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Botulinum Toxin versus Botulinum Toxin with Low Dose GTN for Healing of Chronic Anal Fissure: Prospective, Randomised Trial

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Background: Chronic anal fissure (CAF) is perpetuated by high sphincter pressures and secondary local ischemia. Pharmacological approaches include topical nitrates and botulinum toxin (BT) both help to decrease the sphincter pressure.

Aims & Objectives: The aims of the present study were to assess the efficacy and safety of BT injection and combined treatment with BT injection and lowered dose Glycerlytrinitrate (GTN) cream for the treatment of CAF. We hypothesised that combined treatment would have a synergistic effect on healing & low dose GTN would cause less headaches.

Methods: Forty one consecutive patients with CAF were randomly assigned to receive one of the following treatments; Group A, injection of BT (20 U into internal anal sphincter) and group B, BT injection (20 units) and subsequent thrice daily topical applications of half dose 0.2% GTN cream for six weeks. Patients were followed up at 6 and 12 weeks & were assessed for; healing of anal fissure, by means of visual inspection using fissure grades; for faecal incontinence, using Cleveland Clinic incontinence scores and for fissure pain & headache using a numeric pain rating scale.

Results: Fissure healing was similar in the two groups at 6 and 12 weeks (66% in both groups). Neither the change in pain score from 6 to 12 weeks, nor the overall level of pain was significantly different in the 2 groups. Headaches were suffered by 46% of patients using GTN.

Conclusion: Single agent treatment by means of BT injection alone is well tolerated with no significant differences in healing of CAF.
Initial Experience of Ambulatory Hemi-thyroid Surgery at a New Zealand Tertiary Hospital

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Introduction: The feasibility of ambulatory thyroid surgery (discharge on the day of surgery without overnight stay) has been reported internationally, but does not appear to be practised in Australasia. We report our early experience with ambulatory hemi-thyroid procedures including selection criteria and suggested guidelines for safe practice within a New Zealand tertiary hospital setting.

Methods: A retrospective review of prospectively collected data on all partial and hemi-thyroidectomy patients between 1 November 2009 and 31 December 2012, who were operated on by a single, high-volume endocrine surgeon was performed. Patients considered suitable for ambulatory surgery were identified and the rates of successful ambulatory surgery, post-operative complications and readmission rates assessed.

Results: 82 partial/hemi-thyroidectomy patients were identified, 35 of which were considered suitable for ambulatory surgery based on selection criteria used. A further 45 were discharged the day following surgery, of which 23 had been admitted overnight only due to the distance of residence from a 24-hour medical facility. The remaining 22 were considered unsuitable for ambulatory surgery, however all 22 were discharged from hospital within 24 hours from the time of admission. The remaining two patients required a hospital stay longer than one night, which was expected in both cases. One patient re-presented with an infected seroma. There were no other postoperative complications or readmissions.

Discussion: Our early experience suggests that in well-selected patients, using specific exclusion and discharge criteria, ambulatory hemi-thyroid surgery can be safely achieved and is feasible within an Australasian tertiary hospital setting.

Comparison of Maori and Pakeha of Patients Hospitalised for Heart Failure

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Background: Previous reviews of the New Zealand Heart Failure Registry (NZHFR) showed that Maori present at a younger age with heart failure and have higher prevalence of LV systolic dysfunction. We aim to revisit and compare outcomes for Maori and Pakeha, based on updated NZHFR data.
Methods: NZHFR is a national, prospective, observational, web-based registry. All hospitals in New Zealand admitting patients with acute heart failure have been invited to participate.

Results: A total of 1757 patients are enrolled from Jul 2006 to Feb 2013, and 90-day follow up data is available in 91.9% (1616/1757). There are 400 Maori (mean-age 61.8 years, 69% males) and 1027 Pakeha (mean-age 78.7 years, 60% males). Severe valvular disease, hypertension and AF are the major aetiological factors for heart failure in both groups, with higher prevalence of diabetes in Maori (44% vs. 29.5%, p<0.0001) and IHD more prevalent in Pakeha (23% vs. 11%, p<0.0001). Predisposing factors for hospital admission for Maori are uncontrolled hypertension (10.8% vs. 4.5%, p<0.0001) and non-compliance with medication (16% vs. 3%, p<0.0001), and diet (6.8% vs. 3.7%, p<0.0161). Maori have high prevalence of impaired left ventricular systolic function (LVEF<50%, 85% vs. 67%, P<0.0001). Medications and Outcomes are as shown in table.

<table>
<thead>
<tr>
<th>Discharge medications</th>
<th>Pakeha</th>
<th>Maori</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>96.7% (943/975)</td>
<td>98.4% (383/389)</td>
<td>0.09</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>76.5% (746/975)</td>
<td>79.6% (310/389)</td>
<td>0.22</td>
</tr>
<tr>
<td>ACE-i/ARBs</td>
<td>78.4% (765/975)</td>
<td>87.6% (341/389)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>28.7% (280/975)</td>
<td>40.6% (158/389)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median length of stay</td>
<td>6 days</td>
<td>7 days</td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>5.1% (52/1027)</td>
<td>2.8% (11/400)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mortality at 90-day follow up</td>
<td>12.8% (119/929)</td>
<td>8.5% (32/377)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Hospital readmission at 90-days</td>
<td>17.1% (159/929)</td>
<td>15.6% (59/377)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Conclusions: Maori present at a much younger age with HF and are more likely to have systolic dysfunction and increased use of ACE-i/ARBs and Aldosterone antagonists. There is no difference in in-hospital mortality and 90-day readmission but Pakeha have higher 90-day mortality.

Ketamine Esters: Teaching an Old Drug New Tricks

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Background: Ketamine has been used as a dissociative anaesthetic drug for almost fifty years. Its main advantages are that it does not depress the cardiovascular or respiratory systems, and is a strong non-opioid analgesic. Its most significant
disadvantage – which has resulted in its use being restricted to extreme situations – is that it results in delirium and distressing hallucinations in a large proportion of patients during the recovery period. Because these effects are caused at low plasma concentrations of the drug, they often persist for some hours.

**Aims and Objectives:** Over the last decade a new ultrafast offset opioid (remifentanil) has been developed; in which an ester side chain has been linked to the parent opioid molecule. When this ester is hydrolysed, the resultant water-soluble drug metabolite is rendered inactive. The half life of the drug in the presence of the blood and tissue esterases is only a few minutes. This enables high doses of the drug to be given, but the patient still has a rapid recovery after the anaesthesia. We applied the same principle to the drug ketamine, with the aim of reducing the period of recovery delirium.

**Methods:** A number of different esters were developed at the Auckland Cancer Society Research Centre and their anaesthetic effects tested in animal models, using the loss-of-righting reflex as the end point.

**Results:** We found that the animals given the ester analogues regained their righting-reflex between 10 and 20 times faster than when given the parent compound - ketamine. There also appears to be some differences between the compounds as regards their relative analgesic versus hypnotic potencies.

**Conclusion:** It is possible to dramatically reduce the recovery time for ketamine anaesthesia by using an ester analogue of the drug.

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### Differential Effects of Selenium (Se) on Normal and Malignant Cells Treated with Chemotherapy and Radiation.

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**Background:** Preclinical work has demonstrated that Se compounds potentiate anticancer effects of chemotherapy (CT) and radiation (RT) while reducing normal tissue toxicities. The molecular basis for the therapeutic selectivity has yet to be fully elucidated but includes modulation of intracellular glutathione (GSH) concentrations, endoplasmic reticulum (ER) stress responses, DNA repair, induction of apoptosis and cellular resistance to CT and RT. Our aim was to evaluate the dose-response relationship of the Se compound methylseleninic acid (MSA) on molecular pathways involved in the response of normal and malignant cells to CT and RT.

**Methods:** Peripheral blood mononuclear cells (PBMC) obtained from healthy blood donors and malignant THP-1 human monocytic leukaemia cells were exposed \textit{in vitro} to MSA 2.5, 5 or 15 µM in varying combinations with MSA, RT, cisplatin (Pt), doxorubicin (Dox) and cytosine arabinoside (Ara-C). GSH concentration was measured by ELISA, DNA damage and repair by COMET assay and cell viability by the MTT assay.
Results: MSA was selectively toxic to THP-1 cells and induced a protective increase in GSH in PBMC but a decrease in high concentrations within THP-1 cells. DNA damage induced by Ara-C or Dox in the COMET assay was significantly reduced by MSA in PBMC but increased in THP-1 cells. Cell death after 2 Gy RT was increased by all doses of MSA in THP-1 cells but only by the highest dose in PBMC. The cytotoxicity of Pt, Dox and Ara-C at sublethal doses was significantly enhanced by MSA only in THP-1 cells. The dose-dependence of the Se effect varied between malignant and normal cells.

Conclusions: MSA at clinically-relevant concentrations had a differential effect on cell survival and death responses to RT and CT with relative protection of PBMC and enhanced death of THP-1 cells. Several mechanisms mediate this therapeutic selectivity and these assays could potentially be used in clinical trials to evaluate pharmacodynamic markers of Se effects in conjunction with CT and/or RT.

Economic Analysis of Prostate Cancer Screening

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Introduction: Prostate cancer (PCa) is the most frequently diagnosed cancer for men in New Zealand, accounting for 30.2% of all cancer registrations [1]. Screening for PCa using the prostate specific antigen (PSA) test is common in New Zealand [2], even though it is not recommended by the Ministry of Health [3]. This study estimates the costs of identifying a new case of PCa by screening asymptomatic men in general practice.

Methods: Asymptomatic men aged 40+ who underwent one or more PSA tests in 31 general practices in Midland region in 2010 were identified. A Decision Tree was constructed to map the screening pathway and to document the associated costs. After the medical resources associated with PCa screening were identified, they were multiplied with the unit cost of each type of resource to estimate the total cost. The costs per PCa detected were generated from the total cost and the number of cancer identified. Sensitivity analysis was conducted to assess the uncertainty of the costs.

Results: 7936 men were included in this study, with 29 new cases of PCa identified. We estimated the costs of GP consultations ($119,620), PSA tests ($90,387), first specialist assessment ($18,547), follow-up specialist consultations ($18,864), prostate biopsies ($19,686), pathology report of prostate biopsy ($32,661) and hospitalization due to complications after prostate biopsy ($1,818). The costs per cancer detected were $10,399. The results of sensitivity analysis indicated the number of new cancers, the unit cost/ the volume of GP consultation and the unit cost/ the volume of PSA tests could significantly influence the costs per PCa detected.

Discussion: The costs of detecting a new PCa by screening asymptomatic men were substantial. Most of these costs were attributed to activities in general practice, including GP consultations and PSA tests ordered by GPs. Additional input from GP providing informed consent will significantly increase the costs of identifying a new case of PCa.
A Fast Diagnostic test to Identify the *Mycobacterium Tuberculosis* Rangipo Strain

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**Background:** Tuberculosis (TB) is the second greatest killer worldwide due to a single infectious agent after HIV/AIDS. The incidence of TB disease in New Zealand was seven per 100,000 in 2010 which is higher than the rates for Australia, the United States, and Canada. Infection is usually curable with antimicrobial drugs, but relies upon strict adherence to the antibiotic regime. The Rangipo strain of *Mycobacterium tuberculosis* is responsible for the largest cluster of tuberculosis infections within New Zealand. This cluster has been active for over twenty years and its control has proved difficult owing to its high transmissibility and lack of a rapid test to identify the strain. Molecular typing is used to find and link source cases to contacts, discriminate between endogenous reactivation and exogenous re-infection, and to type strains allowing prompt identification and tracking of specific strains spreading through the population.

**Aims & Objectives:** To develop a fast diagnostic test to identify the Rangipo strain of *Mycobacterium tuberculosis*

**Methods:** Rangipo specific single nucleotide polymorphisms (SNPs) were identified through whole genome sequencing and database analysis. PCR amplification and restriction enzyme digests are used to differentiate between Rangipo and non-Rangipo *Mycobacterium tuberculosis* strains.

**Results:** Whole genome sequencing of 7 clinical isolates has allowed us to identify many Rangipo specific SNPs. Differing nucleotides at SNP positions between Rangipo and non-Rangipo strains are exploited and a triplex PCR/restriction enzyme digest differentiates the strains.

**Conclusion:** I am developing a rapid PCR based diagnostic test to quickly identify this virulent strain, based on Rangipo specific SNPs identified through whole genome sequencing, to aid in the diagnosis and treatment of this disease and limit its spread.

References

Risk Factors Associated with Mortality from Breast Cancer in Waikato – A Case Control Study

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Introduction: New Zealand (NZ) has the 7th highest age standardized breast cancer mortality in the world. Maori women fare even worse with a 60% higher mortality rate compared to NZ European women.

We performed a case control study to identify key characteristics associated with death from breast cancer among women diagnosed with breast cancer in the Waikato between 2002 and 2010.

Methods: All women diagnosed with breast cancer between 2002 and 2010 in the Waikato were identified from the Waikato Breast Cancer Register and NZ Cancer Registry.

Cases – All women who died of breast cancer between 2002 and 2012 with a primary breast cancer diagnosis between 2002 and 2010.

Controls – Age (+/- 1 year) and year of diagnosis matched controls (up to 3 controls per each case) that were alive on the date of death of the case to which they were being matched were identified.

Results: A total of 258 women who died of breast cancer over the study period were identified and 652 age and diagnosis year matched women with breast cancer were identified as controls. Mean age at death among cases was 63.9 years (SD 14.3).

Mean age at diagnosis was 61 years (SD 15.5) for cases and 60.6 years (SD 13.8) for controls. Proportion of Maori women among cases was higher compared to controls (17.4% vs 13.3%). A higher proportion of cases (84.5%) were diagnosed through symptomatic presentation compared to (59.2%) controls. Symptomatic cases had a significantly longer mean duration of symptoms (14.5 weeks) compared to symptomatic controls (mean10.1 weeks, p<0.01). Sixty-one percent of cases had advanced cancers (stage III and IV) compared to only 14.2% for controls. Just over half (50.7%) of cases were found to have poorly differentiated (grade 3) cancers while this degree of undifferentiation was found in only 17.5% controls. Significantly higher (p<0.05) proportion of cases were found to be oestrogen / progesterone receptor negative (27.3% vs. 9.6%) and HER-2 positive compared to controls (30.1% vs. 14.8%). Among cases, compared to NZ Europeans Maori women had more advanced staged (p<0.01), less poorly differentiated (p=0.02), more ER/PR negative (p=0.26) and more HER-2 positive (p<0.01) cancers. Multivariate analysis identified tumour stage, grade and ER/PR status as tumour factors significantly associated with mortality from breast cancer among Waikato women.

Conclusions: Tumour related factors including advanced stage, higher grade, ER/PR negativity and HER-2 positivity were found to be significantly higher among cases compared to controls. Among cases, compared to NZ Europeans, Maori women had more advanced, more ER/PR negative and more HER-2 positive, but less poorly differentiated cancers. Further studies with a bigger sample sizes are needed to
identify the full impact of all factors including tumour related, comorbidities and treatment on ethnic inequities in breast cancer mortality in NZ.

Getting The Message Across: How Effective Is PHARMAC’s Communication About Generic Medicine Switches?

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Background: Generic medicines play an important role in New Zealand’s public health system. Generic medicine switches offer the proven benefits of on-patent innovator medicines at a much lower cost. PHARMAC uses generic medicines switches as part of its pharmaceutical cost containment strategy, and carries out educational campaigns to promote use of generics [1]. The effectiveness of these campaigns have not been evaluated.

Methods: The study consisted of two parts. In the first part, an anonymous questionnaire sent to 500 randomly selected pharmacists to evaluate the effectiveness of PHARMAC’s messaging on pharmacists.

In the second part, prescription records from five pharmacies were examined, and five selected medicines analysed to determine how many patients were on the generic brand. This was supplemented by interviews of pharmacists from these five pharmacies.

Results: There was a fair (37.4\%) response rate to the questionnaires. 68\% of pharmacists supported generic switches, and over 98\% believed it was PHARMAC’s responsibility to inform them of switches. However, less than 40\% of pharmacists were satisfied by PHARMAC’s information about brand switches, and less than 50\% felt they had enough time to prepare. Just over 50\% found PHARMAC’s current campaigns effective. Analysis of prescription records found that most patients were on the generic brand. Pharmacists believed that those patients who opted to pay for innovator brands did so because patients believed these to more effective or had fewer side-effects than the generics.

Conclusion: While pharmacists are supportive of generic medicine switches, they believe PHARMAC’s communication around these switches could be improved.

Reference: