FOSTERING PHYSICAL ACTIVITY AFTER COMPLEX LUMBAR SPINE SURGERY: A RANDOMIZED TRIAL

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Background: Prolonged sedentary lifestyle after recuperation from lumbar surgery is due to fear of spine injury, pain, deconditioning, and habit, and incurs serious long-term adverse consequences (eg Sedentary Death Syndrome). Because the surgical team understands the extent of surgery and spine condition, it ideally can advise and encourage prudent activity.

Purpose: To determine if a behavioral intervention would be effective in increasing prudent physical activity, primarily walking

Sample: 225 patients, RCT 3 months after complex lumbar surgery, subsequent follow-up after additional 4-6 months

Outcome: Paffenbarger Physical Activity and Exercise Index (PAEI)

Methods: During routine postop visits, 111 intervention patients received 1) a booklet about benefits of physical activity/national activity guidelines 2) instruction on how increase lifestyle walking 3) a pedometer calibrated to stride length 4) made a self-contract specifying walking goals and 5) received periodic telephone contract-directed encouragement from study personnel. 114 controls received information about safe physical activity. At enrollment all patients completed the valid 3-domain PAEI measuring number of blocks walked and stairs climbed daily and sports during the past week. Kcal/week were calculated for each domain and for an overall total. The national recommended threshold overall total is ≥2000 Kcal/week. Patients also completed the GAD7 for general anxiety. OR records were reviewed and a Surgical Invasiveness Index (SII) value was calculated (max 10 points/vertebral level); higher is greater complexity. The primary outcome was change in PAEI walking domain Kcal/week after 4-6 months; another outcome was change in overall total Kcal/week.

Results: At enrollment intervention and control groups were similar in mean age (64 vs 64), women (44% vs 50%), median SII value (11 vs 10), PAEI walking Kcal/week (1447 vs 1246), PAEI overall total Kcal/week (1826 vs 1631), and percent meeting the recommended activity threshold (37% vs 30%) (all p>.05). Mean time from surgery to enrollment was 2.9 months, and from enrollment to follow-up was 4.2 months. The within-patient mean increase in PAEI walking was 1132 vs 582 Kcal/week (p=.03) and the increase in PAEI overall total was 1713 vs 1067 Kcal/week (p=.04). In multivariable analysis with change in PAEI walking as the dependent variable, intervention group (p=.02), younger age (p=.003), and more anxiety (p=.05) were associated; more complex surgery was not (p=.26). Similar results were found with PAEI overall total as the dependent variable. At the follow-up more patients in the intervention group met the ≥2000 Kcal/week threshold (63% vs 46%) (OR 2.0, CI 1.2-3.5, p=.009).

Conclusions: A behavioral intervention in the spine care setting succeeded in increasing physical
activity after recuperation from lumbar surgery and in helping patients regain prudent activity to promote subsequent spine and overall health.

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EXPRESSION OF TRPV4 IN HUMAN IVDS AND ITS RELEVANCE IN STRETCH-INDUCED INFLAMMATION
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Introduction
Transient receptor potential (TRP) channels are cation selective transmembrane channels with diverse activation mechanisms and physiological function. Dysregulation of TRP channels is implicated in numerous pathologies. TRPV4 for example is involved in mediating inflammatory swelling in arthritic joints; in addition, TRPV4 regulates transduction of mechanical signals in various cell types. A first study from 2016 indicates that TRPV4 is expressed in the IVD and seems to be associated with reduced osmolarity and pro-inflammatory cytokines.

The aim of this study was to (1) investigate TRPV4 expression patterns in a comprehensive manner and (2) determine whether TRPV4 plays a role in stretch-induced inflammation.

Methods
For the analysis of TRPV4 mRNA expression in human IVDs, a total of n=22 human degenerated (IVD degeneration/herniation) and n=12 non-degenerated IVD tissue samples (autopsies) were used. Gene expression was compared between degeneration and non-degeneration, NP and AF, as well as for various patient characteristics.

In a second step, the relevance of TRPV4 in stretch-induced inflammation (gene/protein), calcium flux and activation of the MAPK pathways was investigated in human AF cells in vitro, using a commercial bioreactor (n≥3, with/without pharmacological TRPV4 inhibition = GSK2193874, 20-500 nM). Results of inhibition studies were confirmed by CRISPR/Cas9.

Statistical analysis was conducted by Student t-tests, Aspin-Welch unequal variance tests or one-way ANOVA with Tukey correction, with a significance level of p < 0.05.

Results
TRPV4 mRNA was detected in all human IVD tissue samples. No statistically significant differences were found between the degenerated and non-degenerate samples, IVD zones, degeneration grade, Modic changes, pain intensity and duration. Based on the constitutive expression of TRPV4, we subsequently investigated its role in IVD mechanobiology.

To determine the relevance of TRPV4 in mechanotransduction, 1 hour of stretching at 20% strain/1 Hz (= high physiological levels) was used, resulting in a significant mRNA upregulation of inflammatory mediators, such as IL-6 (2.6 fold) and COX-2 (8.1 fold). Induction of inflammation could also be confirmed on the protein level for selected targets, such as PGE2. Stretch-induced inflammation was accompanied by a significant MAPK activation and calcium flux. Importantly, pharmacological inhibition of TRPV4 was able to reduce cytokine expression (Fig. 1) and MAPK activation. First results using CRISPR/Cas9-based knockout of TRPV4 verify its relevance in stretch-induced inflammation.

Discussion
TRPV4 was consistently expressed in human IVD samples, indicating its fundamental function in IVD physiology and mechanotransduction. Our results suggest that stretch-induced inflammation is at least in part mediated by TRPV4. TRPV4 may thus constitute a potential target to modulate mechano-immunosensing in the IVD and thus tackle degenerative disc disease.
Fig. 1 Gene expression of IL-6 in human AF cells that were non-stretched (No. Str.), stretched or stretched with simultaneous TRPV4 inhibition with GSK2193874 (Str. antag.) (n=4). *p<0.05, **p<0.01.

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INTRAOPERATIVE SALVAGED AUTOLOGOUS BLOOD TRANSFUSION IS SAFE IN METASTATIC SPINE TUMOUR SURGERY: EARLY OUTCOMES OF PROSPECTIVE CLINICAL STUDY

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Introduction:
Allogeneic blood transfusion (ABT) is the mainstay of blood replenishment; however, it is associated with immune-mediated complications. Salvaged blood transfusion (SBT) has allowed us to overcome such complications. We have proved the safety profile of SBT in MSTS. However, surgeons remain reluctant to employ SBT in metastatic spine tumour surgery (MSTS) due to ill-founded fears of tumour dissemination and disease progression.

We aimed to investigate tumour progression, overall survival (OS), reduction in ABT requirement and to reaffirm safety profile in patients who receive SBT during MSTS.

Methods:
We present a prospective study of 73 patients who underwent MSTS at our institution from 2014-2017. Data collected included demographics, tumor histology, metastatic disease burden, clinical and investigational findings, operative & blood transfusion (BT) details and post-operative complications.

Patients were divided based on BT type into 3 groups: no blood transfusion (NBT), SBT and ABT. Primary outcomes were assessed at 6, 12 and 24 months. Tumour progression was evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) (v1.1). Modified Tokuhashi score was studied for its association with OS. All follow-up investigations (CT chest/thorax-abdomen-pelvis, MRI spine and bone scans) were studied. Patients were then classified into those with non-progressive and progressive disease.

Results:
Seventy-three patients [39 (53.4%) males & 34 (46.6%) females], had a mean age of 61 years [range: 20-84 years]. Overall median follow-up and survival were 26 and 12 months respectively. Most common primary tumours were lung [20 (27.4%)], breast [13 (17.8%)], prostate [6 (8.2%)] and colon [6 (8.2%)]. Overall median blood loss was 500mL [IQR:250-970mL] and BT was 1000 mL [IQR:500-2000 mL]. Twenty-six (35.6%) patients received SBT, 27 (37.0%) ABT and 20 (27.4%) required NBT. Blood loss in NBT group was significantly lower (p < 0.001) than that in SBT and ABT groups.

Females had a lower OS and a higher risk of tumour progression compared to that of males. Higher Tokuhashi score had decreased risk of death and tumour progression. Overall, patients who had received SBT had a better OS (Fig.1) and a reduced risk of tumour progression than those who received ABT. Total blood loss was not associated with tumour progression. Medical complications and SSI were comparable among all 3 groups. Infective complications other than SSI were significantly (p = 0.027) higher in ABT group than that in SBT and ABT groups.

Conclusions:
(i) Patients who had received SBT had outcomes (OS and tumour progression) comparable to or better than ABT and NBT groups.
(ii) This study proves that the use of salvaged blood in MSTS is safe and can become a standard of care for these surgeries.
(iii) To the best of our knowledge, we are the first to report this contemporary practice of the use of SBT in comparison with control groups (ABT and NBT groups) in MSTS.
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Fig. 1: Overall survival curves over follow-up time according to blood transfusion type, adjusted for age group (≥ 60 years vs. < 60 years), gender (female vs. male), total blood loss (in scale) and total Tokuhashi score by the multivariable Cox proportional hazards regression model
CURRENT TRENDS AND PERIOPERATIVE COMPLICATIONS OF SURGERIES FOR SPINAL INFECTIONS IN THE SUPER-AGEING SOCIETY: A MULTI CENTER STUDY

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Purpose: The increase of the elderly and compromised hosts can result in the growing numbers of the patients with spinal infections. Japan is now experiencing a “super-aging” society and this multi-center study aimed to investigate the current characteristics in surgeries for spinal infections in Osaka of which aging rate is above 25%.

Method: A total of 22295 patients who underwent spinal surgeries at 25 institutions around Osaka in Japan were registered prospectively between 2012 and 2017. 341 patients who underwent surgeries for spinal infections were reviewed from this database. The demographic data (age and gender), pathology (pyogenic or tuberculous), affected level, surgical procedures, and perioperative complications were investigated.

Results: The annual ratio of surgeries for spinal infections to those of all spinal surgeries was between 1.21% and 1.98% in the last 6 years. Of the 341 patients, 201 patients were diagnosed with pyogenic spondylitis and 79 patients were tuberculous spondylitis; however, the other 61 patients were not identified due to lack of information. The number of surgeries for pyogenic spondylitis increased during this period; however, that of surgeries for tuberculous spondylitis decreased. The median age of patients with pyogenic spondylitis and tuberculous spondylitis at the time of the surgeries was 70 years (range, 14-91 years) and 74 years (range, 22-88 years) respectively, and the median age did not change significantly during this period both in pyogenic and tuberculous spondylitis. The percentage of the male performed surgeries for tuberculous spondylitis was significantly higher than those for pyogenic spondylitis (53% vs. 33%, p = 0.003). In both pathologies of infection, lumbar spine was more frequently affected than the other levels. The surgical procedures for pyogenic spondylitis consisted of various surgical approaches with or without instrumentation. In contrast, 72% of the surgeries for tuberculous spondylitis were performed with anterior instrumentation and fusion. Perioperative complications occurred in 28 patients (8.2%); 19 of 201 patients (9.5%) in pyogenic spondylitis, 5 of 79 patients (6.3%) in tuberculous spondylitis, and 4 of 61 patients (6.1%) in unknown pathology. In particular, perioperative mortality rate in pyogenic spondylitis was 2.5% (5 of 201 patients), though that in tuberculous spondylitis was 0%. Toxic shock syndrome, hemorrhagic shock, and septic shock were the causes of perioperative death in this study. The mortality rate in pyogenic spondylitis was 25 times higher than that of all spinal surgeries in this data base (0.1%).

Conclusion: The number of the surgeries for pyogenic spondylitis increased during last 6 years in our super-aging society. The perioperative complication rate was relatively high in patients with spinal infections. In particular, perioperative mortality of the pyogenic spondylitis was 2.5%.

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PENETRATION INTO THE INTERVERTEBRAL DISC OF ANTIBIOTICS USED FOR PERIOPERATIVE PROPHYLAXIS IN SPINE SURGERY: IMPLICATIONS FOR THE CURRENT STANDARD AND FOR THE TREATMENT OF DISC INFECTIONS

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Introduction:
Intervertebral discs are avascular, have low pH and disc infections differ from infections of other tissues. The intradiscal penetration of typically used antibiotics and hence their effectiveness may also differ. This could have clinically relevant implications. A high prevalence of Propionibacterium acnes (P. acnes) colonisation in intervertebral disc material obtained from patients undergoing discectomy or microdiscectomy has led to the suggestion that this prominent human skin and oral commensal may exacerbate the pathology of degenerative disc disease. This hypothesis, in turn, raises the possibility that antibiotics could play an role in treating this debilitating condition. In addition, the existence of low-grade disc infections with P. acnes, which is not consistently sensitive to cephalosporins, challenges the current recommendations as to which antibiotic should be used for perioperative prophylaxis in spinal surgery. To date, however, little information about antibiotic penetration into the intervertebral disc is available.

Methods:
Nucleus pulposus material from 54 microdiscectomy patients that had received prophylactic Cefazolin (n=25), Clindamycin (n=17) or Vancomycin (n=12) based on their individual allergies, was used in this prospective cohort study. Indications for surgery were symptomatic lumbar disc herniations with either a fresh paresis or failure of conservative care to relieve neuropathic pain. The administration of the antibiotic followed the standard protocol of the participating institutions. Analysis was performed by means of high-performance liquid chromatography (HPLC), with Cefaclor serving as an internal standard, to determine the concentration of antibiotic penetrating into the disc tissue.

Results:
Intervertebral disc tissues from patients receiving the positively charged antibiotic clindamycin contained a significantly greater percentage of the antibacterial dose than the nucleus material from patients receiving the negatively charged cefazolin (p<0.0001). Also vancomycin, which has a slight positive charge had higher concentrations (p<0.0001) - see table. While Vancomycin reached minimal bactericidal concentration in the nucleus material, none of the 3 antibiotics tested reached minimal biofilm eradication concentration.

Conclusions:
Positively charged antibiotics appear more appropriate for future studies investigating potential options for the treatment of low-virulent disc infections with P. acnes. The current standards for perioperative antibiotic prophylaxis in spinal surgery probably should be reexamined. The expanding knowledge about low-grade disc infections (beyond the better-known pyogenic infections) underlines the already existing need to reexamine currently established standards of perioperative antibiotic prophylaxis in spine surgery, particularly that none of the 3 antibiotics tested appears capable of treating an existing biofilm within the disc.
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<thead>
<tr>
<th>Antibiotic</th>
<th>Cefazolin</th>
<th>Vancomycin</th>
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<td>CMAX</td>
<td>48 (4-199)</td>
<td>10 (9.6-10.6)</td>
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<tr>
<td>MIC*</td>
<td>0.06 (0.06-0.06)</td>
<td>0.06 (0.06-0.06)</td>
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<td>Antibiotic (Sigma-Chemical) or (mS)</td>
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<td>Concentration (mg/mL)</td>
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<td>Matrix:</td>
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**Notes:**
- CMAX: Maximum Concentration
- MIC*: Minimum Inhibitory Concentration
- PO Patients: Patients treated with oral antibiotics
- Antibiotic (Sigma-Chemical) or (mS): Antibiotic concentration in Sigma-Chemical or milligrams per milliliter
IMPACT OF RADIOLOGIC VARIABLES ON ITEM RESPONSES OF ODI AND SRS22 IN ADULT SPINAL DEFORMITY PATIENTS: DIFFERENTIAL ITEM FUNCTIONING (DIF) ANALYSIS RESULTS FROM A MULTI-CENTER DATABASE

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Background
Evaluating whether the responses given to the items in a scale differ by external variables is a method used to evaluate the internal construct validity of the scale. Statistically, items being affected by external factors (e.g., radiological) are deemed biased and this bias is referred to as differential item functioning (DIF). On the other hand, this bias may be useful for clinical purposes and denote a sensitivity of the item to the factors (e.g., radiological) analyzed.

Purpose
To analyze whether responses given to ODI and SRS22 items are influenced by radiological parameters (RP) such as Global Tilt, Sagittal SVA, RSA, Sagittal PT, RPV, PI-LL, RLL, Coronal Balance, Major curve cobb angle, we conducted a DIF study. The hypothesis was that only some items from ODI and SRS22 are directly affected by radiologic changes.

Materials and Methods:
Patients enrolled in a multicentric prospectively collected ASD database who had complete SRS22 and ODI data at baseline and the 1st year (n=923; 774F, 149M; 500 surgical, 423 non-S; average age: 51.97+/−19.5) were analyzed retrospectively. DIF of items in relation to radiological parameters (RP) was analyzed using Mixed Rasch Model to define latent classes derived from personal factors; which yielded results on the presence of DIF and if so, the threshold value(s) associated with it.

Results:
Overall DIF results can be seen in Fig 1. In summary, for ODI; questions (Q) 3, 6, 9 and 10 were found not to be sensitive to any RP whereas Q4 was sensitive to 6, and Q5 to 4. For SRS22; Q3, 5, and 18 were sensitive to almost all RP. More importantly, 12 SRS22 Q were found to be sensitive to MCCA, which attests to its origin as a scale for scoliosis.

Conclusion:
The results of this study demonstrate that both ODI and SRS22 are moderately sensitive to radiological parameters in ASD patients, through certain questions. These items, analyzed separately or assembled as a specific ASD HRQoL scale may be functional in establishing a connection between changes in RP and HRQoL.
Fig 1: Differential item functioning results for SRS 22 and ODI questions. An empty cell denotes insensitivity of the corresponding Q and RP, whereas a value denotes sensitivity at the specified threshold. The items underlined in green are the most sensitive to radiologic parameters changes.

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THERAPEUTIC RADIATION THERAPY IMPROVES SURVIVAL FOR CHORDOMA PATIENTS

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Background:
The role of radiation therapy (RT) for the treatment of axial chordomas remains controversial. Previous large database reviews have not found adjunct RT to improve overall survival, but these studies did not stratify based on high/low dose RT, the modality of RT, or the patient’s surgical margin status. We investigated the National Cancer Database (NCDB) to determine if high dose RT improves survival in patients with positive versus negative surgical margins. Additionally, the study compares the 5-year overall survival between high versus low dose RT and advanced versus conventional delivery methods.

Methods:
1,480 patients were identified in the NCDB between 2004 and 2015 with a histologically confirmed axial chordoma. Survival analysis was performed using the Kaplan Meier method. The 5-year survival was compared between surgical resection alone and surgical resection and adjunct therapeutic RT for the overall cohort, patients with positive surgical margins, and patients with negative surgical margins. Therapeutic RT was defined as a dose greater than 65Gy. For patients treated with RT, the 5-year survival was compared between palliative dose (<40Gy), low dose (40-65Gy), and high dose (>65Gy) RT. Similarly, 5-year survival was compared between proton beam therapy (PBT), stereotactic radiosurgery (SRS), intensity-modulated radiation therapy (IMRT), and conventional external beam radiation therapy (EBRT). A multivariable analysis was performed to determine independent prognosticators associated with 5-year overall survival.

Results:
The cohort included 1,480 chordoma patients; skull base (n=569), sacral (n=551), mobile spine (n=360). The 5-year survival for entire cohort was 76%. The survival for patients treated with surgical resection and adjunct therapeutic RT was greater than surgery alone (85% vs 80%, p=0.04). Therapeutic adjunct RT improved survival compared to surgery alone in the setting of positive surgical margins (82% vs 71%, p=0.03). In the setting of negative surgical margins adjunct RT did not statistically improve survival (p=0.33). Radiation dose >65Gy improved survival when compared to radiation dose between 40-65Gy (85% vs 69%, p<0.001). Comparing the modality of RT, PBT had the greatest 5-year survival (85%), which was statistically greater than EBRT (85% vs 68%, p<0.001). In the multivariate analysis improved 5-year survival was associate with age<65, private health insurance, tumor size <5cm, surgical resection, negative surgical margins, and treatment at an academic facility.

Conclusion:
Adjunct RT (dose >65Gy) was associated with improved survival for patients with positive surgical margins. A survival benefit was not observed for patients with negative surgical margins who were treated with adjunct RT. High dose RT and advanced radiation techniques, specifically PBT, were associated with improved 5-year survival.
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