2020 ASIPP Abstract and Poster Winners

Top Physicians

First Place
Implementing a Machine Learning Algorithm to use Artificial Intelligence to Accurately Diagnosis Spinal Pain Conditions for Enhance Decision Making: A 500 Patient Pilot Study
– Amol Soin, MD

Second Place
Modulation of the Neuron, Astrocyte and Microglia Inflammasome using Differential Target Multiplexed Spinal Cord Stimulation in an Animal Model of Neuropathic Pain
– David L. Cedeno PhD

Third Place
IA CNTX-4975 for OA Pain: Comparison of 5 Treatment Regimens
– Meg Corliss, PhD

Top Fellow

Prescribing Virtual Reality for Chronic Pain
– Rajat Lamington, MD

Top Resident

Comparison of Spinal Cord Stimulation Waveforms for Treating Chronic Low Back Pain: Systematic Review and Meta-Analysis
– Ajex Yang

Top Medical Student

Topical Sevoflurane: A Novel Treatment for Chronic Pain Caused by Venous Stasis Ulcers
– George Jeha, BS
Implementing a Machine Learning Algorithm to Accurately Diagnose Spinal Pain Conditions

Megan Hirschbeck, BS, Michael Verdon, DO, Amol Soin, MD

Introduction
Treating spinal pain is rather expensive, costing the US healthcare system around $90 billion annually. Oftentimes, patients who suffer from spinal pain undergo expensive treatments only to find themselves still suffering from pain. Additionally, spinal pain effects American productivity as it is the most common cause for missed workdays.

Methods
There are many different ways to treat the same condition such as chiropractic, osteopathic, physical therapy, injections, medications and surgical options. We decided to quantify each of those conditions and input data into a machine learning algorithm to track outcomes and eventually attempt to build an algorithm to help physicians determine what type of therapy would be most effective.

We took 250 patients who were separated into the following diagnosis: lumbar radiculopathy, lumbar spondylosis without myelopathy, post laminectomy syndrome, and sacroilitis. We then manually entered their pain scores, functional status scores, pain location, pain duration, pain diaries and several other data points. Approximately 80 unique data points were entered into the system. We also tracked the various interventions the patient had such as physical therapy, injections, or surgery for example.

Results
The end result is a data set that is capable for machine learning to allow a computer algorithm to look at new and unique data sets and then provide the treating physician with guidance to which potential therapeutic option would give the most likelihood of success given the data points presented to the machine. This may result in enhanced decision making by the physician to choose a therapy that may be more beneficial to the patient and eliminate options that may be more costly and ineffective.

Discussion
• Determine which of the 80 data points are the most relevant to establishing an accurate diagnosis and refine those data points to include only those that are necessary
  ➢ This will be important to aid physician history and physical to ensure that appropriate questions are asked, and examinations performed
• In the future we can factor in costs of therapy (surgical or medical intervention) into the algorithm for the computer to weigh the cost-benefit ratio
• The study was limited by patient sample size.
  ➢ Going forward the computer algorithm will be optimized by adding more patients to the study and allowing the computer to synthesize diagnoses based on more patient information
• The study was also limited by the need to exclude data points that went unanswered by patients
  ➢ With patient education we can illicit more responses to data points that are relevant to forming an accurate diagnosis

Acknowledgments
Thank you to Dr. Verdon, Dr. Soin, and The Ohio Pain Clinic for allowing me to be a part of this project.
Modulation of the Neuron, Astrocyte and Microglia Inflammasome using Differential Target Multiplexed Spinal Cord Stimulation in an Animal Model of Neuropathic Pain

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INTRODUCTION
The activation of microglia and astrocytes is crucial for the development and persistence of chronic pain. This promotes neuroinflammation, disruption of the immune system and unbalanced neuron-glia interactions. Recently, our group showed that spinal cord stimulation (SCS) modulates immune and inflammatory processes effectively by using a differential target multiplexed programming (DTMP) approach in which multiple electrical signals are used to modulate neuron-glia interactions by differentially targeting neurons and glial cells.

MATERIALS AND METHODS
The IACUC at IWAU approved the study. Rats (n=10-13) were randomly assigned to 4 groups, in which animals were implanted with an SCS lead and underwent the spared nerve injury (SNI) model of neuropathic pain. Animals in 3 of these groups were treated with SCS using either DTMP, low rate (LR) or high rate (HR). Animals in the other group were untreated (No-SCS). A healthy group of naive animals. SCS-treated animals were stimulated continuously for 48h. All groups were assessed in parallel (Fig 1).

The polarity dorsal quadrant of the spinal cord adjacent to the lead was dissected RNA-sequenced to quantify gene expression. Inflammasomes for neurons, astrocytes, and microglia were based on cell-sorted preparations available in the literature. Gene expression for naive animals and SCS-treated animals relative to No-SCS were obtained for the three inflammasomes.

RESULTS
Correlations between DTMP and naive were strongly positive and significant for all inflammasomes. HR produced moderate positive correlations with naive for glia inflammasomes and a weakly positive one for the neuron inflammasome. In contrast, LR correlated weakly positive and significantly with naive for the neuron inflammasome only. The factor analysis required three factors (fit of 0.98) to explain the inflammasome expression levels of naive, DTMP, HR and LR. DTMP-SCS and No-SCS were highly loaded onto each of the factors: DTMP in factor 1, LR in factor 2, and HR in factor 3. Expression of naive also loaded heavily onto factor 1.

CONCLUSION
Separate statistical analyses indicate that DTMP has the strongest effect on the expression of genes involved in inflammatory processes of neurons, microglia and astrocytes. Pearson correlations between DTMP and naive are strong and positive for all inflammasomes. These are congruent with the alignment of gene expression of DTMP and naive onto the same factor in the factor analysis. In contrast, HR correlates moderately with naive for glia inflammasomes, while LR only correlated weakly with the neuron inflammasome. This work provides evidence that DTMP modulates the inflammasome of neurons and glial cells in the direction of naive animals for an animal model of neuropathic pain, thus contributing to the reduction of pain-like behavior effectively.

ACKNOWLEDGEMENT: The authors would like to thank funding from Millennium Pain Center and Stimgenics.

Figure 1. Experimental design and timeline.

Figure 2. Heat maps of cell-specific inflammasomes. Genes with expression change of >10% due to pain model relative to naive are not shown.

Table 2. Factor analysis load coefficients for the three inflammasomes combined

<table>
<thead>
<tr>
<th></th>
<th>RC1</th>
<th>RC2</th>
<th>RC3</th>
</tr>
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<tbody>
<tr>
<td>Naive</td>
<td>0.93</td>
<td>-0.08</td>
<td>0.14</td>
</tr>
<tr>
<td>DTMP</td>
<td>0.87</td>
<td>0.21</td>
<td>0.26</td>
</tr>
<tr>
<td>HR</td>
<td>0.24</td>
<td>0.12</td>
<td>0.96</td>
</tr>
<tr>
<td>LR</td>
<td>0.05</td>
<td>0.99</td>
<td>0.12</td>
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* denotes p < 0.01. R ≥ 0.6 represents a strong correlation.
Intra-articular CNTX-4975 (Capsaicin) for Osteoarthritis Pain: Comparison of 5 Treatment Regimens

Randall M. Stevens, MD; Peter G. Hansen, DVM, PhD; Paul Tiseo, PhD; Kimberly Gueule, RN, BSN; James N. Campbell, MD; James Connolly, MA; Stephanie Ragain, BS; Mag Carlin, PhD; Valérie H. Smith, MD; Ignacio Rodriguez, MD

INTRODUCTION

- CNTX-4975 is a highly purified, synthetic capsaicin monopalmitate ethanolate for the management of chronic pain associated with osteoarthritis (OA).
- A phase 3a, double-blind, randomized, placebo-controlled (FINPAIN: NCT02364859) single-blind, open-label (OFINPAIN: NCT02847857) study was performed in 358 subjects with moderate to severe knee OA pain. CNTX-4975 subjects received 1 mg intra-articular injections.
- Clinical benefit was observed from day 3 through week 6 post-injection.
- Secondary outcomes were consistently improved in all CNTX-4975 groups vs placebo (ITT population). Significant reductions in pain with walking were observed as early as day 3 post-injection.
- These findings will provide clinicians with more flexibility regarding the optimal choice of treatment.

METHODS

Subjects

- Key inclusion criteria:
  - Kellgren-Lawrence grade 1–4.
  - Age ≥50 years.
  - BMI ≥25 kg/m².

Exclusion criteria:

- Current or previous knee surgery (within 5 years).
- Current or previous injection therapy for knee OA.
- Current or previous participation in a clinical trial.
- Current or previous participation in a clinical trial.

Study Design

- Single-blinded approach.
- Subjects received unilateral or bilateral injections of CNTX-4975 1 mg.
- Subjects were randomized to 1 of 5 treatment groups for knee pain.

Endpoints

- Primary endpoint: Physician satisfaction.
- Secondary endpoints: Procedural pain, knee pain with walking, need for additional pain management.

RESULTS

- Many significant reductions in pain with walking were observed as early as day 3 post-injection.
- These findings will provide clinicians with more flexibility regarding the optimal choice of treatment.

CONCLUSIONS

- CNTX-4975 is an effective and safe treatment for osteoarthritis pain.
- Significant reductions in pain with walking were observed as early as day 3 post-injection.
- These findings will provide clinicians with more flexibility regarding the optimal choice of treatment.

REFERENCES

- Guidelines from the American Academy of Orthopaedic Surgeons.
- American College of Rheumatology.
- American Academy of Orthopaedic Surgeons.

ACKNOWLEDGMENTS

- The authors thank the patients and staff at the participating centers.
- The authors thank the patients and staff at the participating centers.

SOURCES

- American Academy of Orthopaedic Surgeons.
- American College of Rheumatology.
Prescribing Virtual Reality for Chronic Pain
Rajat Lamington, M.D., Urshil Patel, M.D.

Background
Virtual Reality (VR) has been shown to be effective in decreasing pain for procedural or acute pain. However, there’s little known about its benefits in chronic pain. With the rising opioid crisis and concerns around their safety, noninvasive treatment options for chronic pain are further becoming scarce. Hence, the use of VR as a treatment option is gaining popularity.

Objective
To investigate different uses of VR in chronic pain patients that currently exist across outpatient practices.

Methods
We performed searches using two databases: Cochrane and MEDLINE (via PubMed). The review looked at articles from 2000 to 2019, focusing on studies concerning ways in which VR can augment pain relief. Articles needed to: be written in English, include adult subjects living with chronic pain, involve any form of VR therapy, and assess pain by quantitative or qualitative outcome measures.

Results
VR can diminish a patient’s subjective pain experience. VR can provide a non-invasive way to improve range of motion. The use of VR with behavioral interventions can maximize results. VR can directly facilitate analgesia in chronic pain patients.

Discussion
The results demonstrate many novel mechanisms of VR treatment for chronic pain that show promising results. Large randomized controlled studies are needed to confirm the safety and efficacy of VR for chronic pain.

The Future of Chronic Pain Management
Large-scale studies need to confirm the safety and efficacy of VR for chronic pain.

Efficacy over repeated sessions speeds up pain rehabilitation and increases the range of motion.

Numerous scientific questions remain and the cost of the device and software is still too high.

Ultimately, an important advancement would be the portability of VR for widespread use in private practice and eventually in homes where patients can use it for chronic pain, physical therapy, long-term rehabilitation and other associated symptoms.
Case of Posterior Spinal Cord Injury following Bilateral, Multilevel Cervical Radiofrequency Ablation

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Background on RFA

- Radiofrequency ablation applies electric current to create lesions at pain-inducing nerves.
- Treats chronic pain caused by cervical/lumbar, less commonly thoracic facet arthropathy.
- Data on complications are limited to case reports outlining cutaneous numbness, temporary dizziness, ataxia, and dysesthesias [1].
- More severe neurological complications include one case of Dropped Head Syndrome requiring surgical fixation [2].
- Review of the literature did not reveal cases of RFA procedures leading to Spinal Cord Injury

Procedural Details

A 61 year old male with chronic neck pain refractory to conservative treatment responded to diagnostic C5-6 and C6-7 intra-articular facet injections. Treatment with RFA was planned.

Patient underwent RFA to bilateral C5, C6, and C7 medial branch nerves. He assumed a lateral decubitus position, and was sedated with midazolam and fentanyl. Injection sites were identified with fluoroscopy (photos were not saved). A radiofrequency cannula was advanced to the middle of lateral masses of the C5, C6 and C7 vertebrae. Sensory and motor stimulation screening was negative. A methylprednisolone and lidocaine mixture was injected at each site. Bilaterally, RFA heat lesions were made to the C5, C6, and C7 medial branches. The cannula was turned 30 degrees away from the foramen and the heat lesion was repeated. The patient was asymptomatic in recovery.

Post Procedure Course

- The patient woke the next day with numbness of his body below the neck.
- Initial cervical MRI next day was negative for abnormalities.
- Neck to waist area improved; numbness below the waistline persisted.
- Repeat cervical MRI later revealed focal area of enhancement at the dorsal aspect of the spinal cord at the C5-6 disc space level (absent on pre-procedural MRI), suggesting posterior spinal cord injury

Discussion & Key Considerations

No cases of SCI associated with cervical or lumbar facet RFA are reported in the literature. Could this case represent a novel instance of RFA leading to a spinal cord injury? Important considerations exist:

- Posterior SCI caused by compromise to the spinal cord or to its arterial supply.
- Lack of direct proximity between the catheter and the spinal cord: RFA is performed via a posterior approach with catheter aimed at the dorsal spinal ramus located near the mid-articular pillar, lateral to the spinal canal [3].
- Two posterior spinal arteries supply the posterior spinal cord. Each receives segmental supply from radicular arteries traversing the anterior foramen (variants exist whose radicular arteries traverse the posterior foramen) [4].
- Injection of particulate steroids in similar procedures has been associated with paraplegia.
- Positioning and sedation pose risks: IV sedation can interfere with motor/sensory testing, compromising patient safety [5]. Prolonged positioning combined with sedation could cause compression of the spinal cord or to arteries supplying the posterior cord.

Methods of procedural standardization can improve safety profiles associated with RFA procedures: using non-particulate steroids, or avoiding IV sedation.

References

ECAP-Controlled Closed-Loop SCS: Double-Blind, Randomized Trial for the Treatment of Chronic Pain: 12-month Outcomes

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Introduction

Spinal cord stimulation (SCS) intends to deliver therapy to the spinal cord via electrical energy. The challenge with SCS is that the electrode-to-spinal cord distance is everchanging with movement, including physiological, involuntary movement such as the cardiorespiratory cycle (i.e., heartbeat, respiration) and voluntary movement such as posture changes (figure 1). This is turn results in everchanging levels of SCS therapy reaching the intended target.

Results

The primary endpoint demonstrated statistical superiority of closed-loop (figure 2).

Objective Neurophysiological Measures

SC activation levels (ECAPs) during actual usage outside the clinic were recorded (2×4 CL and 2×8 OL) and compared to the programmed target level identified in clinic (2×4 CL and 2×8 OL) (figure 3).

Discussion

In this ongoing study, ECAP-controlled closed-loop SCS provided statistically superior pain relief. Closed-loop had >83% of patients reaching the ≥50% responder threshold and >56% of patients reaching the ≥80% high responder threshold in overall back and leg pain. Of importance is the indirect, parallel improvements in other validated patient reported outcomes (sleep quality, physical/emotional functioning, and HR-QoL) and opioid reduction with closed-loop improving on all measures to a greater degree than open-loop.

This randomized, double-blind study design was developed to preserve objectivity and minimize bias. The randomization produced well-matched treatment groups. Additionally, none of the patients or investigators were unblinded to the treatment assignment. Aside from the difference in stimulation modes, study design and execution provided the same care for both treatment groups. The differences in outcomes between closed-loop and open-loop SCS cannot be attributed to procedure technique, programming parameters, frequency of programming visits, programming duration, device usage, patient baseline characteristics, or underlying neurophysiology (i.e., ability to recruit and activate the same nerve fibre types), as these were demonstrated to be equivalent in both treatment groups.

Materials and Methods

The 12-month results of a double-blind randomized (1:1) controlled trial conducted under an Investigational Device Exemption to compare the safety and efficacy of ECAP-controlled closed-loop (CL) stimulation (investigational group) and open-loop (fixed output) stimulation (OL, control group) to treat chronic back and leg pain (NC 1029341219) are presented (1).

The device, procedure, and programming was equivalent in both groups. The only difference between groups was enabling the closed-loop feature of the device which adjusts the stimulation output automatically to maintain spinal cord activation at the target level. ECAPs were utilized in both groups to confirm the intended target was being activated (SC activation achieved) in clinic. ECAPs were then measured and recorded outside the clinic in both arms to capture actual device usage.

The primary endpoint was ≥50% reduction in overall back and leg pain with no increase in pain medications. Opioid usage and other patient-reported outcomes including emotional/physical functioning, sleep quality, and quality of life were collected. Objective neurophysiological data, including SC activation and the percent time SC activation was in the therapeutic range, were recorded on the device.

Safety

There were no differences in the safety profiles between treatment groups, and the type, nature, and severity of adverse events were similar to other SCS studies. Three serious adverse events in three (2%) patients were study related, but not stimulation related (wound infection, epidural abscess, and lead breakage or fracture). There have been no unanticipated adverse device effects (UADEs).

References

Multiplex analysis of 230 medications and 30 illicit compounds in dried blood spots and urine

Tagwerker C., Baig I., Brunson E., Dutra-Smith D., Corias M.J., Ranulu S., Smith D.

Alcala Testing and Analysis Services (Alcala Labs)

INTRODUCTION

A novel method is described for qualitative and quantitative multiplex analysis of 230 parent drugs, 30 illicit drugs and 43 confirmatory metabolites by HPLC-MS/MS. This method is applicable to dried blood spot (DBS) specimens collected by volumetric absorptive microsamplers (VAMS™) and confirmable in urine specimens - Figure 1:

Drugs of abuse and medication reconciliation testing can benefit from analysis methods capable of detecting a broader range of drug classes and analytes. Mass spectrometry analysis of a wide variety of commonly prescribed medications and over-the-counter drugs per sample also allows for application of a drug-drug-interaction (DDI) algorithm to detect adverse drug reactions (ADR).

RESULTS

A patient cohort (n = 67) providing simultaneous urine specimens and dried blood spots resulted in 100% positive predictive values (PPV) of medications or illicits confirmed by detection of a parent drug and/or its metabolite during routine medication adherence analysis. An additional 5508 dried blood spot specimens screened (n = 5575) showed all positive results matching the provided medication list (consistent positive). A drug-drug interaction (DDI) algorithm applied to all positive results, revealed 17% with serious and 56% with moderate drug-drug interaction warnings, with the added advantage of detecting drug-drug interactions.

DISCUSSION

Six Sigma metrics for DBS (dried blood spot):

Six Sigma metrics for Urine:

Mitra® Microsampling offers the unique opportunity to collect consistent volumes of WB independent (+/-15%) of the hematocrit. Previous studies suggest therapeutic drug monitoring (TDM) is feasible using Mitra® microsampling (1-4), although some controversy exists in the literature as to measured drug levels based on different blood sampling sites.

Results in this study have shown some patient DBS concentrations of commonly monitored drugs in plasma (venipuncture) fall within known TDM ranges. Appropriate bridging studies of all 230 medication levels described in this study found in capillary blood versus venipuncture specimens have not yet been confirmed.

This study is the first to our knowledge that directly compares urine as the gold standard in the field of toxicology to DBS collected by Mitra® Microsampling beyond 60 compounds, showing a reliable alternative to urine specimens prone to adulteration. Overall, DBS analysis by Mitra® Microsampling offers low rejection rates (<5%), improves patient comfort, requires no cold chain shipping and increases operational efficiencies.

REFERENCES


