Top Posters

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 health care 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

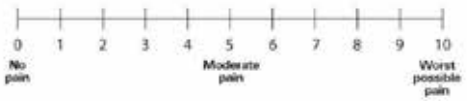

Figure 4: Visual Acuity Score

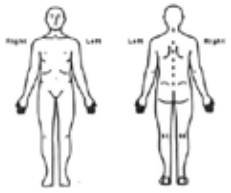

Figure 1: Patient Pain Dagrami

Pain Radiation Locations Evaluated

- L/R Buttock
- L/R Hip
- L/R Thigh
- L/R Shin
- L/R Calf
- L/R Foot

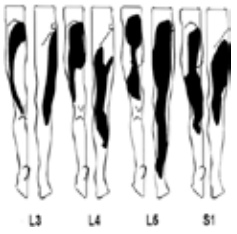

Figure 2: Pain referral from lumbar interspinal ligaments (Lumbar Facet Pain)

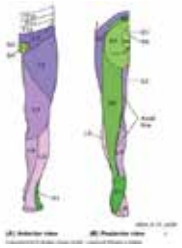

Figure 3: Dermatome Map
Evaluating L3-L5, S1

Other data points evaluated but not pictured

- Muscle Quality
- Gluteus Minimus Trigger Point
- Gluteus Medius Trigger Point
- Multifidi Trigger Point
- Quadratus Lumborum Trigger Point
- Piriformis Trigger Point
- Iliolumbar Ligament
- SI Ligament Pain Referral Pattern
- Hip Pain
- SI Pain
- Radiation of Symptoms
- Modifying Factors
- Time of Day
- Associated Symptoms

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

ASIPP® 2020 ANNUAL MEETING
SEPTEMBER 4-6, 2020 | VIRTUAL MEETING

David L Cedeño PhD[1,2]; William J Smith BS[1,3]; Dana M Tilley PhD[1]; Courtney A. Kelley MS[1,2]; Alejandro Vallejo, BS[4]; Samuel M Thomas, BS[5]; Ricardo Vallejo MD, PhD[1,2,6]

[1] Lumbrera LLC, Bloomington, IL, USA; [2] Department of Psychology, Illinois Wesleyan University, Bloomington, IL USA; [3]Geisel School of Medicine, Dartmouth College, Hanover, NH, USA; [4] Chicago College of Osteopathic Medicine, Midwestern University, Downers Grove, IL, USA; [5] Des Moines College of Osteopathic Medicine, Des Moines, IA, USA; 6 National Spine and Pain Centers, Bloomington, IL, USA.

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-glial 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-glial interactions by differentially targeting neurons and glial cells. This study provides evidence that cell-specific inflammasomes of a rodent animal of neuropathic pain are effectively modulated by DTMP in the direction of their profile in naïve animals.

MATERIALS AND METHODS

The IACUC at IWU 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 consisted of naïve animals. SCS-treated animals were stimulated continuously for 48h. All groups were assessed in parallel (Fig 1). The ipsilateral 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 naïve animals and SCS-treated animals relative to No-SCS were obtained for these inflammasomes. Pearson correlations and factor analysis were used to quantify the effects of the SCS treatments.

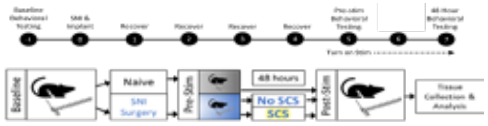

Figure 1. Experimental design and timeline.

RESULTS

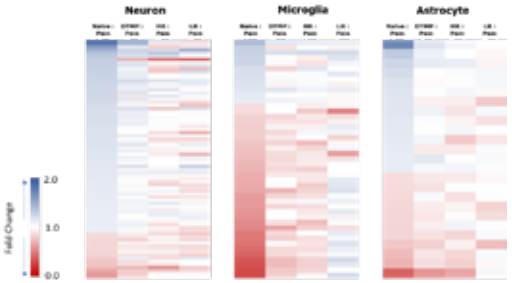

Figure 2. Heat maps of cell-specific inflammasomes. Genes with expression change of <10% due to pain model relative to naïve are not shown.

Table 1. Correlation coefficients (R) for each SCS:Pain vs Naïve:Pain and percentage of genes modulated toward naïve (%) by each SCS in each inflammasome.

	Neuron (n=252)		Microglia (n=132)		Astrocyte (n=90)	
	R	%	R (p)	%	R (p)	%
DTMP	0.77*	78	0.58*	79	0.67*	73
HR	0.28*	53	0.53*	66	0.46*	60
LR	0.18*	55	-0.12	50	0.06	47

* denotes $p < 0.01$. $R \geq 0.6$ represents a strong correlation

RESULTS (continued..)

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

	RC1	RC2	RC3
Naïve	0.93	-0.08	0.14
DTMP	0.87	0.21	0.26
HR	0.24	0.12	0.96
LR	0.05	0.99	0.12

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

CONCLUSION

Separate statistical analyses indicate that DTMP has the stronger effect on the expression of genes involved in inflammatory processes of neurons, microglia and astrocytes. Pearson correlations between DTMP and naïve are strong and positive for all inflammasomes. These are congruent with the alignment of gene expression of DTMP and naïve onto the same factor in the factor analysis. In contrast, HR correlates moderately with naïve 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 naïve 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.

Intra-articular CNTX-4975 (Capsaicin) for Osteoarthritis Pain: Comparison of 5 Treatment Regimens

Randall M. Stevens, MD[1]; Peter D. Hanson, DVM, PhD[1]; Paul Tiseo, PhD[1]; Kimberly Guedes, RN, BSN[1]; James N. Campbell, MD[1]; James Connolly, BA, MA[1]; Stephanie Ruggiero, BS[1]; Meg Corliss, PhD[1]; Valerie H. Smith, MStat[2]; Ignacio Rodriguez, MD[3]

[1]Centrexion Therapeutics Corp, Boston, MA; [2]Premier Research, Durham, NC; [3]Miramar Pain Medicine, Hialeah, FL

INTRODUCTION

- CNTX-4975 is a highly purified, synthetic capsaicin, non-opioid analgesic in phase 3 clinical trials for the management of moderate to severe knee pain associated with osteoarthritis (OA)
  - In a phase 2b, double-blind, randomized, placebo-controlled study (TRIUMPH; NCT02559439), a single intra-articular (IA) injection of 1 mg CNTX-4975 provided a significant ($P<0.0001$) and clinically meaningful reduction (≥50%) in chronic, moderate to severe OA knee pain, with the effect persisting for up to 24 weeks[1]
- Intra-articular injection of CNTX-4975 produces short-term post-injection pain
  - A phase 1b, open-label, clinical study (NCT03472677) compared the effectiveness of an ice pack placed on top of the knee and several circumferential cooling methods and injection schedules for managing procedural pain after CNTX-4975 1 mg IA injection in subjects with moderate to severe knee OA pain[2-4]
  - Circumferential cooling methods (a circulating ice water wrap and an ice gel pack) were more effective in reducing IA knee temperature and procedural pain than a standard ice bag[2-4]
- We report results from the phase 3 VICTORY-3 study (NCT03691996) that further evaluated cooling and administration procedures for IA injection of 1 mg CNTX-4975 in subjects with chronic, moderate to severe knee OA pain

METHODS

Subjects

- Key inclusion criteria
  - Healthy adults (aged 40–95 years) with a body mass index (BMI) ≤45 kg/m^2
  - Confirmed knee OA according to
    - American College of Rheumatology diagnostic criteria
    - Kellgren-Lawrence (K-L) grade 1–4 by radiography
  - Moderate to severe knee OA pain (Numeric Pain Rating Scale [NPRS] score 5–9) for ≥6 months before study entry
  - Previously failed ≥2 therapies
- Key exclusion criteria
  - Corticosteroid injection in the index or nonindex knee ≤90 days before screening
  - Joint replacement surgery at any time, open surgery ≤24 months before screening, or arthroscopic surgery ≤6 months before screening in the index knee
- The study protocol was approved by an independent institutional review board and subjects provided written informed consent before any study-related procedures were performed

Study Design

- 8-week, open-label study designed to compare the comfort and ease of use of various cooling and study drug administration regimens, and to evaluate the safety of a single CNTX-4975 1 mg IA injection in subjects with chronic, moderate to severe, painful knee OA
- Subjects were assigned to received unilateral or bilateral CNTX-4975 IA injections based on the presence of unilateral vs bilateral OA moderate to severe pain and joint replacement status (**Figure 1**)
- Subjects were then administered 1 of 5 treatment regimens based on randomization at the study-site level
- Data reported here are for the intent-to-treat (ITT) population and for subjects with moderate to severe OA pain in both knees who received bilateral IA CNTX-4975 1 mg injections

Endpoints

- **Primary efficacy endpoint, ITT population**
  - Assessment of the circulating ice water wrap cooling control, as the standard cooling regimen, was compared with the other cooling regimens using a composite measure of 3 assessments on day 1 for the index knee and day 8 for the nonindex knee
    - Procedural pain 30 minutes after CNTX-4975 injection rated on a scale of 0 (none) to 4 (severe)
    - Subject satisfaction (SS) and investigator satisfaction (IS) with the cooling and administration procedures rated separately on a scale of 1 (completely dissatisfied) to 7 (completely satisfied)
- **Secondary outcome measure, subjects with bilateral knee OA pain**
  - Clinical benefit was assessed from day 3 through week 8 postinjection
    - Average daily knee pain with walking was scored (0, none; 10, worst) on the NPRS
    - Subjects with bilateral injections rated each knee separately, and results for each knee and an average score for both knees were reported

Statistical Analysis

- The efficacy analysis was performed in the ITT population
  - Procedural pain, SS, and IS scores were converted to equivalent scales before summing the 3 scores for the composite score
    - Procedural pain was reverse scored and normalized (1, severe; 7, none) for equal weighting in the composite score
  - Geometric least squares (LS) means for each regimen, and the geometric means ratio (GMR) and 95% confidence intervals (CIs) for each treatment regimen vs the circulating ice water wrap cooling control group were calculated using an analysis of covariance model on the natural log-transformed primary combined outcome with cooling and injection procedure as the main effect, and baseline index knee radiographic K-L grade category, BMI category, sex, and baseline reverse-scored and normalized index knee procedure pain as covariates
  - A treatment regimen was considered clinically acceptable if lower limit of the 95% CI was >0.7
- For the secondary outcome measure, LS means, 95% CIs, and P values were calculated for change from baseline (CFB) in NPRS scores using a mixed model for repeated measures

RESULTS

Subject Disposition

- Of 654 subjects enrolled, 848 subjects with moderate to severe OA knee pain received unilateral or bilateral CNTX-4975 1 mg IA injections into the index knee (and nonindex knee for bilateral painful knee OA)
  - Overall, 93.8% of subjects completed the study
    - Completion rates were similar across treatment groups
  - Subject withdrawal (2.7%) and loss to follow-up (1.5%) were the most common reasons for study discontinuation

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics were similar across treatment groups (**Table 1**)
  - The majority of subjects were female (59.9%), mean (standard deviation [SD]) subject age was 63.1 (9.43) years, and mean (SD) BMI was 31.3 (6.25) kg/m^2
  - Most subjects had bilateral radiographic OA (81.7%) and index knee K-L grades 2–4 (87.4%)

Figure 1. Study Design

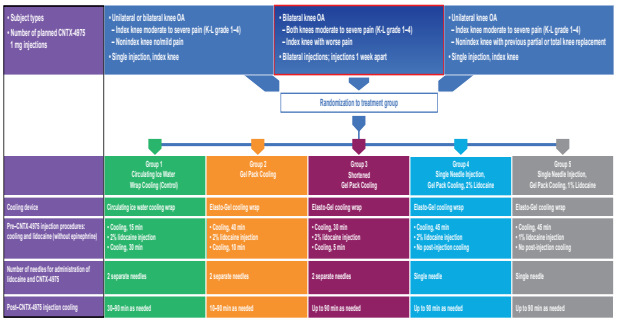

Table 1. Baseline Demographics and Disease Characteristics, ITT Population

	Group 1 Circulating Ice Water Wrap Cooling (Control) n=162	Group 2 Gel Pack Cooling n=179	Group 3 Shortened Gel Pack Cooling n=175	Group 4 Single Needle Injection Gel Pack Cooling 2% Lidocaine n=160	Group 5 Single Needle Injection Gel Pack Cooling 1% Lidocaine n=172
Age, mean (SD), y	62 (9.5)	62 (8.8)	64 (9.2)	63 (9.4)	65 (9.9)
Female, n (%)	104 (64)	101 (56)	104 (59)	99 (62)	100 (58)
Race, n (%) White	129 (80)	157 (88)	143 (82)	100 (63)	116 (67)
BMI, n (%)					
≥30 kg/m^2	85 (53)	79 (44)	89 (51)	84 (53)	99 (58)
≥35 kg/m^2	38 (24)	35 (20)	53 (30)	46 (29)	49 (29)
OA type-radiographic, n (%)					
Unilateral	9 (6)	43 (24)	31 (18)	22 (14)	50 (29)
Bilateral	153 (94)	136 (76)	144 (82)	138 (86)	122 (71)
Time since diagnosis, mean (SD), y	4 (4.3)	2 (3.3)	6 (5.4)	6 (7.5)	9 (7.9)
Kellgren-Lawrence grade in index knee, n (%)					
1	17 (11)	41 (23)	13 (7)	21 (13)	14 (8)
2	36 (22)	53 (30)	36 (22)	36 (23)	37 (22)
3	72 (44)	46 (26)	73 (42)	48 (30)	61 (36)
4	37 (23)	39 (22)	50 (29)	55 (34)	60 (35)

Efficacy

Comparison of Cooling and Administration Procedures, ITT Population

- All CNTX-4975 cooling and administration regimens were clinically acceptable (**Table 2**)
  - Evaluated cold gel–pack wraps were at least as effective as circulating ice water wrap cooling in reducing post-injection pain despite the difference in cooling times evaluated

Table 2. ANCOVA Model of the Primary Combined Outcome in the Index Knee, Normalized Scale, by Cooling and Administration Procedure, ITT Population

	Group 1 Circulating Ice Water Wrap Cooling (Control) n=162	Group 2 Gel Pack Cooling n=179	Group 3 Shortened Gel Pack Cooling n=175	Group 4 Single Needle Injection Gel Pack Cooling 2% Lidocaine n=160	Group 5 Single Needle Injection Gel Pack Cooling 1% Lidocaine n=172
Mean (SD)	17 (2.7)	18 (2.0)	17 (2.9)	18 (3.1)	16 (3.1)
Range	7–21	9–21	7–21	6–21	3–21
Comparison vs circulating ice water wrap cooling control group					
Clinically acceptable?		Yes	Yes	Yes	Yes

ANCOVA, analysis of covariance.

Clinical Benefit in Subjects With Bilateral Moderate to Severe OA Knee Pain

- 523 subjects had bilateral moderate to severe OA pain and received bilateral CNTX-4975 IA injections
  - 427 subjects received IA CNTX-4975 in both knees
    - 96 subjects did not receive an injection in the nonindex knee; for those subjects, the "average" NPRS score for pain with walking was the score for the index knee only
- Significant reductions in pain with walking after CNTX-4975 injection were observed as early as day 3 for the index knee and day 8 + 3 days for the nonindex knee, and improvements were maintained at week 8 for both knees (**Table 3**)

Table 3. Pain While Walking After Single IA Injection of CNTX-4975 1 mg in Subjects With Bilateral Moderate to Severe OA Knee Pain, NPRS

	Subject Type 2: Bilateral Injection (moderate to severe pain in both knees[a]) n=523		
Outcome	Index Knee[b]	Nonindex Knee[b]	Both Knees, Average
Baseline	n=523	n=427	n=523
Mean (SD)	7.42 (1.347)	6.08 (1.480)	6.88 (1.276)
Day 3	n=520	n=424	
CFB (SD)	−4.52 (2.638)	−0.18 (1.474)	
LS mean (SE)	−4.21 (0.103)	−0.20 (0.076)	NA
95% CI	−4.41, −4.01	−0.35, −0.05	
P value	<0.0001	0.01	
Day 8	n=430	n=427	
CFB (SD)	−4.53 (2.689)	−0.13 (1.678)	
LS mean (SE)	−4.23 (0.105)	−0.14 (0.082)	NA
95% CI	−4.43, −4.02	−0.30, 0.02	
P value	<0.0001	0.085	
Day 8 + 3 days	n=426	n=426	n=426
CFB (SD)	−4.04 (2.474)	−3.83 (2.159)	−4.39 (2.095)
LS mean (SE)	−4.63 (0.095)	−3.84 (0.093)	−4.20 (0.086)
95% CI	−4.82, −4.45	−4.02, −3.65	−4.37, −4.03
P value	<0.0001	<0.0001	<0.0001
Week 8	n=401	n=414	n=401
CFB (SD)	−4.33 (3.124)	−3.73 (2.709)	−4.06 (2.833)
LS mean (SE)	−4.02 (0.118)	−3.72 (0.122)	−3.78 (0.110)
95% CI	−4.25, −3.79	−3.96, −3.48	−3.99, −3.56
P value	<0.0001	<0.0001	<0.0001

[a]In subjects receiving bilateral CNTX-4975 injections, the index knee was defined as knee with worse pain; [b]index knee, CNTX-4975 injection day 1; nonindex knee, CNTX-4975 injection day 8. Data reported as a pretreatment. Statistics were based on a mixed model of repeated measures.
NPRS, range, 0 (no pain) to 10 (worst pain).

CONCLUSIONS

- All CNTX-4975 1 mg IA cooling and administration regimens evaluated in the VICTORY-3 study for moderate to severe painful knee OA were clinically acceptable
  - Cold gel–based wraps were at least as effective as the circulating ice water wrap cooling in reducing post-procedural pain and provided similar levels of subject and physician satisfaction
  - These results are consistent with cooling results from the phase 1b studies[3,4]
- Significant reductions in pain with walking were observed early and maintained at week 8 in both knees in subjects with bilateral knee OA pain who received injections in each knee
- A single IA injection of CNTX-4975 1 mg into each knee with moderate to severe OA pain may provide a valuable new option for fast and long-lasting relief
- These findings will provide clinicians with more flexibility regarding the optimal choice of cooling methods in their practices

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3. Stevens RM, et al. Assessment of cooling methods for reducing procedural pain associated with CNTX-4975 injection for management of painful knee osteoarthritis [poster]. Presented at: Florida Society of Interventional Pain Physicians; July 19-21, 2019; Hollywood, FL.
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ACKNOWLEDGMENTS

This study was sponsored by Centrexion Therapeutics Corp, Boston, MA. Medical writing assistance was provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and was funded by Centrexion Therapeutics Corp.

DISCLOSURES

RMS: Stock shareholder and employee of Centrexion Therapeutics Corp; PDH: Stock shareholder and employee of Centrexion Therapeutics Corp; PT: Employee of Centrexion Therapeutics Corp; KG: Stock shareholder and employee of Centrexion Therapeutics Corp; JNC: Stock shareholder and employee of Centrexion Therapeutics Corp; JC: Employee of Centrexion Therapeutics Corp; SR: Employee of Centrexion Therapeutics Corp at the time the study was conducted; MC: Stock shareholder and employee of Centrexion Therapeutics Corp; VHS: Consultant to Centrexion Therapeutics Corp; IR: Grant/research support from and consultant to Centrexion Therapeutics Corp.

Presented at the American Society of Interventional Pain Physicians Annual Meeting, September 4–6, 2020, Dallas, Texas

The Future of Chronic Pain Management

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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 provides a 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

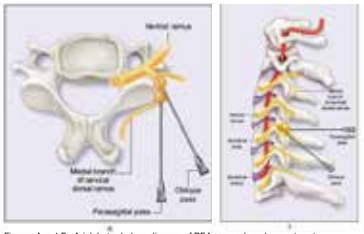
The results demonstrate many novel mechanisms of VR treatment for chronic pain that show promising results.
Large randomized control studies are needed to reproduce similar results.
VR may have the ability to help reduce opioid use and misuse among chronic pain patients.
Efficacy over repeated sessions, 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

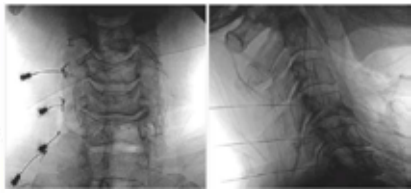
Authors: Sun, Jennifer MD[1]. Polson, George V MD[1]. Karri, Jay MD[1]. Glaser, Scott, MD[2].
[1]Dept. of Physical Medicine & Rehabilitation, Baylor College of Medicine, Houston, TX [2]Pain Specialists of Greater Chicago, Burr Ridge, IL

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



Figures A and B.: Axial, Lateral plane diagram of RFA approach and nerve target: (Source: Lord et al, 1996)



Figures C and D: Fluoroscopic radiographs, AP and lateral respectively, with electrode positioning during radiofrequency ablation of medial branch nerves in cervical spine (Source: Shin et al, 2006)

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.

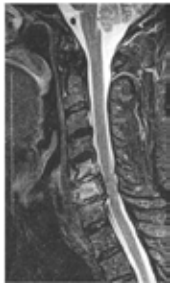


Figure D. MRI C-spine prior to procedure. Multi-level degenerative changes, no cord lesion

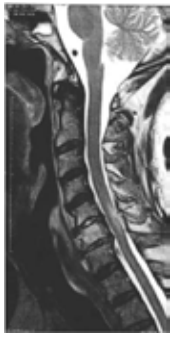


Figure E. MRI C-spine 1 week after procedure, with dorsal cord lesion to C5-C6 (arrow sign)

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

Timothy R. Deer, MD[1]; Jonathan Carlson, MD[2]

[1]*The Spine and Nerve Center of The Virginias, Charleston, WV;* [2] *Hawaii Pain and Spine, Kailua, HI*

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 in turn results in everchanging levels of SCS therapy reaching the intended target.

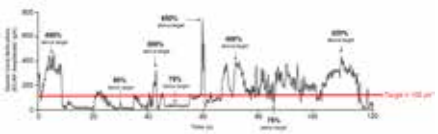

Figure 1. Example of SC Activation in Fixed-Output, Open-Loop SCS

For >50 years of SCS, there has been no knowledge of the neural tissues being stimulated in-vivo. Evoked compound action potential (ECAP) recording provides an objective measure of spinal cord (SC) activation during SCS and merges evidence-based medicine with mechanism-based medicine.

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 (NCT02924129) 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.

Results

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

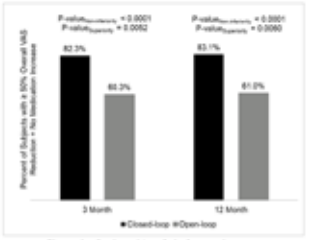

Figure 2. Back and Leg Pain Responders

Closed-loop was also statistically superior in the rate of high responders (≥80% reduction in back and leg pain) (figure 3), and in parallel, had a higher rate of voluntary opioid reduction (figure 4).

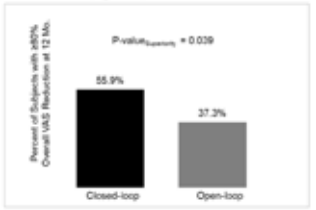

Figure 3. Back and Leg Pain High Responders

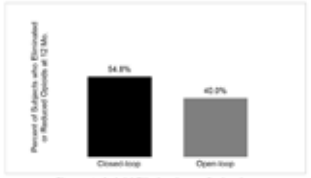

Figure 4. Opioid Elimination or Reduction

Objective Neurophysiological Measures

SC activation levels (ECAPs) during actual usage outside the clinic were recorded (27uV CL and 4.5 uV OL) and compared to the programmed target level identified in clinic (27uV CL and 16uV OL). (figure 5).

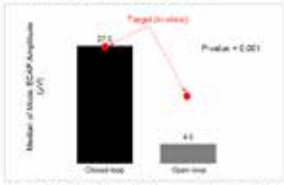

Figure 5. SC Activation Outside Clinic vs. in Clinic Target SC Activation at 12-months

SC activation was better maintained within the therapeutic range with closed-loop (figure 6).

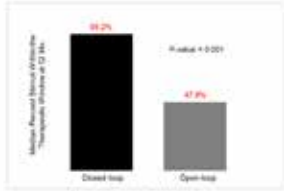

Figure 6. Therapeutic Window

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).

Disscussion

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 with the same device, procedure technique, and programming methods utilized in both 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.

Differences between groups were observed in SC activation. The time spent in the therapeutic range was almost double and the most frequent SC activation level was six times greater with closed-loop compared to open-loop. Thus, greater rates of improvement in subjective outcomes coincided with higher, more consistent SC activation within patients' therapeutic range of activation in the closed-loop group. This suggests that the level and consistency of SC activation (i.e., lack of variability in stimulation reaching the target), regardless of algorithm, may be mechanistically important for outcomes with SCS.

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FINANCIAL SUPPORT: This study was conducted with support from Saluda Medical.

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

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

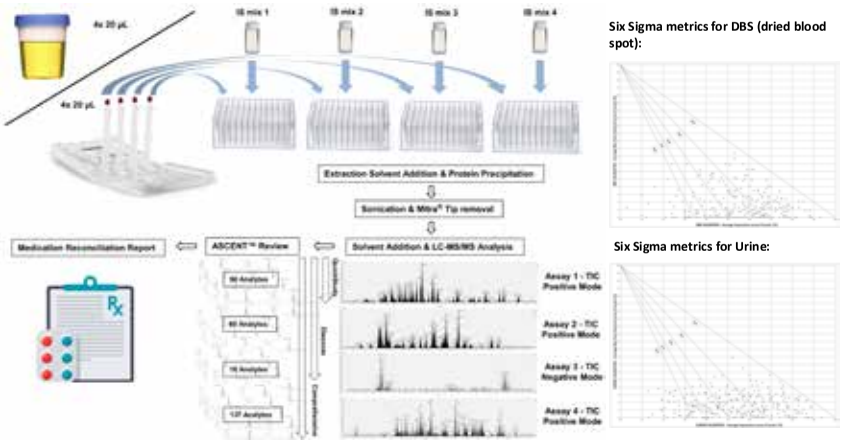
Alcala Testing and Analysis Services (Alcala Labs)

INTRODUCTION

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 (ADRs). In order to prevent adulteration of commonly collected clinical samples such as urine, dried blood spots (DBS) collected by Mitra® Microsampling present a reliable alternative.

METHODS

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:



Six Sigma metrics for DBS (dried blood spot):

Six Sigma metrics for Urine:

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 5428 (97%) with an inconsistent positive compared to the provided medication list (including caffeine, cotinine or ethanol metabolites), 29 (0.5%) with no medication list and no unexpected positive results (consistent negative), and 22 (0.4%) 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. Comprehensive dried blood spot analysis proves a reliable alternative to urine drug testing for extended medication reconciliation, with the added advantage of detecting drug-drug-interactions.

DISCUSSION

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 is an efficient method (24-hour turnaround time) applicable to patient medication reconciliation and determination of patient compliance. Over 90% of prescription drugs and illicits covering 26 drug classes used by the general US adult population can be measured, although therapeutic drug monitoring ranges remain to be verified on a per compound basis. Mitra® Microsampling offers low rejection rates (<5%), improves patient comfort, requires no cold chain shipping and increases operational efficiencies.

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