Abstracts: Neuromodulation & Imaging

MP2.01: Sacral neuromodulation in pediatric age group : parents acceptability and therapy effectiveness and safety in our Saudi Patients.

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Introduction: Bladder dysfunction and constipation are common in pediatrics. Sacral neuromodulation (SNM) is a minimal invasive therapy for lower urinary tract symptoms. It is not FDA approved for pediatrics and need highly educated cooperative parents. The objective of our research is to assess parents' acceptability and therapy effectiveness and safety in our Saudi Patients.

Methods: A prospective cohort study was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. We included pediatric patients with normal upper tract and diagnosed to have urine incontinence , fecal incontinence, high PVR and using intermittent catheterization (CIC) to empty bladder and patients who are refractory to the maximum medical treatment ,or discontinued therapy because of side effects. Candidate child's parents are counselled in the clinic for sacral neuromodulation , technique, risks and benefits. The procedure was done in two phases under General anesthesia.

Results: Candidates' parents counselled in clinic were 105, only 39 pediatrics underwent phase one procedure. Parents acceptance rate were 37.1% .Successful phase one was in 29 with Implantation rate 74% (29/39). Patients age were from 8 to 16 years .Diagnosis were spinal bifida 8, Posterior urethral valve 2, Hinman's syndrome 18, fecal incontinence 1. Patients post implantation become urine continent in 60% (18/28) fecal continence rate was 66% (6/9), medications were discontinued in 50% (15/29) . Intermittent catheterization was stopped in 40% (12/28), see table1.Complications included electrode migration in 1 patient, loss of efficacy in 1, and 2 device explanation for normalized nerve function after device is turned off for 1 year.

Conclusions: Sacral neuromodulation showed safety and effectiveness in selected pediatric patients. Parents acceptability of therapy is low as a newly introduced off label therapy and need cooperative , highly educated parents . The reported normalized nerve function suggests early treatment with neuromodulation may lead to permanent resolution of symptoms which will need more studies.

Diagnosis (n)	Continence rate	Anticholinergic medications use	Intermittent catheterization (CIC)
Spina bifida (8)	Fecal and urine continence rate 60% (5-8)	Stopped 30% (3/8)	Stopped 50% (4/8)
Posterior urethral valve (2)	1 urine continent	1 stopped medication	decreased frequency of CIC
Hinman's Syndrome (18)	60% urine continence (12/18)	60% stopped medications (10/18)	40% stopped CIC (8/18)
Fecal incontinence + functional constipation	Fecal continence Regular bowel movement 2xday Resolved constipation	Stopped medications	NA

Table 1 : Patients diagnosis, continence rate, medications and CIC use post sacral neuromodulation.

MP2.02: Multicentre study For the effect of COVID-19 lockdown on sacral neuromodulation implanted patients

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Introduction: The massive spread of the COVID-19 pandemic affected many aspects of medical and surgical services. Many patients with Sacral neuromodulation (SNM) devices were in need of integrated follow-up and close communication regarding the programming of the device. In this study, we aim to explore the effect of COVID-19 on SNM implanted patients.

Methods: This was a multi-center study designed and done in 4 centers doing sacral neuromodulation (Toronto Western Hospital Toronto Canada, KingAbdulaziz University Hospital Jeddah Saudi Arabia, Alamiri Hospital Kuwait city at Kuwait and Austin and Western Health, University of Melbourne at Australia). An online questionnaire was created through google forms and circulated among implanted SNM patients in all 4 mentioned centers. Questionnaire was sent to patients during the forced lock down period in each country.

Results: A total of 162 responses were received by September 2020. Data showed that most of the patients had their device implanted before the Lockdown period 92.5% (150 out of 162). Most patients didn't experience any contact difficulties 91.9% (149 of 162). When patients were requested for their preference of programming, 89.5 % (145 of 162) preferred remote programing. Correlation analysis didn't show any significant relation between patient diagnosis and COVID-19 related difficulties or preferences.

Conclusions: The difficulties with access to care experienced during the pandemic and patient's expressed willingness to participate in virtual care should provide impetus for manufacturers of sacral neuromodulation devices to move forward with developing remote programming capabilities.

MP2.03: Protocol for a multicenter, randomized, sham-controlled, double-blind clinical trial investigating transcutaneous tibial nerve stimulation for treating neurogenic lower urinary tract dysfunction (bTUNED)

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Introduction: Many patients with neurological diseases suffer from neurogenic lower urinary tract dysfunction (NLUTD), which often severely impairs quality of life, due to urinary urgency with or without incontinence and voiding dysfunction. High intravesical pressures may jeopardise the upper urinary tract caused by detrusor overactivity with concurrent detrusor sphincter dyssynergia and/or low bladder compliance. The treatment of NLUTD is a challenge since conventional conservative therapies often fail and more invasive treatments such as onabotulinumtoxinA injections, bladder augmentation, and urinary diversion must be considered. Neuromodulation therapies may be alternative non-invasive treatment options. Tibial nerve stimulation (TNS) is an effective and safe treatment for idiopathic overactive bladder proven in randomized controlled trials (RCTs), but its transcutaneous application (TTNS) and value in neurological patients is still unclear.

Methods: bTUNED is a multicenter, randomized, sham-controlled, double-blind clinical trial performed in 7 centers worldwide (Basel, Bellinzona, Antwerp, Florence, Rome, São Paulo, Zürich). 240 patients (refractory NLUTD) will be included, randomized 1:1 into verum or sham TTNS and stratified by study center and cause of NLUTD. The intervention is performed twice a week for 30 minutes during a period of 6 weeks. The primary outcome is the success of TTNS defined as reduction in incontinence rates, reduction in micturition/catheterization frequency and reduction of post void residual. Secondary outcomes are changes in clinical symptom scores, bladder diaries, urodynamic and neurophysiological parameters. Safety of TTNS as the tertiary outcome.

Results: Over the course of 2 years the preparatory phase of bTUNED has been successfully completed. To harmonize all study procedures among study centres, standardized procedures and checklists have been developed and implemented. Pilot verum and sham TTNS to evaluate and improve patients' comfort and blinding techniques revealed positive results. The RCT has been approved by the respective ethics committees and recruitment has started 06/2020. However, the coronavirus pandemic delayed patient inclusion in all but one center in which a total of 12 patients have been enrolled.

Conclusions: bTUNED is the first adequately powered, randomized, sham-controlled, double-blind trial assessing TTNS for treating NLUTD. It will provide significant insights into efficacy and safety of TTNS in patients suffering from NLUTD and has the potential to completely revolutionize the management of NLUTD in daily clinical practice.

MP2.04: The Role of Interferential Current (IFC) Electrical Stimulation in Pediatric Urology: A Systematic Review of Randomized Controlled Trials

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Introduction: In recent years, Interferential current (IFC) electrical stimulation has been studied as a novel treatment for various lower urinary tract dysfunctions in children. As the findings of multiple studies may vary, we aimed to evaluate the current view on IFC in pediatric Urology problems based on the findings of randomized clinical trials (RCTs).

Methods: We performed a systematic search in the Embase, Medline, and SCOPUS databases in accordance with the latests Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline. Eligible studies comprised studies evaluating IFC for lower urinary tract problems in children. The studies' quality was assessed using the Cochrane risk of bias (RoB) tool 2.

Results: A total of 125 articles were initially obtained, among which 40 articles were duplicates. There were seven eligible RCTs with an overall low risk of bias. All subjects underwent 10 to 15 sessions of treatment. Two studies compared IFC to TENS and oral desmopressin for nocturnal enuresis. Five studies compared IFC with placebo for enuresis, underactive bladder, overactive bladder, non-neuropathic incontinece and bladder neck dysfunction. The outcomes measured consisted of alleviation of symptoms and urodynamic parameters. The trials reported that 61 to 90% of patients responded positively to the treatment. Both IFC and TENS generated improvements in the subjects. However, overall the IF group showed better immediate and short term improvement compared to the TENS group. Desmopressin was shown to be more effective than IFC based on the higher average response from the group, nevertheless the IFC group had less recurrence rate compared to desmopressin.

Conclusions: IFC is a promising therapy for bladder dysfunction and enuresis in children. More comparative RCTs are required in the future to quantitatively determine the superiority of IFC to other alternatives through a meta-analysis. The safety aspect of the treatment should also be studied further before it can used in a clinical setting as the standard and protocol for children is still unclear.

MP2.05: Two-staged sacral neuromodulation procedure for the treatment of non-obstructive urinary retention: a multi-center study assessing predictors of success

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Introduction: Non-obstructive urinary retention (NOUR) is a voiding disorder that affects millions of people worldwide. Most patients with NOUR use clean intermittent catheterization to ensure timely drainage of the bladder. Sacral neuromodulation (SNM) can be offered to restore voiding and abolish the need for catheterization. A tined lead test phase precedes the implantation of a neuromodulator. The aims of this study were to 1) determine the success rate of the tined lead test phase in patients with NOUR, 2) to determine predictive factors of a successful test phase, and 3) to determine long term efficacy and patient satisfaction.

Methods: The first part was a multi-center retrospective study performed at two centers in the Netherlands. Ethical committee approval was obtained. Patients with NOUR received a 4 week tined lead test phase. Success was defined as ≥50% reduction of clean intermittent catheterization frequency or post-void residual. We analyzed possible predictors of success with multivariable logistic regression. Secondly, all patients received a questionnaire to assess efficacy, perceived health (PGI-I) and treatment satisfaction.

Results: This study included 215 consecutive patients (82 men and 133 women) who underwent a tined lead test phase for the treatment of NOUR. The success rate in women was 62% (83/113) and in men 22% (18/82). In women, lower age and a history of psychiatric illness, including post-traumatic stress disorder (PTSD), significantly predicted first stage SNM success. In men, lower age and prior transurethral resection of the prostate and/or bladder neck incision were significant predictors of success (Table 1). Of the patients with a successful first stage, 75% (76/101) responded to the questionnaire at a median follow-up of 3 years. Eighty seven percent (66/76) of these patients continued to use their SNM system.

Table 1 Multivariable logistic regression model to predict first stage SNM success in men. BNI = bladder neck incision; TURP = transurethral resection of the prostate; UDS = urodynamic study.

	OR	95% CI	p value
Age (10 years)	0.42	0.25-0.72	0.00
Inability to void during UDS			
No	Ref		
Yes	3.16	0.85-11.7	0.09
Psychiatric illness			
No	ref		
Yes	4.50	0.75-26.8	0.10
Orthopedic surgery			
No	ref		
Yes	0.78	0.18-3.34	0.74
TURP and/or BNI			
No	ref		
Yes	7.64	1.43-40.8	0.02

Conclusions: This study identified lower age and psychiatric illness, including PTSD, in women, and lower age and transurethral resection of the prostate and/or bladder neck incision in men to be predictors of first stage SNM success.

MP2.06: Brain stem relay of lower urinary tract control: Group level correspondence of periaqueductal gray parcellations

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Introduction: The periaqueductal gray (PAG) is a brainstem area indicated to play an essential role in lower urinary tract (LUT) control. Post-mortem human and animal studies have indicated that the PAG is symmetrically organized in functionally and anatomically distinct columns which are involved in sympathetic or parasympathetic control of the LUT. In earlier work, we have shown that in vivo parcellation of the PAG into symmetrical clusters can be accomplished using 7T resting-state fMRI. The current study aims to find consistency across subjects and identify homologous clusters between subjects.

Methods: For this follow up analysis we evaluated data from 10 female participants. During a bladder filling protocol, we ran a resting-state fMRI scan while participants experienced a strong desire to void. Data were preprocessed using BrainVoyager and normalized to MNI space. PAG voxels were selected based on a mask covering the PAG of the MNI template. A voxel-by-voxel correlation matrix of the PAG was created and parcellated using the Louvain module detection algorithm. The similarity of resulting clusters between participants was then assessed by computing the Dice similarity coefficient for all cluster comparisons.

Next, we ran 1000 permutations in which we created randomized correlation matrices based on the original data and parcellated these matrices using the Louvain module detection algorithm. From these 1000 parcellation maps we computed the Dice similarity coefficient for 100.000 randomly selected cluster comparisons.

The Dice coefficients between cluster pairs were assessed statistically by ranking them to the Dice values observed in the permutations.

Results: We observed a significantly higher similarity between cluster pairs across subjects compared to permutations.

Conclusions: These results show that the PAG can be parcellated into distinct clusters which show a similar spatial distribution at group level. This analysis is a crucial step to determine the agreement between in vivo PAG parcellations and the functional and anatomical columnar organization of the PAG which is known from previous research. These advancements may enable us to identify the relationship between LUT symptoms, such as urgency, and activity patterns in the PAG in normal and pathological situations.

MP2.07: Low Pressure Voiding Induced by Pudendal Nerve Stimulation and Block Using Wire Electrodes in Spinal Intact Cats

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Introduction: We have shown that detrusor sphincter dyssynergia (DSD) in spinal cord injured (SCI) cats can be blocked with high frequency, bilateral pudendal nerve stimulation using cuff electrodes. Also, we showed that combining this block with 30 Hz unilateral stimulation resulted in low-pressure (≤50 cmH2O) voiding in SCI cats. In this experiment, we sought to determine whether wire lead electrodes could be used to block and stimulate the pudendal nerve in spinal intact cats to achieve low-pressure voiding

Methods: Under α chloralose anesthesia, bilateral pudendal nerves were dissected for placement of wire hook electrodes. Two experiments were performed. In the first experiment (n=4 cats), we tested the ability to block the pudendal nerve with a wire hook electrode. Three monopolar wire hook electrodes were placed alongside pudendal nerve: one electrode delivering 1 kHz stimulation, another electrode delivering 30 Hz stimulus pulses, and a third electrode placed closet to the EUS to test how the blocking electrode suppresses. A urethral catheter was inserted to both perfuse and measure pressure. In the second experiment (n=5 cats), we tested to see if combined nerve block and stimulation resulted in low pressure voiding. A double-lumen catheter was inserted into the bladder dome to allow infusion and recording of intravesical pressure. With the bladder partially full, 1kHz blocking stimulation was applied bilaterally, and 30 Hz stimulation was applied to induce bladder contraction

Results: In the first experiment, The 1 kHz stimulation blocked pudendal nerve conduction for ≥2 mins, and this blocking stimulation resulted in nerve conduction block and not EUS fatigue. Also, we found that block duration increased with increasing amplitude and duration of the stimulation. In the second experiment, 30 Hz stimulation alone induced high-pressure voiding, but when the 30 Hz stimulation followed the bilateral 1 kHz block, the 30 Hz stimulation resulted in low-pressure voiding. Also, the combined block and stimulation significantly ($p=0.0203$) increased voiding efficiency by 80%.

Conclusions: Our study demonstrated that the pudendal nerve can be blocked by a wire electrode. Combining the bilateral block and unilateral stimulation in spinal intact cats resulted in low-pressure voiding that was highly efficient.

MP2.08: Lumbosacral spinal cord changes after acute spinal cord injury: preliminary results of an MRI study

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Introduction: Damage to the spinal cord (SC) often leads to loss of motor and sensory functions as well as impairment of bladder, sexual and bowel function. Besides the focal damage at the injury site, a cascade of secondary pathological processes has been shown to result in tissue loss above and below the level of injury. Atrophy of the SC can be quantified by measuring cross-sectional area (CSA) of the SC, grey matter (GM) and white matter (WM) using magnetic resonance imaging (MRI). The lumbosacral cord contains important neurons innervating the lower urinary tract. Assessments of the lumbosacral enlargement (LSE) and the conus medullaris (CM) opens up the possibility to examine the neural basis of neurogenic lower urinary tract dysfunctions. The aim of this study was to investigate volumetric differences in the LSE and CM between acute spinal cord injury (SCI) patients (1-month after injury) and healthy controls.

Methods: Siemens FLASH sequence (3T Siemens Prisma) was used to acquire 20 axial slices (5 mm thickness) in the lumbosacral cord of 10 SCI patients and 7 healthy controls. SC and GM were segmented manually, providing values of SC and GM CSA. White matter was obtained by subtracting GM from SC SCA. The slice with the highest SC CSA was defined as the “LSE slice”. Tissue-specific total volume (TV) measures were calculated at the LSE for a 15 mm long segment of 3 adjacent slices around the "LSE slice". TV measures in the CM were calculated from a variable number of slices (from the "LSE slice" down to the tip of CM). Volumetric metrics were compared between SCI patients and healthy controls using a two-sample t-test (unpaired, one tailed, $p<0.05$).

Results: Preliminary results show reduced grey matter volume (-16.9%, $p=0.030$) in the CM in SCI patients.

Conclusions: This is the first MRI investigation indicating remote tissue-specific volumetric changes in the CM in SCI patients. Further work is needed to establish whether such changes are related to clinical scores (e.g. impaired bladder function). Furthermore, a larger study is needed to confirm and further explore volumetric changes in the lumbosacral cord after acute SCI.

MP2.09: Efficacy and safety of sacral neuromodulation for neurogenic lower urinary tract dysfunction: a randomised, sham-controlled, double-blind, multicentre clinical trial

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Introduction: Although neurogenic lower urinary tract dysfunction (NLUTD) is a highly prevalent and disabling condition, standard treatments remain often unsatisfactory. Sacral neuromodulation (SNM) is a well-established therapy for non-NLUTD, but there is a lack of randomised controlled trials in neurological patients. We therefore assessed efficacy and safety of SNM for NLUTD in a randomised, sham-controlled, double-blind, multicentre clinical trial.

Methods: Patients with refractory NLUTD and intended SNM were eligible for this sham-controlled, double-blind multicentre randomised controlled trial. After minimally invasive bilateral tined lead placement into the sacral foramina S3 or S4, patients underwent SNM testing. If successful (≥50% improvement in key bladder diary variables), the neurostimulator was implanted for permanent SNM. For two months, the effectiveness of SNM was optimised using sub-sensory stimulation with individually adjusted parameters. Participants were then randomly assigned in a 1:1 ratio to either SNM verum or sham stimulation and re-evaluated after a two-month double-blind intervention phase. The primary outcome was success of SNM verum versus sham stimulation compared to baseline. The trial protocol was approved by the responsible scientific ethics committees.

Results: Of 124 patients undergoing SNM testing, 65 (52%) tested positive and 60 (median age, 49.5 years; 17 men) were randomised. After two-month intervention, SNM remained successful in 22 (76%) of 29 patients receiving verum and in 13 (42%) of 31 receiving sham stimulation (odds ratio, 4.35; 95% confidence interval, 1.43-13.21; P=0.009). During the entire study period, there were 10 adverse events (6 resulted in dropout). No dropout occurred during the intervention phase.

Conclusions: SNM is effective and safe for treating refractory NLUTD in well-selected neurological patients. These findings support the implementation of SNM into the care pathway of NLUTD.

MP2.10: Impact of stimulation parameters on sensory evoked potentials of the urethra

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Introduction: Lower urinary tract (LUT) symptoms are prevalent and frequently related to alterations of the LUT sensory pathways. Particularly the role of urethral afferents is not well understood and not covered by clinical standard investigations such as urodynamics. Previous studies have shown that LUT sensory evoked potential (LUTSEP) assessment is a feasible method that could provide objective information on LUT functional integrity. Following our suggestions for bladder SEP recordings, we here aim to optimize the settings for an efficient evaluation of urethral afferents.

Methods: Fifty healthy subjects (20 females, 18-34years) underwent two sessions of cortical SEP (Cz-Fz) assessments using repetitive (0.5Hz/1.1Hz/1.6Hz, pulse width=1ms; 5 runs of 100 stimuli) electrical square wave stimulation at the proximal, membranous (only males), or distal urethra. Before each measurement, the bladder was filled with 60mL of contrast medium and stimulation intensity was adapted to a strong, non-painful level. After 0.5-70Hz band-pass plus 50Hz notch filtering and artifact rejection, data were segmented and averaged. The stimulation frequencies and runs were compared based on the whole curve shape and the manually set markers. Linear mixed models were performed.

Results: Over all, stable SEPs with P1, N1, P2 components were recorded with a high responder rate (RR, 100%, exception: membranous urethra 1.6Hz: 90%). A better signal-to-noise ratio (SNR) and higher peak-to-peak amplitudes were demonstrated for lower compared to higher stimulation frequencies (P2N1 amplitude: 0.5Hz vs. 1.6Hz: $p<0.05$ for all three localizations (estimates between -2.5µV and -3.9µV); 0.5Hz vs. 1.1Hz: $p<0.05$ for proximal urethra (estimate: -2.6µV) and distal urethra (estimate: -2.9µV)). Latencies did not differ betweenn frequencies. Amplitudes, SNR and RR decreased with continuing stimulation.

Conclusions: Urethral electrical stimulations induce similar scalp potentials as known from literature and from bladder SEP assessments. Similar to bladder SEPs, the best SNR, RR and size of amplitudes were observed when using 0.5Hz. The gradual decrease in amplitude, SNR and RR over time shows that the total number of stimuli can be optimized to achieve stable urethral SEPs and at the same time reducing acquisition time. This is important for LUTSEP implementation into daily clinical practice, however, further studies including patients are needed.

MP2.11: Sacral neuromodulation device biofilms possess unique microbial composition in the context of pain and are reconstitutable *in vitro*

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Introduction: Sacral neuromodulation (SNM) is an effective therapy for overactive bladder, urinary retention, and fecal incontinence. To understand the transition from the colonized (wherein bacteria are present but not pathological) asymptomatic to symptomatic (painful) states, we sought to determine microbial biofilm composition and characteristics on devices, and association with clinical factors. We hypothesized SNM devices would consistently harbor bacteria in the form of biofilms, and that biofilm formation could be reconstituted in vitro.

Methods: Urological patients scheduled to undergo removal or revision of SNM devices for any indication were consented per IRB-approved protocol. Devices were swabbed intraoperatively upon exposure during explantation, with safeguards to avoid contamination. Swab samples and controls were subjected to next-generation sequencing. Association between microbial diversity and pathogen abundance, and clinical variables was then analyzed using t-tests and ANOVA. Clinically relevant isolates were identified and cultured in vitro to assess reconstitution of biofilm formation in a continuous-flow stir tank chemoreactor with coupons of different material types, designed to mimic subcutaneous tissue with an indwelling device.

Results: 33 devices were included in the study. 90% of devices harbored statistically detectable microbiota by next-generation sequencing. Escherichia/Shigella was the most commonly detected pathogenic taxon. There was lower overall pathogen ($p=0.02$) and commensal microbial ($p=0.04$) abundance in devices explanted for pain ($n=4$). Clostridium (log2 fold change +4.5, $p<0.001$), Klebsiella (+4.0, $p<0.001$), and Bradyrhizobium (+3.9, $p<0.001$) were more abundant in device biofilms explanted for pain, whereas Sphingomonas (-9.4, $p<0.001$), Methylbacterium (-9.0, $p<0.001$), and Lactococcus (-4.6, $p<0.001$) were less abundant. Isolate strains consistently reconstituted biofilm formation in vitro, and there was differential biofilm formation both by strain (Staphylococcus aureus greatest) and material type (titanium least).

Conclusions: 90% of explanted devices harbored microbiota and possessed a unique microbial profile in the context of pain. Microbes isolated from SNM devices consistently reconstituted biofilm in vitro and there was differential biofilm formation based on material type. The results open new avenues for investigation of biochemical changes occurring during the transition from colonized asymptomatic to symptomatic states, and identify preventive strategies. Further, our approach may be used to test novel material types and coatings for biofilm resistance.