyaline cartilage.

Functional cartilage relies upon a homeostasis between water, chondrocytes (cartilage cells), macromolecules and type II collagen. The sparseness of cells, the unique architecture of cartilage and the fact that it is avascular, aneuric and alymphatic, give it superior loading characteristics but also the inability to spontaneously heal. [3,4]

Injury to articular cartilage is common following sporting injuries, road accidents and even accidental falls in every day life. The injured cartilage produces a very poor healing response due to the lack of blood supply and limited inflammatory reaction, which is required for healing.

The 'scarring' that occurs in cartilage is inadequate and biomechanically inferior, making the surface more prone to accelerated wear and premature degenerative osteoarthritis. It would therefore seem logical to diagnose and subsequently treat articular cartilage defects early. The concepts that small lesions are insignificant is not supported and a recent study of elite soccer players demonstrated persistent knee pain due to chondral defects, even in lesions less than 10mm in diameter.[5] Pain probably occurs due to the irritation of nerve endings in subchondral bone.

Significant advances have been made in the field of prosthetic joint replacement but articular cartilage defects in younger patients (under 50 years of age), remains a problem due to the limited lifespan of these prostheses.

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Making The Diagnosis

With respect to diagnosis, as is the case in all medical conditions, a thorough evaluation of the symptomatic patient including history, examination and assessment of investigations, is the key to diagnosing chondral lesions in the knee.

Examination should document Body Mass Index (BMI), lower limb alignment, gait patterns, patellofemoral, meniscal and ligamentous evaluation, as well as signs attributable directly to cartilage lesions such as point tenderness, crepitus, catching and an effusion.

Weight bearing radiographs can demonstrate arthritic changes, but isolated cartilage lesions are best seen on high resolution MRI (Magnetic Resonance Imaging) or under direct vision using arthroscopy.

MRI

MRI is becoming increasingly useful in the diagnostic assessment of cartilage defects. Newer MRI sequences are being developed to assess the biomechanical and functional profile of articular cartilage. Some sequences will potentially have the ability to assess proteoglycan content,[6] a molecule crucial to adequate cartilage functioning.

Arthroscopy

Inspection of the articular cartilage surfaces using arthroscopy may indeed be

the gold standard for cartilage assessment. (Figure 1) Despite being performed as an outpatient procedure and through "key-holes" it is still an invasive investigative tool. It does, however, allow critical assessment of cartilage surfaces as well as assessment of the rest of the knee including ligaments, menisci and global arthritic changes.

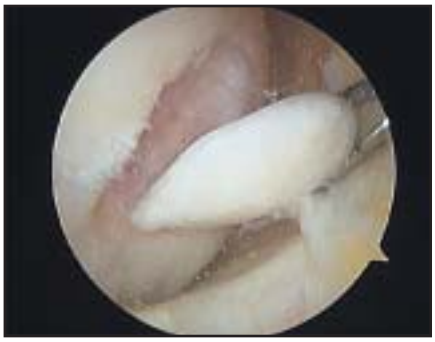


Figure 1. *Arthroscopic photo demonstrating removal of a loose full-thickness cartilage lesion*

The next stage in diagnostic arthroscopy is visualization of the joint through an arthroscope the size of an 18 guage needle so the "procedure" can be performed in the doctor's office under local anaesthetic. This device is currently in use in selected units in the United States. *("Innervue" Arthrotek)*

In recent years, two new surgical treatments have become available for focal cartilage defects which may cure these lesions and prevent arthritic progression:

1. Autologous Chondrocyte Implantation (ACI) or cartilage grafting. This is where cartilage cells are cultured in laboratory and transplanted to the patient with a transport membrane which covers the defect.

2. HemiCAP resurfacing. This is where the defect is filled with a metallic device which is contoured to be congruent with the joint surface.

The largest numbers of both types of procedures have been piloted at St. Vincents Clinic in the Orthopaedic Unit. Joints operated include knee, shoulder and ankle.

This paper will discuss both these newer techniques and attempt to explain the current indications, risks versus benefit and analyse results to date.

Part B: Autologous Chondrocyte Implantation

Basic science research into the homeostasis of cartilage and increasing number of clinical reports has helped define a list of indications and contraindications for cartilage transplantation.

Indications for ACI
Age 15-55 years old
Isolated, full thickness cartilage defect
Femoral or Patellofemoral defect that is contained
Compliant rehabilitation patient
Stable knee (intact ligaments)
Intact meniscal cartilage
Normal alignment to lower extremities

Contraindications to ACI
Inflammatory or crystal arthritis
Active infection
Widespread advanced cartilage loss
Age (relative)

Some of these indications/ contraindications can be controlled and patients can be made more "appropriate" for this surgery. For example, a malaligned knee can be corrected at the same time as the implantation of cartilage cells. Similarly, an unstable knee can have a ligament reconstruction and even a joint without a meniscus can have an artificial meniscus inserted. Age is relative and a patient's "physiological age" is often a more reliable indicator of surgical candidacy.

The Procedure

as per Matrix enhanced Autologous Chondrocyte Implantation (MACI)

The completed process is a two stage surgical procedure.

Stage 1 – Cell Harvest

The first surgery is arthroscopic and is often undertaken to diagnose and initiate treatment for suspected lesions. At arthroscopy, once a cartilage lesion is identified, good cartilage cells are harvested from the non-weight bearing area of the intercondylar notch (the area that is commonly cleared during cruciate ligament reconstruction).

Approximately 200 mg of cartilage cells are desired. In practical terms, this is effectively, less cartilage than a "tic-tac". The piece of cartilage is aseptically transferred to the cartilage laboratory and the chondrocytes are extracted. Under strict highly regulated conditions the cartilage cells are multiplied in vitro, seeded on to a porcine collagen bilayer membrane and then cryopreserved. The cells can then be stored until elective re-implantation.

Stage 2 – Re-implantation

The elective re-implantation can be performed as soon as the cells have multiplied adequately over the membrane (as soon as 4 weeks) or can be postponed until a more convenient time is available. An open arthrotomy is required for this part of the procedure. The cartilage defect is prepared to accept the graft (Figure 2a) and then the patient's chondrocyte-seeded membrane is fixed to the defect with fibrin glue (Figure 2b). Concomitant procedures to improve biomechanics (cruciate ligament reconstruction, patellofemoral re-alignment, osteotomy) are usually performed with this surgery. The patients can be discharged home in 1-2 days usually dependant upon the concomitant procedures.

Timing of surgery

A time lag up to one year has traditionally been offered to patients between these two cartilage implantation stages. This "wait and see how your knee goes" now seems unwise due to irreversible changes seen in the ultrastructure and durability of articular cartilage when the conforming surfaces are altered.[7] It is becoming increasingly evident that significant defects in cartilage that are left unattended cause irreversible damage to adjacent surfaces. Intuitively this seems obvious as a "pot-hole" on one side of the joint must rub and wear the opposing surface. Translating this into clinical practice, however, is difficult but implies that once a full thickness cartilage lesion is identified, cartilage transplantation should be considered as soon as practicable.

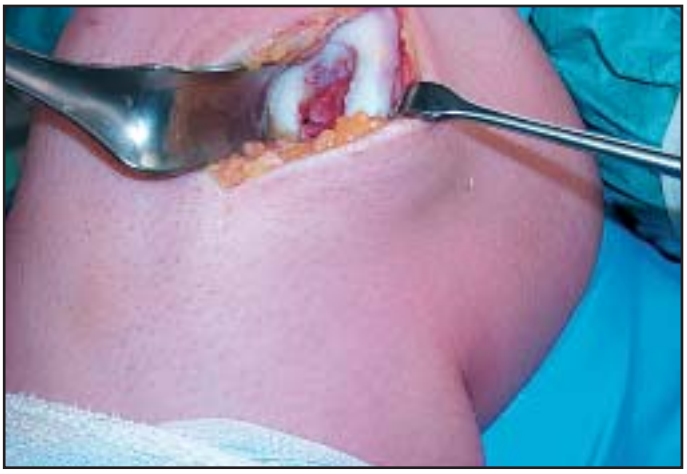


Figure 2a. Stage II: *The lesion is debrided using an open arthrotomy*

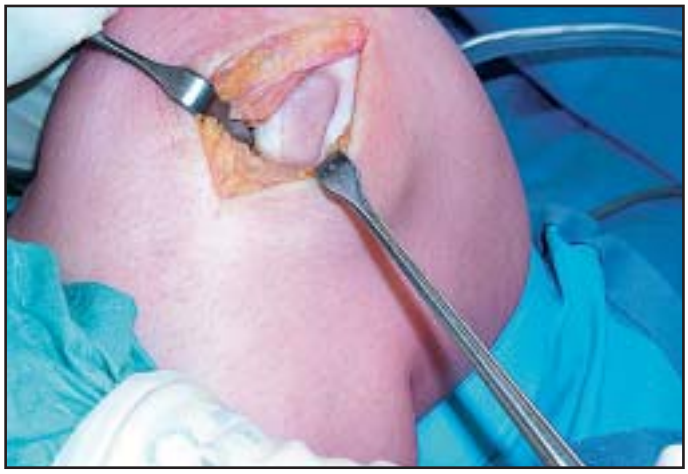


Figure 2b. Stage II: *The cartilage graft is fixed to the defect using tissue glue*

Rehabilitation

Research focused specifically on rehabilitation after ACI is currently in a rapid growth phase with new basic science studies and clinical results reported every month.

The lack of definitive research, however, on the stress required to disrupt the cartilage graft has resulted in an over-conservative approach to rehabilitation programmes. The past two years have seen rehabilitation recommendations shorten from 18 months to 12 months. This will shorten further as our understanding of this procedure improves.

Current Recommendations

The rehabilitation becomes specific depending on the site of the cartilage defect. A femoral condylar lesion needs to be protected from weight bearing but knee flexion is safe as long as it is undertaken in a manner to minimize shear forces. Comparatively, a patellofemoral lesion needs maximum protection from flexion/shear loads but will allow weight bearing. This means weight-bearing with the knee straight is allowed with patella lesions but stair climbing needs to be avoided in the early stage.

In brief, this means bracing and alteration in weight bearing for up to 3 months and restriction in sports from 6-12 months depending upon what the sport involves.

Results

72% good to excellent results have recently been described in elite level soccer players.[8]

Fu et.al. reported over 80% of patients following ACI to femoral lesions had improvement in pain and function after 3 years follow-up.[9]

Peterson et al found 82% patients were good to excellent 5-11 years after ACI.[10]

This durability of ACI was found to be due to the hyaline-like cartilage repair tissue.

Graft survivorship after 2 years is excellent.

Cost

ACI is a newer technique and more costly than traditional conservative therapies. However, there is more in evaluating the relative merits of a surgical procedure than its dollar value. Cartilage lesions cause pain, disability and time off work. The economic burden of a cartilage defect has recently been evaluated by Lindahl et al. Assessing 57 patients over 10 years they found the cost of absenteeism and disability due to a cartilage lesion to be USD $122,807 compared to USD $5,875 for the surgery.[11]

Conclusion

In summary, autologous cartilage transplantation to treat articular defects in the knee is now readily available. Good to excellent clinical results are approaching 15 years. Patients need to be appropriately selected and counseled on the limitations of this technique and advised of the comprehensive rehabilitation required to ensure the success of this procedure.

Part C: HemiCAP Resurfacing

The Hemi"CAP" (Contoured Articular Prosthesis) device was developed as an alternative treatment to ACI. While 70% of patients undergoing ACI have had good or excellent results at 5 years post surgery, the procedure is expensive, requires two operations and has a prolonged convalescence and recovery period.

The HemiCAP is a two-piece metal implant, designed to be implanted through minimal incision surgery, which can cover the cartilage defect with immediate full weight-bearing as tolerated, and a much quicker recovery time.

The implant has been developed by Arthrosurface, Inc., a small bioengineering company in the USA devoted to joint preservation surgery, as an alternative to joint replacement.

The Concept

A resurfacing device that allows the surgeon to intaoperatively map the patient's anatomy so that the cap is the same height and radius of curvature as the patient's joint surface. (See Figures 3a & 3b).

The Device

The HemiCAP instruments enable the surgeon to accurately locate the implant and precisely measure the antero-posterior and medio-lateral curves of the articular surface, in real

Figure 3a: *HemiCAP device seated*

time under direct visualization, with no angle-induced error that might exist with MRI or Xray imaging techniques.

HemiCAP objectives

- Joint preservation
- Pain relief
- Restore a continuous smooth load bearing surface
- Delay need for joint replacement
- Minimise impact on further surgery
- Maintain normal soft tissue tension
- Rapid return to normal joint function

Clinical evaluation

To date, most scientific data about the implant is in animal models.[14,15] The human clinical trials are out to over two years now in the US (see Figure 4), and over one year in Australia, with a large group from St. Vincents's Clinic. We know that cartilage lesions lead to arthritis if not treated, and that the CAP is biocompatible and seems to prevent progression of the lesion. The device is slightly recessed to the native articular cartilage to allow normal cartilage to grow over the sides of the Cap and smooth the surface. (See Figure 5.)

Human Studies

Currently, the authors are involved in a prospective evaluation of cases done in the knee and shoulder in Australia. We are also embarking on a collaborative animal study in sheep of the device with a control group of cartilage defects in the opposite limb of the same animal for clinical, radiological and histological evaluation. This work is being conducted with Prof. Bill Walsh at the Orthopaedic Research Laboratories, University of NSW.

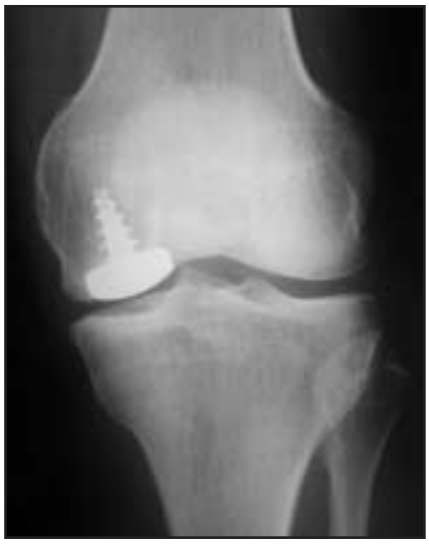


Figure 3b: *Xray left knee showing HemiCAP implanted in cartilage defect of medial femoral condyle*

Personal Experience

At the time of writing, the total number of hemiCAP implantations number 13, with the device first used at St. Vincent's in Australia on 12 April 2005. All procedures have been performed in the knee in this group. There are 8 females and 5 males, average age 39.9 years (range 31-65). Three patients had previously failed ACI procedures. (See Figures 6a and 6b)

Figure 5: *Cross section of implant in medial femoral condyle of goat harvested at 3 months post surgery. Hyaline articular cartilage has grown up to and over sides of implant with bone integration onto anchoring screw.*

Outcomes were assessed using a clinical, subjective and Xray scoring system to classify results as excellent, good fair or poor.

Results: 10 excellent, 2 good. 1 patient has a poor result and is pending revision to a partial knee replacement.

Satisfaction rate in this small group is 85% (there are 2 patients of the 13 who regret having had the surgery.)All implants look stable and osseointegrated.

Average length of stay is 1.25 days, with the procedure performed in Day Surgical Unit.

There have been no significant complications.

US Knee Multicenter Clinical Trial
Average % Improvement

Time Point	Pain	Stiffness	Function	Global WOMAC
3 months (n=14)	89%	68%	81%	84%
6 months (n=13)	89%	69%	82%	86%
12 months (n=4)	97%	69%	99%	96%

Figure 4: *Results of USA multicentre study of HemiCAP. Outcomes were measured using a visual analogue score, as well as WOMAC wellness scale (Western Ontario McMasters Assessment Criteria).*

Time to recovery of normal knee function (including return to normal activities with strenuous sport if willing) is about 12 weeks.

Conclusions

The HemiCAP resurfacing device shows promise in the surgical treatment of full thickness cartilage defects before the onset of osteoarthritis. It should be regarded as a joint preserving operation rather than a joint replacement procedure.

The device appears to be safe and biocompatible, and demonstrates excellent results in human short term studies. The implant is relatively inexpensive, and technically simple to implant in a day surgical environment, with rapid return to normal joint function and relief of pain.

HemiCAP resurfacing is an alternative to ACI particularly in older patients. However, further basic science and longer-term clinical studies are necessary, and are in progress.

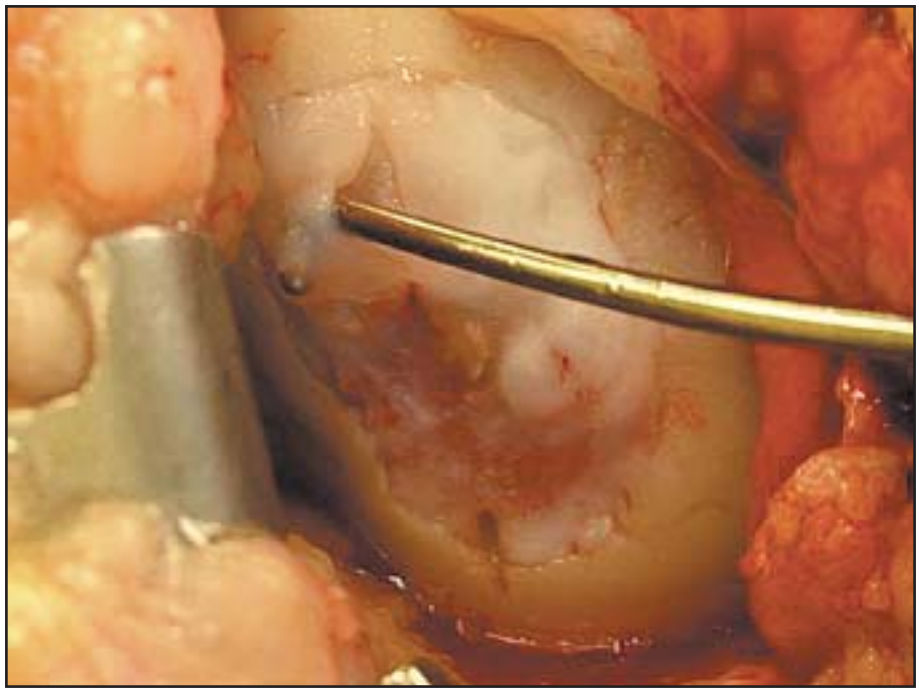
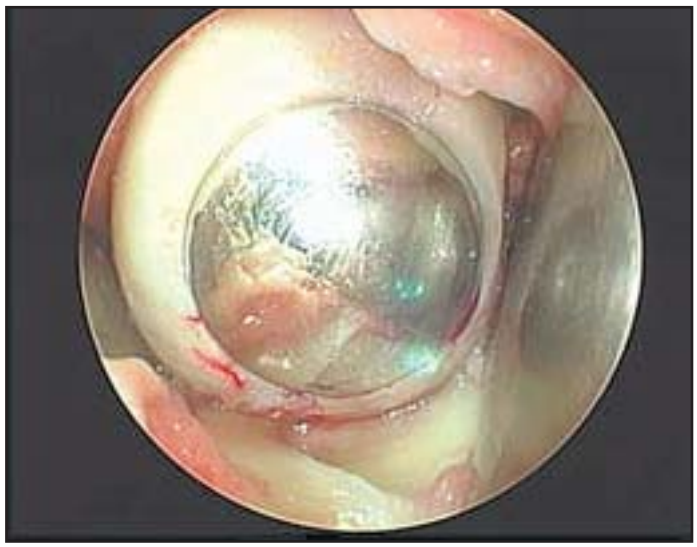


Figure 6a: *Failed ACI graft showing softening of transplanted cartilage in medial femoral condyle right knee joint.*

Figure 6b: *HemiCAP prosthesis covering defect shown in fig 6. Implant size was 20mm diameter in 11, and 15mm in two. Eleven lesions were located in the medial femoral condyle, and 2 in lateral femoral condyle.*



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Preliminary Experience and Follow-up with the Orbit® DCS Detachable Coil System in the Treatment of Intracranial Aneurysms

Dr Richard Parkinson

INTRODUCTION

The purpose of this paper is to review the approach to the treatment of intracranial aneurysms, particularly those with potentially unfavourable anatomy, using a new catheter based coiling system, and its results in five illustrative cases.

Endovascular coiling of intracranial aneurysms works by packing platinum coils inside an aneurysm, inducing thrombosis in the aneurysm which can then cause an inflammatory reaction and endothelialization/healing over the aneurysm neck. The treatment of intracranial aneurysms with coils has some limitations in patients with broad-necked aneurysms (neck >4mm, dome/neck ratio <2) as the coils can herniate into the vessel (potentially causing stroke or vessel damage), and a stable coil pack in the aneurysm can be difficult to achieve. Recurrence also remains a significant concern if the aneurysm is not adequately packed.

Adjuncts to coiling which have addressed these problems include stenting, balloon-assisted coiling, and bioactive coils (coated with prothrombotic or inflammation inducing materials). Each of these adjuncts has potential additional risks which must be considered.

The orbit DCS coil system was developed to address these issues. The coil fills concentrically and is comprised of 30 per cent more platinum than equivalent coils while maintaining equivalent softness. The concentrically filling nature of the coil and the complex deposition allow for tighter aneurysm coiling and excellent neck bridging. The coil is also easy to use with rapid detachment and reliability.

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This work was undertaken in the USA in conjunction with Dr Bernard R. Bendok MD, Northwestern University, Chicago USA

LITERATURE REVIEW

Since the introduction of the first series of coiled aneurysms by Guglielmi in 1991 and the FDA approval for coil endovascular treatment of cerebral aneurysms in 1995, there has been an immense effort to improve the mechanical, metallurgic, and rheologic properties of coils to better occlude an aneurysm, and safely. This is due to the significant recanalization rate and technical failures experienced with first generation coils. These improvements, primarily the introduction of microcoils with 3D memory, aim to facilitate better aneurysm packing, occlusion of the aneurysm neck, minimization of coil compaction, and successful coiling of more complex aneurysms. Geometric factors which make aneurysm coil embolization more challenging include wide neck (>4mm), unfavorable dome-neck ratios (<2:1), non-saccular anatomy, and large (>20mm) or small (<3mm) size. Recent research has suggested the primary goals for a successful result may be the occlusion of the aneurysm inflow zone (hence the importance of stable neck occlusion) and stable packing of the aneurysm dome, which will resist compaction and therefore recanalization of the inflow zone and recurrence of the aneurysm with risk of rehemorrhage and growth. Efforts to address this problem have included efforts to design coils which better conform to complex geometry, the use of bioactive coil coatings to induce inflammation/thrombosis, and the application of stents to provide support for coiling of sidewall aneurysms.

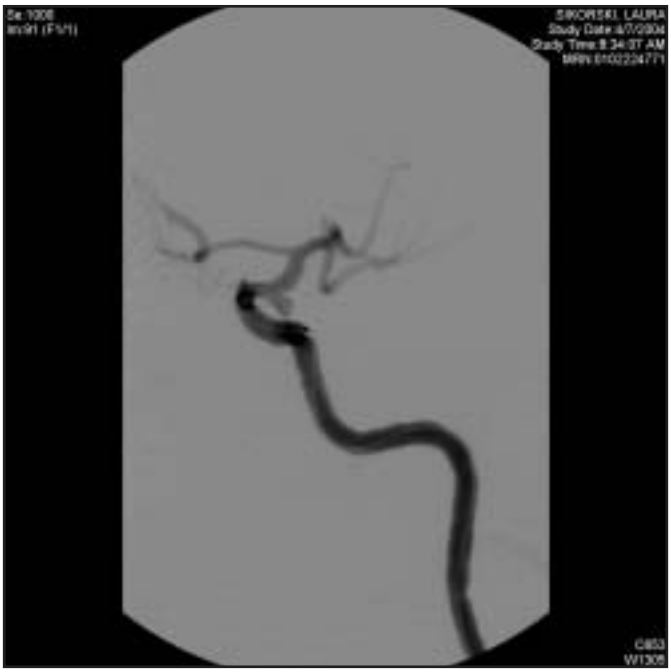


Figure 1. *An Orbit fill coil showing the three dimensional fill characteristics and the break points. The coil break points are random, which allows for favorable repositioning if the initial coil position is unsatisfactory.*

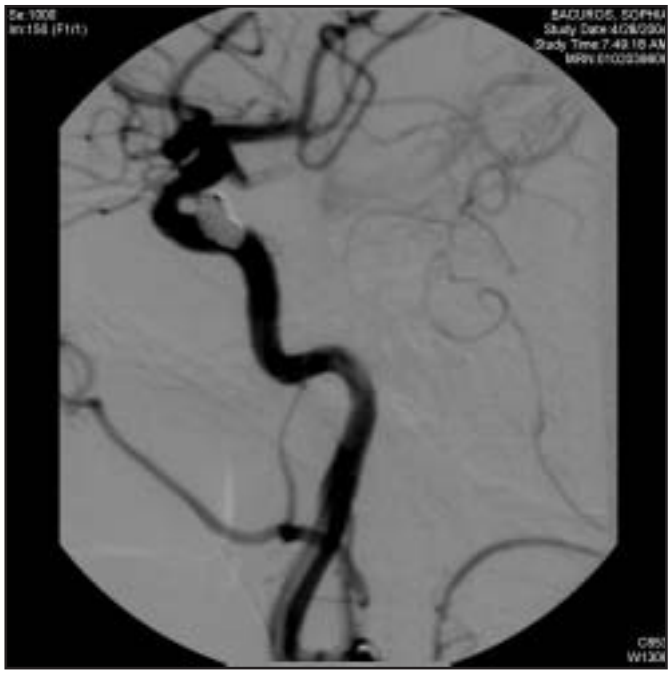


Figure 2. *The hydraulic detachment zone of the coil. The proximal end of the coil catheter is attached to an hydraulic pressure device similar to a balloon inflator. A pressure gauge allows visual confirmation of detachment.*

Piotin et al, in an in vitro study, compared packing density using complex (3-D/spherical), and helical (spring shaped) coils. They used a silicone aneurysm model, and introduced coils until herniation of coil into the vessel was observed. Coiling was attempted in a concentric fashion, using either DCS coils or helical coils as fill coils. There was a statistically significant increase in packing density using complex 3-D coils initially followed by either helical or complex fill coils, compared with helical coils alone. There was a non-significant trend toward better packing density using only complex coils. The use of an initial 'framing' 3-D coil before concentric fill coil introduction was therefore associated with better packing of the aneurysm.

Technical features of the Orbit DCS® system

The Orbit® DCS 3D coil system was introduced to the USA after preliminary experience in Europe and was granted FDA approval in 2003. The Orbit® system offers complex coils in mini, complex, and standard sizes with both spherical and fill coils (Figure 1). The primary coil outer diameter is 0.012". These coils were designed to be deformable, with varying diameter loops, and with smaller break points to minimize microcatheter extrusion and to allow better spherical packing of the aneurysm in a concentric fashion from the outside in. These features also allow the coil to assume a different random position in the aneurysm (if the initial position is unsatisfactory) by pulling back the coil in the microcatheter and then redeploying without having to change the catheter position.

The larger amount of platinum delivered per coil is offset by the softness of the Orbit® system, and also allows less coils to be delivered to achieve the same result as smaller helical and 3D coils.

The Orbit® DCS system also incorporates a hydraulic detachment system (Figure 2) which allows immediate detachment with visual confirmation. This system is useful for rapid detachment and redeployment of further coils, which may be critical if there is a periprocedural rupture of the aneurysm.

The Cases

Five illustrative cases where DCS Orbit coils were used for treatment are presented. Follow-up was at six and twelve month intervals. For these five cases, no complications at follow-up have been noted, and no aneurysm recanalization or growth has occurred.

All patients were treated consecutively by a single endovascular surgeon after appropriate consultation with a cerebrovascular team. A 6F Envoy® catheter and either a Prowler Plus® or Prowler 14® microcatheter were used to deliver the coils (Cordis Inc., Miami Lakes, FL USA). A Prowler® Select microcatheter was used in one case. In almost all cases the Agility® soft micro wire was used. No coil fracture or migration occurred and all coils were detached without difficulty.

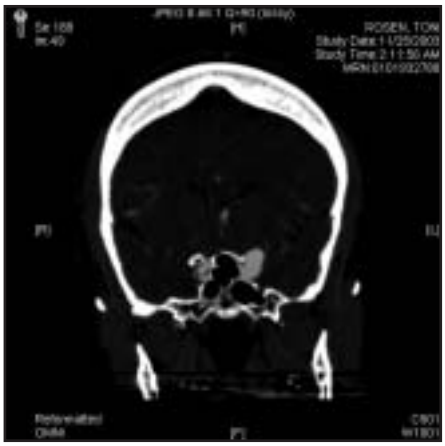
Illustrative Cases

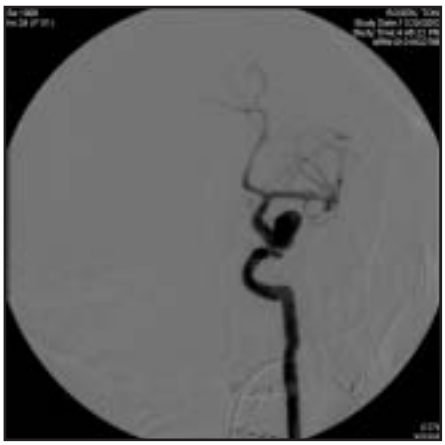
Illustrative Case 1

A 40 year old female presented for elective coiling of a left posterior communicating artery aneurysm (Figure 3) following craniotomy for ruptured aneurysm on the other side. This aneurysm had a small daughter sac on the inferior fundus, and therefore the microcatheter tip was kept away from it.

Technical Aspects of the Case

A Prowler 14® two tip catheter was navigated into the posterior fundus of the aneurysm over an Agility Soft 14® microwire. A 3 x 3 Orbit® minicomplex fill coil was initially used as the primary coil, followed by another 3x3 minicomplex coil and a 2x2 minicomplex coil. An excellent angiographic result was achieved (Figure 4), and there were no perioperative complications.





Figures 3 and 4. *Working views pre and post coiling of a ruptured posterior communicating aneurysm. The microcatheter is deliberately positioned away from the fundus.*

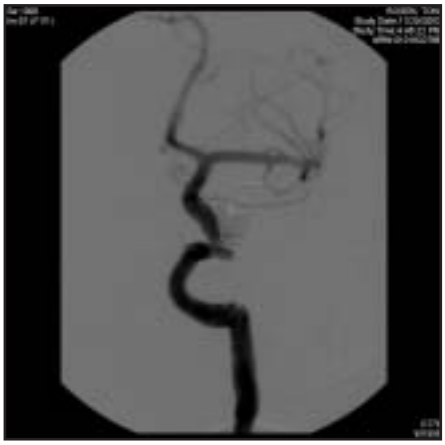


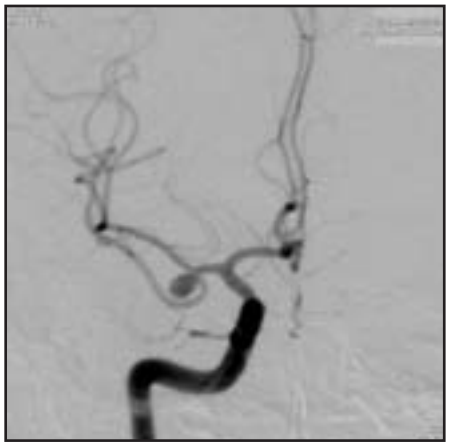
Figure 5. *CT angiography coronal view showing a petrous internal carotid aneurysm on the left. Two smaller petrous carotid aneurysms are also visible- these were not subarachnoid and were therefore not treated.*

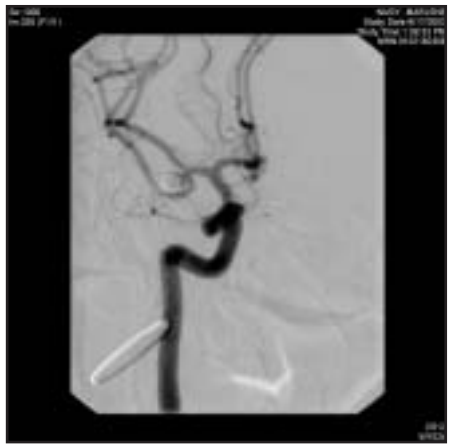
Illustrative Case 2

A 50 year old female who presented with a Grade 1 subarachnoid hemorrhage. CT angiography (Figure 5) and digital subtraction angiography (Figure 6) showed a large cavernous/paraclinoid left aneurysm with two proximal petrous ICA aneurysms. CT scanning showed no subarachnoid hemorrhage. The patient was taken to the interventional radiology suite for coiling the next day.

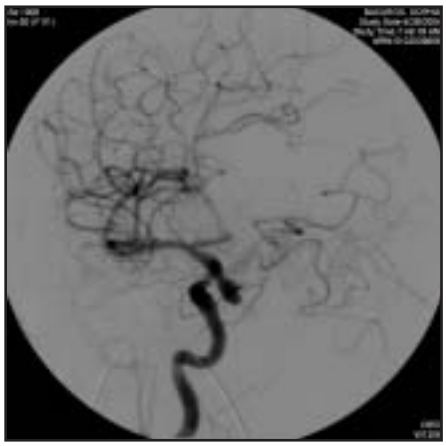
Technical Aspects of the Case

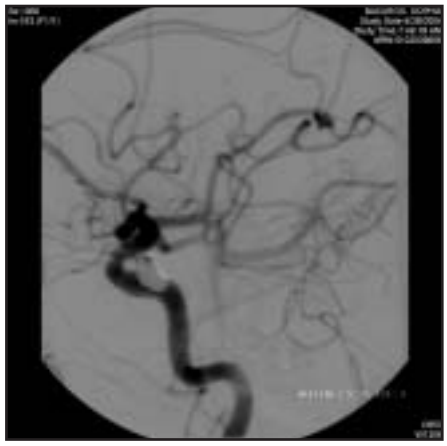
A Prowler Plus® two tip microcatheter was placed into the aneurysm over an Agility® microwire. Coiling proceeded without difficulty (Figure 7). Coils used were: 14x30 standard, 12x30fill, 10x30fill, 8x24fill,7x21fill,6x15fill,5x15fill, 4x10fill,4x7fill,4x10fill,4x3fill,3x3fill.



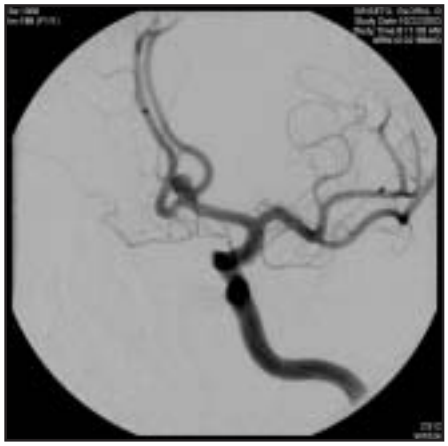


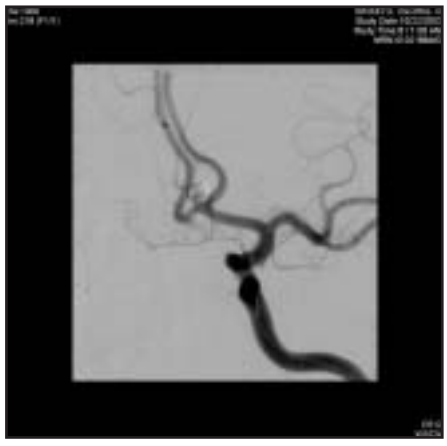
Figures 6 and 7. *Pre and post coiling digital subtraction angiography showing the working view of the left petrous carotid aneurysm.*





Figures 8 and 9. *Pre and post coiling working views of a middle cerebral artery aneurysm. In this case, the working view shows an excellent delineation between the aneurysm neck and the parent vessels.*

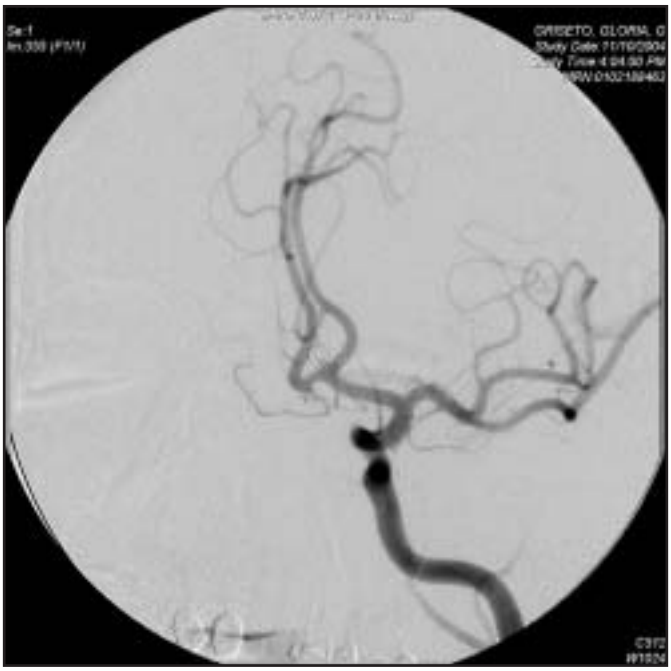




Figures 10 and 11. *Pre and post coiling working views of a supraclinoid carotid aneurysm.*

Illustrative Case 3

A 60 year old female with a history of severe pulmonary disease presented for elective coiling of a right middle cerebral artery bifurcation aneurysm, measuring approximately 5x7mm (Figure 8). Her primary care physician did not think she could tolerate general anesthesia so she was treated with mild sedation.



Figures 12 and 13. *Pre and post coiling working views of an anterior communicating artery aneurysm. A single loop of coil has herniated into the parent vessel, which appears to have compacted in the 12 month follow up study.*

Technical Aspects of the Case

A 6F Envoy® catheter was placed in the right internal carotid artery via a 6.5F sheath. A Prowler 14® with steam-shaped tip was then placed in the aneurysm fundus over a Transcend Platinum® microwire. Sequential 3D and fill coils were then placed. The aneurysm neck could not be completely filled due to an M2 branch which was partially arising from it. A good result, however, was achieved (Figure 9). Coils used were: 3x3 mini, 3x3 mini, 2x2 mini.

Illustrative Case 4

A 74 year old female admitted with vertigo had a supraclinoid ICA aneurysm diagnosed on workup (Figure 10).

Technical Aspects of the Case

A 6F Envoy® guide catheter was used with a Prowler 14 Select® microcatheter with preshaped end. Coils used were 8x15 fill coil, followed by 7x13, 6x15, 5x10, 4x3, 4x7 fill coils (Figure 11). This case illustrates how an irregular aneurysm can be treated with complex fill coils to achieve fundus and neck occlusion. No perioperative complications were seen.

Illustrative Case 5

A 78 year old female presented with benign frontal headache for workup. A broad-necked anterior communicating artery aneurysm was diagnosed on CT and CT angiography. A 6F Envoy® guide catheter in the left internal carotid artery was placed (Figure 12), and a Prowler 14® microcatheter placed in the A1 and into the aneurysm. A 5x15 coil was used initially to provide stability. Two further down sized complex fill coils were then used to fill the fundus (Figure 13). This case is an example of how a standard coil can be used to provide stability, to allow the stable lodgment of fill coils and occlusion of the aneurysm neck. No complications with the procedure were seen. Repeat angiography at 12 months showed no recurrence (Figure 14).

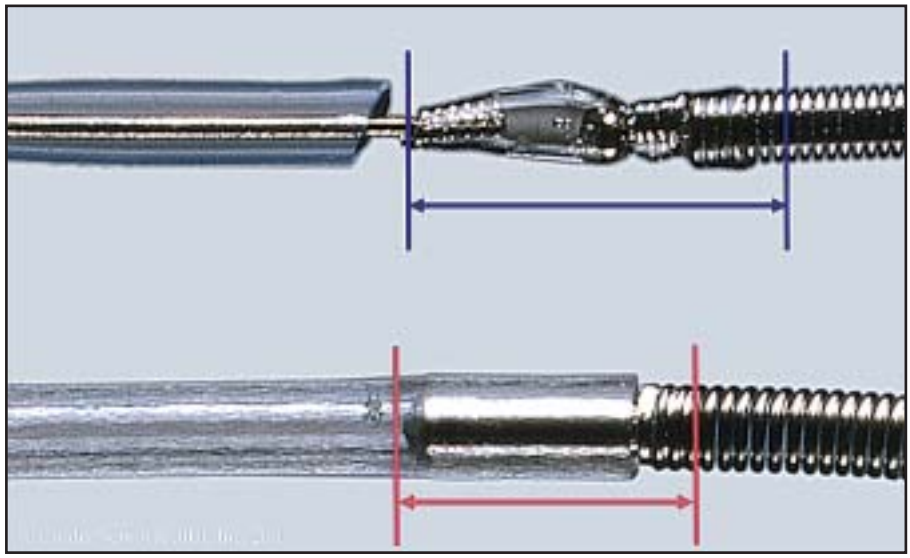


Figure 14. *Similar working view of the same case 12 months later at follow up.*

Conclusions:

In our experience the Orbit® system allows ease of delivery, reliable detachment, easy retrieval, and excellent three-dimensional packing of the dome and coverage of the neck by using initial 3D coils to create an outer framework which conforms to the complex aneurysm shape, and using softer complex fill coils to achieve packing density from the outside in. The coil has 30 per cent more platinum compared with other comparably sized bare platinum coils, and because greater packing density can therefore be achieved it is possible that less coils are needed to treat each aneurysm. This may reflect in economic savings and decrease in procedural time.