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Short Papers of Distinction

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Perioperative Care/Nutrition 0091

The effect of beta-blockade on objectively measured physical fitness in patients with abdominal aortic aneurysms - A blinded interventional study

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Aims: Perioperative beta-blockade is still widely however its influence on physical fitness assessment utilising cardiopulmonary exercise testing (CPET) is unknown. We hypothesized that beta-blocker therapy would significantly improve CPET derived physical fitness variables in a cohort of abdominal aortic aneurysm (AAA) patients.

Methods: We prospectively recruited 57 consecutive patients with AAA (< 5·5 cm) under active surveillance. Two cohorts were recruited (i) chronically beta-blocked group and (ii) acutely beta-blocked group. All patients underwent two CPETs; on and off beta-blockers. The 'chronic' group underwent a first CPET whilst on their present medication; the beta-blocker was then stopped for one week before a second CPET. The 'acute' group underwent the first CPET without any alteration in medical therapy, then, one week later, a second CPET was performed after the commencement of weight adjusted bisoprolol, 48 hours prior to the test. Oxygen uptake (Vo 2) at estimated lactate threshold (LT) and Vo 2 at peak were primary outcome variables. A linear mixed-effects model was fitted in order to investigate any difference in CPET variables when on and off a beta-blocker.

Results: Fifty-five patients (47 male) underwent the first CPET, 48 patients underwent a second CPET and completed the study. Adequate beta-blockade was achieved. No differences in Vo 2 at LT and Vo 2 at peak was observed, however, a significant decrease in V E /co 2 at LT and peak, an increase in workload at LT , O 2 pulse and heart rate both at LT and peak was found with beta-blockers. A significantly lower Vo 2 and workload at LT and peak and lower absolute Vo 2 at peak was found in the 'chronic' group.

Conclusions Beta blockade significantly impacts the results from CPET, albeit no changes in our primary outcomes were found. Chronically beta-blocked patients, have a worse performance on CPET, regardless of whether the CPET is performed on or off medications.

Basic and Applied Clinical Science 0163

Tissue Proteinase Levels, Tumour Pathology and 10 Year Survival Analysis in Colorectal Cancer

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Aims: Proteinases and their inhibitors are involved in tumour invasion and metastasis. The study will determine the levels of matrix metalloproteinase (MMP) and plasminogen activator (PA) system components in colorectal cancer and correlate these with the tumour pathology and ten year survival status.

Methods: Paired tumour and normal mucosal tissue from 101 colorectal cancer patients were analysed for the expression of MMP and PAS components by enzyme linked immunosorbent assays (ELISAs); MMPs–1, 2, –3 and –9, the tissue inhibitors, TIMP-1 and TIMP-2, urokinase and tissue type PA (uPA, tPA), the PA inhibitors, PAI-1 and PAI-2 and the receptor for uPA, uPAR. Tissue levels were correlated with tumour pathology; Dukes stage, differentiation, tumour depth, vascular and lymphatic invasion (< 0·05, Spearman's correlation). Ten year survival analysis was performed (< 0·05 Kaplan Meier). The study had ethics approval.

Results: The levels of all studied MMPs, uPA, uPAR, TIMP-1 and PAIs were significantly greater in colorectal tumour tissue than normal mucosa (< 0·05 Mann Whitney) e.g. PAI-1: tumour, median 14·9 (range, 0·2–80·2)ng/mg total protein; normal, 2·1 (0·1–65·0). However tPA levels were significantly greater in normal mucosa. Tumour levels of MMPs, uPA, uPAR and PAI-1 significantly correlated with Dukes' stage e.g. MMP-1: Adenoma, 0·9 (0·2–6·8); Dukes A, 4·7 (0·1–23·0); Dukes B, 11·9 (0·6–86·9); Dukes D, 16·3 (0·3–30·8). PAI-1 and uPA tumour levels also significantly correlated with lymphatic invasion, TIMP-1 and PAI-1 with tumour depth and PAI-2 with vascular invasion. The proportion of active MMP-2 and MMP-9 in tumour tissue significantly correlated with both disease free and overall 10 year survival, with patients with higher levels of these factors having poorer survival.

Conclusions: Tumour levels of proteinases and inhibitors from both the MMP and PA proteinase systems correlated with tumour pathology. However, only active MMP-2 and MMP-9 levels correlated with disease-free and overall ten year survival.

Basic and Applied Clinical Science 0427

Changes in Key Cellular Micrornas Are Reflected in the Exosomal but not Microparticle Compartment of Tumour and Stromal Cells

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Aims: Exosomes are secreted nanoparticles (30–100 nm) with a lysosome-endosome origin and complex synthetic pathway. Microparticles (MPs) are larger vesicles (100–1000 nm) which pinch off from the cell membrane. Exosomes and MPs have been shown to contain cancer-associated microRNAs (miRNAs). MiR-21 inhibits translation of tumour suppressor proteins whereas miR-200b inhibits epithelial-mesechymal transition (EMT). We aim to: (i) identify exosomal microRNAs which are upregulated in human colorectal cancer fibroblasts; (ii) ascertain the effect of myofobroblast transdifferentiation on exosomal miR-21; and (iii) ascertain the effect of EMT on exosomal miR-200b.

Methods: Three models were used: paired human cancer-associated and normal fibroblasts from colorectal resections; TGF-beta treated and untreated HFFF2 fibroblasts (myofibroblast transdifferentiation); and SIP-1 induced and uninduced DLD-1 colorectal cancer cells (EMT). MPs and exosomes were isolated by selective centrifugation and validated by transmission electron microscopy, western blotting and flow cytometry. A cancer microRNA array (Quantimir) was used to screen for 95 specific microRNAs. Quantitative PCR with TaqMan probes was used to measure relative miR-21 and miR-200b concentrations.

Results: Relative concentrations of let-7 family, miR-7, miR-133a, miR-141, miR-95, miR-200a and miR 206 were at least 10 fold lower in primary colorectal cancer fibroblasts compared to normal colorectal fibroblasts. Cellular miR-21 concentration was exponentially higher in myofibroblasts than fibroblasts. This was reflected at the exosomal (2·28+/–0·03 vs. 1·00+/–0·04) but not the MP level. SIP induced colorectal cancer cells had 13 fold less miR-200b than uninduced cells. Again, this was reflected at the exosomal (0·24+/–0·01 vs. 1·00+/–0·04) but not the MP level.

Conclusions: Microarray screening highlighted key miRNAs which are significantly down regulated in cancer associated fibroblasts. In the myofibroblast and EMT models, exosomal but not MP miRNA concentrations changed significantly and mirrored that of the parent cells. Compared to MPs, exosomes originate deep within the cytoplasm and their proximity to the nuclear machinery may explain this phenomenon.

General 0523

Stapled Versus Milligan Morgan Haemorrhoidectomy in the Management Of 3 Rd and 4 Th Degree Haemorrhoids: A Randomized Trial

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Aims: Many trials have been performed comparing stapled versus Milligan Morgan Haemorrhoidectomy with conflicting results. We present the results of our randomized trial. We hypothesized that stapled haemorrhoidectomy is associated with reduced hospital stay and reduced early post-operative pain as compared to open haemorrhoidectomy in the management of 3rd and 4th degree haemorrhoids.

Methods: Seventy patients with 3rd and 4th degree piles were randomized in a teaching hospital after ethical committee approval into two groups by lottery method from Jan-Dec 2013. Group A, underwent stapled haemorrhoidectomy and group B, Milligan-Morgan haemorrhoidectomy. The primary outcomes were hospital stay and post-operative pain (assessed by Visual Analog Scale score), whereas secondary outcomes were early post-operative bleeding and the return to daily activities.

Results: The mean age in group A was 39·3 ± 8·4 years and in group B was 39·7 ± 7·4 years. Fifty five percent patients were male in group A and 57% were male in group B. In group A, 29 (83%) patients had a hospital stay less than 24 hours and in group B, there were 3 (7%) patients ($p < 0·001$, OR = 0·0194, RR = 0·1875, CI 95%). In group A, 28 (80%) patients had a VAS score at 3 hrs less than 3. In group B, 10 (29%) patients had a VAS score at 3 hrs less than 3 (< 0·001, OR = 0·1, RR = 0·28, CI 95%). In group A, 2 (6%) patients had post-operative bleeding within the first 24 hours and in group B, 5 (14%) patients had post-operative bleeding within the first 24 hours ($p = 0·428$, OR = 0·3636, RR = 0·4, CI 95%).

Conclusions: Hemorrhoidectomy with a circular staple device achieves better results than the Milligan-Morgan technique by reducing early post-operative pain, hospital stay and cost.

Basic and Applied Clinical Science 0700

The Interaction Between Bacterial Products and the Immune System as an Aetiological Factor for Idiopathic and Crohn's Anal Fistulae

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Aims: The pathogenesis of Crohn's disease (CD) involves an interaction between genetic, microbiological and immunological factors. The cryptoglandular hypothesis implicates bacteria as an aetiological factor for idiopathic anal fistulae. Studies looking into the bacteriology of cryptoglandular fistulae failed to identify pathogenic bacteria, and only low numbers of organisms were found, dismissing permanent infection as a major contributing factor to fistula persistence. Dendritic cells express Toll-Like receptors (TLR), which are pattern recognition receptors that are activated by bacterial ligands. We aimed to compare the expression of TLRs and microbiota profiles of CD and idiopathic fistulae.

Methods: Biopsies were taken from Crohn's and idiopathic fistulae at surgery. Dendritic cells were identified as HLA-DR-positive and lineage-negative, and characterized by flow cytometry using fresh samples. The expression of TLR2 and 4 was determined. Immunohistochemical techniques determined the expression of TLR2, TLR4 and TLR9 on paraffin-imbedded biopsies. DNA was extracted from frozen samples and bacterial 16S rRNA genes were sequenced using a MiSeq sequencer.

Results: TLR2 and 4 were expressed on dendritic cells from both Crohn's and idiopathic perianal fistulae using flow cytomtery techniques. There was no significant difference in TLR2 ($p = 0·27$) or TLR4 ($p = 0·45$) expression on CD and idiopathic fistulae. Immunohistochemical techniques have show equal expression of TLR2 ($p = 0·42$) and TLR4 ($p = 0·11$) on lymphocytes. TLR9 expression was significantly higher in CD fistulae ($p = 0·01$). Microbiota were classified into those that were common and abundant, infrequent and rare. The total number of operational taxonomic units (OTUs) observed in Crohn's fistulae was significantly higher than idiopathic ($p = 0·02$).

Conclusions: Bacterial products are present in perianal fistula tracts. There is evidence of expression of Toll-Like receptors which are activated by gram-positive, gram-negative bacterial ligands as well as bacterial DNA. The microbiome-immune system interaction may be implicated in the persistence of Crohn's and cryptoglandular perianal fistulae.

Education and Training 0744

The ASiT Survey 2014: A Nationwide Exploration of Trainee Perspectives on the Use of Workplace-Based Assessments in UK Surgical Training

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Aims: Despite widespread uptake, evidence for the utility of Workplace Based Assessments (WBAs) is disputed. Questions regarding 'in vivo' use of WBAs remain scientifically unanswered, while anecdotally seeming to be ubiquitously known among trainees and trainers alike. This research project aimed to ascertain the views of UK surgical trainees regarding WBA use.

Methods: An online questionnaire was developed for a national survey conducted via the Association of Surgeons in Training (ASiT). Evaluation of 906 completed trainee responses, across all specialties and training levels (CT1-ST8), employed mixed methods in a combined interpretation of quantitative and qualitative data from the questionnaire.

Results: The sample permitted a 3·0% confidence level based on JCST trainee numbers with acceptable internal consistency (Cronbach's alpha 0·755). Formative use was supported by 72·5%, summative use rejected by almost as many (66·3%). WBA use was perceived to deviate grossly from that recommended by JCST. Significant misuse was identified and elements perceived as dishonest appear commonplace across the breadth of surgical specialties. 'Dishonest completion' was acknowledged by 89·6% of respondents, and trainers appear complicit, 147 individuals (16·2%) having reported this to trainers and 40·9% aware of 'unobserved sign-off' and 33·6% 'password disclosure' by trainers. Furthermore, a majority of trainees felt the ARCP respected WBA numbers over competence (55·4%) and almost a third felt pressure to overstate the number completed (32·0%). Reasons for misuse appeared largely centred upon time restraints, lack of engagement and a will to achieve the required targets for career progression.

Conclusions: Based on these worrying novel findings and insights from the wider literature, recommendations for future use and development of WBAs are made. These include reducing and capping minimum numbers, formal ARCP examination of content, simplification of assessments and ISCP user interface, improved assessor training, contractual recognition of active and effective training, and formal JCST consideration of additional assessment methods.

Audit and Outcomes Research 0841

Surgical and Obstetric Care is Highly Cost-Effective in an African District Hospital: A 3 Month Single Centre Study of Costs and Outcomes in Elective and Emergency Surgery

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Aims: Surgery is a much neglected branch of global medicine, partly due to the perceived challenges and costs in providing suitable facilities and staff. There are very few studies detailing the cost-effectiveness of surgery in low and middle income countries, although the limited data suggests it compares favourably to the much championed treatment of infectious diseases. This study demonstrates the cost-effectiveness of surgery in a district hospital in Zambia.

Methods: All surgical and obstetric admissions requiring one of eight index procedures between September and December 2012 were assessed for diagnosis,

interventions, outcomes and length of stay. Fully loaded cost data was collected. The number of disability adjusted life-years saved by treatment was calculated using World Health Organisation Global Burden of Disease methodology and patient outcome data. Cost in year 2000 US$ was calculated per DALY averted for a range of surgical interventions.

Results: Four hundred and twenty eight patients underwent one of eight procedures (amputation, emergency and elective caesarean section, laparotomy, emergency and elective hernia repair, manipulation of fracture or fixation of fracture). Treatment prevented a loss of a total of 10774 DALYs. Mean cost effectiveness per procedure (Table 1) varied from $3·26 per DALY (emergency hernia repair) to $164·04 per DALY (fracture fixation). Average cost per DALY saved across all procedures was $8·75.

Conclusions: This is an at present unique study, utilising real patient and hospital outcomes and costs in a rural Southern African hospital. It demonstrates that surgery and obstetric care are highly cost-effective interventions in this setting. There is a paucity of good quality research into surgical effectiveness, let-alone cost-effectiveness, that is partly addressed by this study. The data presented demonstrates the important role of surgery in the global health agenda and could be used to guide future policy decisions - a current hot topic of debate.

Basic and Applied Clinical Science 0984

Epigenome-Wide DNA Methylation Profiling in Inflammatory Bowel Disease

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Aims: Epigenetic alterations including DNA methylation may provide important insights into gene-environment interaction in complex immune diseases such as inflammatory bowel disease (IBD). Whilst whole tissue methylation changes may provide clinically useful biomarkers, epigenetic changes are cell-type specific. This study aimed to characterise the circulating methylome in IBD, and relate changes seen in whole blood to the methylation profile in separated leucocytes, gene expression data, as well as our previous data in childhood-onset disease.[1]

Methods: The Illumina 450 k array was used to assess whole blood leucocyte DNA methylation at over 485,000 CpG sites across the genome. Differentially methylated sites discovered in whole blood were investigated in immunomagnetically separated leucocytes (CD4+ & CD8+ lymphocytes, CD14+ monocytes).

Results: The discovery cohort consisted of 240 patients (121 Crohn's disease, 119 ulcerative colitis) and 191 controls. There were 439 differentially methylated CpG sites meeting epigenome wide significance as defined as a Holm corrected p value of $< 0·05$(uncorrected $< 1·1 \times 10^{-7}$). There were 55 differentially methylated regions (DMRs) with unidirectional methylation change in 3 or more adjacent markers, each achieving Benjamini-Hochberg adjusted significance.

Compelling genes pertinent to disease pathogenesis are heavily implicated. The most significantly differentially methylated position in whole blood (RPS6KA2 [corrected $p = 1·2 \times 10^{-16}$]) was also hypomethylated in monocytes in ulcerative colitis (uncorrected $p = 3·5 \times 10^{-6}$). The most significantly differentially methylated region VMP1/miR21(most significant probe corrected $p = 2 \times 10^{-14}$) strongly replicates the same finding in our previous study.

Conclusions: This is the largest epigenetic analysis carried out in IBD to date. The findings strongly validate this approach in complex disease, replicate and expand on previous data, and provide clear translational opportunities. Differentially methylated CpG sites provide important potential biomarkers. Those genes implicated by whole blood, cell-specific differential methylation as well as expression changes may be implicated in disease pathogenesis, and provide novel targets for therapy.

References

1. Inflamm Bowel Dis. 2014;20(10):1784–93.