

Acute Pain

Managing Acute Traumatic Pain in HIV-infected Patients: Knowledge and Practice Trends among Emergency Physicians of Major Tertiary Care Hospitals of a Developing Country

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Aim: Pain management in patients infected with human immunodeficiency virus (HIV) is complex as they suffer with concomitant painful conditions. We conducted a survey to assess knowledge and practice trends in managing traumatic pain in HIV-infected patients among emergency physicians of four hospitals.

Methods: In this cross-sectional survey, emergency physicians were requested to fill a structured questionnaire after obtaining informed consent.

Outcome / Results: The responses to practice-related questions are provided in Table 1, and to knowledge related questions in Table 2.

Table 1

Practice Trends	Responses	Percentage
What drugs do you use to treat acute pain?		
Opioids	16	19.0%
NSAID	9	10.7%
Paracetamol	7	8.3%
Combination	40	47.6%
Is pain assessment done for all patients?		
Yes	61	72.6%
No	23	27.4%
Are any guidelines available for managing pain?		
Yes	48	57.1%
No	33	39.3%
Is multi-modal therapy used for managing pain?		
Yes	21	25.0%
No	11	13.1%

Table 2:

Questions related to knowledge	Frequency	Percentage
What dose of opioid drugs is required to treat pain in these patients?		
Usual dose	42	50.0%
More than usual dose	23	27.4%
Less than usual dose	9	10.7%
Is management of pain more complex in these patients?		
Yes	42	50.0%
No	35	41.7%
Is pain under-reported and under-treated in these patients?		
Yes	26	31.0%
No	51	60.7%

Conclusions: There are considerable gaps in knowledge regarding management of acute traumatic pain among emergency physicians. Guidelines are required for improving pain management in this group of patients and educational sessions need to be arranged for enhancing knowledge.

Acute Pain

Prevalence of Persistent Post-surgical Pain in a Tertiary Care Hospital of a Developing Country: A Cross Sectional Survey

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Background: Persistent post-surgical pain (PPP) is defined as pain that lasts two months or more after surgery. Research has shown significant prevalence of PPP after many surgical procedures. However, little is known about its prevalence in the Southeast Asian region. Research in this area will guide us in making strategies for its prevention and management.

Objective: To assess the prevalence and characteristics of PPP after total knee replacement (TKR) and total abdominal hysterectomy (TAH) at a university teaching hospital.

Methods: Approval for this cross-sectional survey was obtained from the Ethics Review Committee and informed consent was taken from all patients scheduled for elective TAH and TKR from February 01, 2016 to May 31, 2016. Patients with history of chronic pain, those taking regular analgesics or having a language barrier were excluded. A designated nurse called the patients three months and one year after surgery and filled out a questionnaire.

Results: 201 patients were included, 119 (59.2%) following TAH, and 82 (40.8%) after TKR. At three months 28 (13.9%) patients reported pain, 15 following TAH (12.6%) and 13 (15.8%) following TKR. Twenty (71.4%) complained of pain at the operative site, while 8 (28.6%) had pain in the surrounding area. Twenty-five patients had burning and throbbing pain while 3 patients reported stabbing pain. Average pain score was 2.63 ± 0.87 . At one year, five (17.9%) patients reported pain score of 3 to 6. Two of these patients (1.7%) had undergone TAH, while three (3.7%) had TKR.

Conclusions: Prevalence of PPP at our tertiary care hospital was found to be lower than that reported from other centres. PPP was found in 12.6% of patients after TAH and 15.8% after TKR at three months and in 1.7% after TAH and 3.7% after TKR at one year.

Acute Pain

Comparison of the Analgesic Effect of Patient-Controlled Oxycodone and Fentanyl in Patients undergoing Robotic Gastrectomy

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Background: Robotic gastrectomy has been increasingly considered as an alternative, minimally invasive technique. Nevertheless, still the patients undergoing robotic gastrectomy suffer from the postoperative pain. Pain after robotic gastrectomy at ward has been controlled with intravenous patient-controlled analgesia (IV-PCA) consisting of opioid or NSAID. Recently, oxycodone, which is a μ -opioid receptor agonist is used as IV-PCA for postoperative pain relief. Previous studies have reported that oxycodone alleviated the postoperative pain effectively and reduce the amounts of rescue analgesics in colorectal surgeries and gynecologic surgery.

Objective: Therefore we investigated effects of oxycodone-based IV-PCA on pain attenuation in patients undergoing robotic gastrectomy in comparison with fentanyl-based IV-PCA

Methods: A total of 21 consecutive patients undergoing robotic gastrectomy between May and June 2017 were retrospectively reviewed. Patients received oxycodone-based IV-PCA (Group O, n=10) or fentanyl-based IV-PCA (Group F, n=11). The primary outcomes were to evaluate postoperative analgesic effects. Secondary outcomes were to assess additional rescue analgesics consumption and the numbers of delivery and attempts of IV-PCA.

Results: The mean numeric rating score (NRS) levels at 24 postoperative hours in Group O is lower compared to those of Group F (5.3 ± 1.6 vs. 7.0 ± 1.8 , $P=0.03$). Patients in Group F needed significantly more additional rescue analgesics between 0 and 6 hours after surgery compared to those in Group O (1.7 ± 1.2 vs. 0.6 ± 0.7 , $P=0.03$). Between 0 and 6 hours after surgery the number of delivery was significantly lower in Group O ($P=0.03$) compared to those of Group F but, the number of attempts in Group O was lower (94.5 ± 107.9 vs. 275.0 ± 287.9) with no statistical significance.

Conclusion: Oxycodone-based IV-PCA can be a feasible alternative to fentanyl-based IV-PCA in patients undergoing robotic gastrectomy.

Acute Pain

Idiopathic Costochondritis-Gender Differences in this Little Known Chest Pain Syndrome

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Background: Patients with chest pain may remain undiagnosed. Idiopathic costochondritis (IC) has been described as one of the most common causes of chest pain. It is characterized by chest pain and costochondral junction tenderness. Higher prevalence of IC in women has been reported. We compare female and male IC patients' demographics, treatment results and investigate their pain levels with VAS

Methods: We analyzed 443 patients accepted with IC diagnosis in our outpatient clinic in 4 years period. Demographics, treatments were recorded from prospective database.

Results: A total of 259(58.5%) female (mean age, 41.8 ± 17.4 years) and 184(41.5%) male (mean age, 41.8 ± 17.4 years) patients with IC were evaluated. All patients were treated with non-steroidal anti-inflammatory drugs (NSAID) (diclofenac sodium 100 mg or flurbiprofen 200 mg) for a minimum of 2-3 weeks. VAS 3 is most frequent pain score in admission (p0.05). Pain disappeared more frequently in 3 weeks (P= 0.62) in two groups. Age and duration of pain until admission were statistically different between the two groups (P=0.04 and P=0.001, respectively) table 1.

Conclusions: We found gender differences between IC patients. We found also that regular use of anti-inflammatory drugs for a certain period of time increases the success of treatment. We propose minimum 3 weeks of NSAID use in the treatment of IC.

Table 1: Demographic differences between two groups

	Female (259/58.5%)	Male (184/41.5%)	p
Age (years±SD)	41.8 ± 17.4	38.3 ± 16.25	0.04
Duration of pain(<5day/5day-2 week)	96(37.1%)/67(25%)	96/(52%)/46(25%)	0.001
Painful ribs number in left side: %(patient no/%)	3(70 /27%)	3 (46%25%)	0.13
Painful ribs number in right side: %(patient no/%)	3(20/10.4%)	2(20/10.9%)	0.39
Side of disease (left): %(n)	57.5%(149)	57%(105)	0.44
healing:2-3 week %(n)	91.1%(236)	89.7%(165)	0.62
Recurrence:%(n)	4.6%(12)	3%(6)	0.47

Acute Pain

Effects of *Sonchus Asper* and Apigenin-7-Glucoside on Nociceptive Behaviors in Mice

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Background: *Sonchus asper* is an important herbal medicine that traditionally used to treatment of digestive system infections and heart disease.

Objective: To evaluate of anti-inflammatory and antinociceptive effects of *Sonchus asper* hydroalcoholic leaf extract (SALE) and one of its major constituent, apigenin-7-glucoside (Ap7G), in male mice.

Methods: In this experimental studies were used nociceptive assessment tests, which include writhing, tail-flick, and formalin-, and glutamate-induced paw licking tests. In addition, xylene test was used for evaluating of anti-inflammatory effect of SALE and Ap7G.

Results: In tail-flick, writhing and glutamate-induced paw licking tests, application of a dose of 300 mg/kg of extract showed significantly ($p < 0.01$) antinociceptive effect compared to the control group. In the formalin test, treatment with a dose of 100 mg/kg of extract reduced the pain scores in the tonic phase compared with the control group ($p < 0.05$). In formalin model, also naloxone (an opioid non-selective antagonist) plus the extract (300 mg/kg) reduced licking and biting in mice. Moreover, the use of morphine decreased the nociceptive activity in all assessment tests. In addition, in xylene test, treatment with dose of 100 mg/kg of SALE increased the inhibition (49%) comparing to the control group. The Ap7G showed significant antinociceptive and anti-inflammatory effects in all tests.

Conclusion: SALE and Ap7G have both antinociceptive and anti-inflammatory effects under the experimental conditions performed in this study. The modulation of the glutamatergic system by opioid receptors could be involved, at least in part, in these effects.

Alternate Trial Design Approaches

Three Dimensional Imaging Angiography vs Cone Beam CT (Fluoroscopy) to Reveal Intravascular Injection during Lumbar Transforaminal Steroid Injection

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Aim: Comparison of the performances of 3 D imaging Angiography (3D-IA) and Cone beam CT (CB-CT) (Fluoroscopy) in determining the incidence of accidental intravascular injection during lumbar transforaminal anterior epidural steroid injection (TAESI).

Methods: We assessed 20 (9 male, 11 female) patients (with total 40 levels) whose images were received during TASEI simultaneously guided by 3D-IA and CB-CT between January 2016 and September 2016. Injections were carried out in the lumbar fourth intervertebral space bilaterally and performed in the same way in all of the cases by the same pain therapist (Dr. ONA)

Results: The mean age and BMI of the patients were 47.9 ± 2.72 years and 26.95 ± 1.21 . There were ten patients with disc herniation, seven patients with spinal stenosis and three patients with failed back surgery syndrome. It was decided that the needle was in the correct position in 28 (70%) images, twelve (30%) levels the needle was in the incorrect position in the 3D image. Given the location of the needle in the wrong place, two of them were anterior, two of them were in the outside at posterior, six were in the canal but more distally and two were in the canal but more medially. In the 3D imaging, vascular escape was detected in the seven levels (17.5 %) which were thought to be no escape in the two- dimensional imaging (Cone beam CT).

Conclusions: The advice of using 3D imaging rather than Cone beam CT to avoid intravascular injections during TASEI, in accordance with previous studies. We supposed that technological advances in three- dimensional images will allow us to achieve more accurate results with lower cost in the future.

Back Pain

Diagnostic Accuracy of Standardized Qualitative Sensory Tests to Assess Lumbar Lateral Stenosis involving the L5 Nerve Root

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Misdiagnosis of a symptomatic lumbar lateral stenosis (LS) may result in an unfavorable prognosis after surgical treatment. This purpose of this study was to access the diagnostic accuracy of the standardized qualitative sensory test (SQST) for the presence of a symptomatic LS in patients who had degenerative spinal disorders involving L5 spinal nerve. 75 patients were prospectively selected and 60 met the criteria. Lateral recess stenosis at the L5 level or foraminal stenosis at the L5/S1 level on MRI was identified and graded by one neurosurgeon blinded to any clinical information. The reference test for the diagnosis of a symptomatic LS was a grade III LS on MRI and the relevant clinical symptoms. Cutaneous sensory functions of the L5 dermatome on the symptomatic side were evaluated by the SQST. Each item of the SQST had a good performance for diagnosing LS (sensitivity=0.455~0.727, specificity=0.868~1.0).

The stepwise selection model identified low-strength von-Frey, high-strength von-Frey, and vibration to be the best predictors of a symptomatic LS with an area under the receiver operating characteristics curve of 0.9563 (95% confidence interval=0.9003~1.0). In combination with MRI, SQST is a good diagnostic tool to predict a symptomatic LS involving L5 nerve roots.

Back Pain

Effect of Drugs Administration in to the Epidural Space during Epiduroscopy

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Background: Epiduroscopy is a proven method of diagnosis and treatment for chronic radicular pain after spine surgery appointed as Failed Back Surgery Syndrome (FBSS).

Objective: The aim of the study was to compare efficacy of drugs (enzyme Hyaluronidase and corticosteroid DEPO-Medrol) administrated into the epidural space during epiduroscopy.

Methods: 48 patients with diagnosed FBSS were randomized into the two groups before epiduroscopy. Group A received the standard treatment - mechanical lysis of fibrotic tissue in the epidural space. Second group B received also drugs during procedure. Subjects were followed for 6 and 12 months via planed double blinded examinations by pain physicians. Leg-pain and back-pain intensity was assessed by 11-point numerical rating scale and patient`s functional disability was assessed by Oswestry Disability Index (ODI).

Results: Study subjects had in both groups significant decrease of ODI score (p0,05) also we noticed significantly lower pain scores measuring leg-pain (p0,05) and back-pain (p0,05) after 6-months follow-up. However we recorded at the 1-year follow-up return to the baseline ODI values, as the same as most of all monitored pain scores in the both groups (p0,05). We registered improvement only in NRS for back-pain at the 1-year follow-up (p0,05).

Conclusions: In this first trial focused on drugs effect was not found significant outcome in leg-pain and ODI measurements after drugs administration than without them. We recognize significant improvement of back-pain after 1-year follow-up in the B group.

Chronic Pain

What`s the Message?!

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"More than 100 million people in Europe suffer from chronic pain ...One reason for this is that clinical trials remain poor in assessing pain, disability and measuring meaningful improvement." SOPATE 2017 home page

What is the message? Could it be related to technology, design, protocol, procedure, assessment or something else? Could it be related to the questions asked, interpretation of the answers received? Perhaps it is more fundamental. Could it be related to the assumptions upon which the aforementioned are built?

What if, rather than assuming chronic pain to be the problem, that is the normal physiological process gone awry (the pathology), it was viewed as a persisting messenger relating to underlying disorder? What if, rather than attempting to decipher the message through a 20th century biomedical understanding, 21st century understanding was used? What would be the effect on clinical trial design? Would the message become clearer? Could the suffering of more than 100 million people in Europe be alleviated?

What`s the message!

Chronic Pain

Effects of Rate on Analgesia in KiloHertz Frequency Spinal Cord Stimulation: Initial results of the PROCO Randomised Controlled Trial

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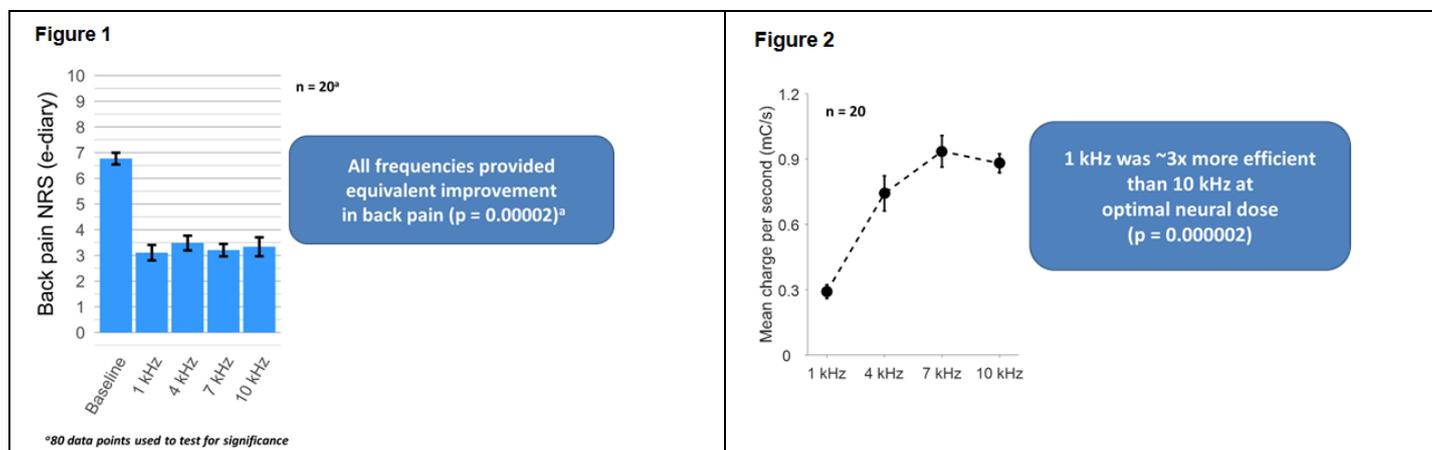
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Background and objective: The PROCO (Evaluation of Stimulation Pulse Rate On Clinical Outcomes in Patients Whose Pain Is Controlled by KiloHertz SCS) RCT was a multicentre, double-blind study that investigated effects of stimulation frequency on analgesia.

Methods: The crossover design of this study has the equivalent statistical power of a parallel design study with over 100 patients. Patients were implanted with SCS systems and underwent an 8 week search during which up to 14 stimulation locations were tested to identify the best location (“sweet spot”) of stimulation at 10 kHz within the searched region (T8–T11). An electronic diary (e-diary) prompted patients for pain scores 3 times per day. 10 kHz responders ($\geq 30\%$ back pain relief per e-diary) proceeded to rate randomization during which 1 kHz, 4 kHz, 7 kHz, and 10 kHz were assigned in random order for blinded evaluation and used for 4 weeks each while stimulating at the same sweet spot. Pulse width and amplitude were adjusted to optimize therapy.

Results: 20 patients completed rate randomization. Pain scores for each patient were averaged over the 5 day evaluation period for each rate, yielding 80 data points for statistical analyses. All rates provided equivalent back pain relief (Figure 1). 1 kHz was ~ 3 times more efficient than 10 kHz (Figure 2).

Conclusions: The double-blind PROCO RCT provides Level I evidence for equivalent pain relief from 1 kHz to 10 kHz with appropriate neural dosing. 1 kHz was ~ 3 times more efficient than 10 kHz at the optimal neural dose.



Chronic Pain

Relative Frequency of Chronic Postoperative Pain in Patients Operated for Chronic Otitis Media

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Background: Chronic postoperative pain may lead to physical disability and psychosocial distress.

Objective: In this longitudinal observational study, for the first time we evaluated the relative frequency of chronic postoperative pain in patients operated for chronic otitis media (COM) at two university hospitals in north & center of Iran.

Methods: Patients were questioned about pain at the site of the surgical incision 3–6 months after the operation, and again 3 months after the first visit. Pain intensity was quantified by visual analogue scale (VAS). T test, Chisquare test, and logistic regression were used for analyzing data and multivariate analysis.

Results: In 155 patients (42 male, 113 female, mean age: 38.57 ± 10.66 years), chronic postoperative pain was observed in 50 cases (32.3 %). A significant decrease in the average score of VAS was observed from 5.18 to 2.64 within 3 months ($P = 0.0001$). Statistically significant correlation was observed between chronic postoperative pain and age, sex, acute postoperative pain and history of Irritable Bowel Syndrome or migraine, but after multivariate analysis, only the age group and severe acute post-operation pain were effective on incidence of chronic post-operative pain.

Conclusion: surgery for COM is followed by chronic pain in about 32 % of patients, and some risk factors for the development of chronic postoperative pain after this surgery exist, including age and severe acute post-operation pain.

General/Other

Advantages of Timely Reporting of Pain Area, Location and Intensity: A Preliminary Study of Fine Body Mapping

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Background: Clinicians rely on patients' recollection of pain symptoms during anamnesis to assist reasoning and assess treatment responses.

Objectives: Determine whether reporting pain intensity and area in real-time enhances the accuracy of pain recall and investigate in detail the spatiotemporal changes associated with a commonly used surrogate model of low back pain.

Methods: All participants (N=10) received an injection of hypertonic saline (0.5ml, 5.8%) into the gluteus medius. Immediately following the injection, the drawing (N=5) and non-drawing (N=5) groups reported pain intensity on a numerical rating scale (NRS, 0-10) and only the drawing group reported pain area on a digital body chart every 30sec for 15min to create a detailed time-lapse (see fig.1). Recall of peak pain and area was assessed one-week post-follow-up. Additionally, the recall accuracy of a predetermined arm pain drawing was assessed during both the injection and recall sessions.

Results: The drawing and non-drawing groups reported similar pain intensity during the injection and no difference was found when pain was recalled one week later (4.8 ± 1.3 and 3.6 ± 1.4 ; 3 ± 1 and 3 ± 0.7 , $p=0.56$). However, the distribution and overlap in pain area differed between sessions for the drawing group (mean difference: $76.5 \pm 84.6\%$, $p=0.004$). There was no difference in total area for the recall session between the groups (mean difference: $-62.2 \pm 76.3\%$, $p=0.15$) (fig. 2). Notably, the timing of peak pain intensity differed from peak area ($p=0.09$).

Conclusion: The area and distribution of pain is poorly recalled regardless of real-time reporting and thus should be acquired at relevant time-points. Fine body mapping offers novel insights into time course of pain referral for surrogate models of acute pain.

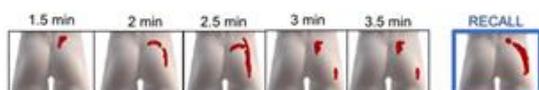


Fig. 1: An example of a drawing pain distribution during the injection and recall session of one participant.

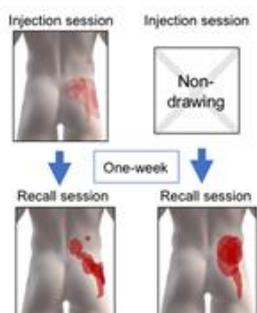


Fig.2: Pain distribution overlays of all the participants from the drawing (left) and non-drawing (right) group during the pain and recall session.

General/Other

Effects of the Application of a Sensorymotor Stimulus on Dizziness and Postural Balance: Retrospective Study

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Introduction: Body balance disorders, such as dizziness and disequilibrium, are commonly observed. In most cases, these disorders are consequence of proprioceptive dysfunction. To preserve the body balance, the central nervous system depends on afferent information of visual, vestibular and somatosensory systems and promotes the interaction between body and space in association with cognition.

Objective: To analyze dizziness and body balance before and after pressure sensoriomotor stimulus over atlanto-occipital joint.

Method: This is a retrospective study with a sample of 167 patients. From these patients, 70 constituted the experimental group and have undergone intervention, 67 patients composed the control group that had not undergone any treatment. All patients had complaints related to balance disorders and no etiological diagnosis of vestibular and neural imbalance. Comparative statistical analyses among the groups were used to evaluate the treatment outcome. Visual Analogic Scale (VAS) was used to evaluate dizziness, Romberg Test, and FukudaUnterberger Test was used to Balance, opened eyes spontaneous nystagmus, closed eyes spontaneous nystagmus and directional nystagmus for posture. Was used The Cochran's Q test, McNemar's test and Chi-square test evaluated the Romberg, Fukuda Tests. The Mann-Whitney's test, Wilcoxon's test and Friedman's test evaluated the Visual Analogic Scale scores.

Results: Was observed statistically significant differences for VAS dizziness, static and dynamic balance, opened eyes spontaneous nystagmus, closed eyes spontaneous nystagmus before and after 7, 30 e 180 days of the stimulus within the experimental group and between the experimental and control groups.

Conclusion: The intervention with the pressure sensoriomotor stimulus over atlantoccipital joint show statistically significant differences in patients symptoms of dizziness, static and dynamic balance, and nystagmus, when compared before and after the intervention, and also when compared to the control group.

Keywords: Proprioceptive dysfunction, posture, balance, equilibrium, dizziness, pressure stimulus

Methodology and Evidence

Challenges with Recruitment in Randomized Controlled Trials Investigating the Efficacy of Analgesics in Cancer-related Pain and Characteristics of Patients Included

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Background: Pain is one of the most bothersome symptoms associated with malignant tumors. Further improvements in cancer pain therapy are needed requiring clinical investigation. A major challenge remains recruitment for these investigations. This might be related to trial design or site/country/population characteristics.

Objective: We evaluated participating sites, countries, recruitment rate, demographic and medical history parameters of patients in 2 randomized controlled trials investigating efficacy and safety of strong analgesics in chronic cancer-related pain.

Methods: Data from 2 double-blind Phase 3 trials with approximately 6 week treatment duration were included: 1 randomized-withdrawal, placebo- and active-controlled trial, and 1 randomized, active-controlled, parallel-group, non-inferiority trial.

Results: In the placebo-controlled trial (conducted between 2007 and 2012), 71 sites in 16 countries and in the active-controlled trial (conducted between 2013 and 2015), 42 sites in 14 countries enrolled subjects at a rate of 0.15 and 0.21 subjects/site/month, respectively. For the Safety Set, mean age, Body-Mass-Index and baseline pain intensity (assessed under prior pain treatment, including opioids) were comparable in the 2 trials. Most subjects (at least 75%) were in advanced disease stage (Stage IV / presence of metastases) and more than 30% had bone metastasis in both trials. Slight differences between both trials were observed in most frequent types of cancers. Most frequently used prior opioid was tramadol in both trials.

Conclusion: Although designed differently, both trials recruited a similar population at similarly low rates. The study of novel cancer-pain treatments is and remains challenging.

Methodology and Evidence

Methods for Identifying Quantitative and Qualitative Subgroup Interactions for Pain Outcomes in Osteoarthritis (OA) Behavioral Intervention Clinical Trials

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Background: Clinical trials of behavioral interventions in OA patients have shown modest overall effects on pain. However, heterogeneity of treatments effects (HTE) exist with large improvements in pain for some patients and little to no improvements for others, known as quantitative subgroup interactions. In trials with two active treatments, there may be HTE via qualitative subgroup interactions, where one treatment may work better for one subgroup while the other treatment may be better for another.

Objectives: Advanced statistical methods to discover HTE are applied to multiple behavioral trials in OA patients. The first trial examined the effectiveness of a combined patient and provider OA self-management intervention (n=300). The second trial compared the effect of physical therapy (PT) and internet-based exercise training (IBET) among knee OA patients (n=282).

Methods: Quantitative subgroups in the first trial were identified using a regression tree-based method (Virtual Twins) which searches for cutpoints of predictor variables where the differential treatment effect exceeds a pre-specified threshold. In the second trial, three different qualitative subgroups of patients will be identified: 1) treatment PT IBET; 2) treatment IBETPT; or 3) neither treatment better using a data-driven clustering method (Qualitative Interaction Trees (QUINT)). This algorithm searches for inclusion and cut-points of predictors where treatment difference is optimal and subgroup sample size is reasonable. For both methods, parameters for split criterion, minimum sample size per subgroup, and maximum number of tree splits can be specified.

Results: In the first trial, preliminary results indicate that the patient and provider intervention had a larger effect on pain and function in OA patients with higher baseline pain and younger patients with lower baseline pain. Results for qualitative interactions in the second trial are forthcoming.

Conclusions: New state-of-the-art data-driven methods are available for identification of subgroup interactions in clinical trials with the goal of identifying optimal treatment for patients based on demographic and clinical characteristics.

Neuropathic Pain

Alternative RNA Splicing Control – A Potential Analgesic Target

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Vascular endothelial growth factor-A (VEGF-A) is known to promote angiogenesis in solid tumours, and in inflammatory conditions such as arthritis. It is now recognised that VEGF-A is also implicated in pain, particularly neuropathic pain such as traumatic, diabetic and chemotherapeutic neuropathy. VEGF-A is alternatively spliced to produce two different families of VEGF proteins – VEGF-A_{xxx}a and VEGF_{xxx}b, where xxx denotes the number of amino acids. These differ only in the terminal 6 amino acids, but this difference results in distinct receptor interaction and function. VEGF-A_{xxx}a is associated with pain following nerve injury whereas VEGF-A_{xxx}b is anti-nociceptive and potentially neuroprotective. The splicing to VEGF-A_{xxx}a isoforms is controlled by a splicing kinase SRPK1, with SRPK1 inhibition resulting in a reduction in the proportion of VEGF-A_{xxx}a and an increase in VEGF-A_{xxx}b. We have used VEGF-A isoforms and inhibitors of SRPK1 to study the contribution of this splicing control in in vivo and in vitro models of neuropathic pain, and neuronal sensitisation.

The effect of recombinant human (rh)VEGF-A₁₆₅a, and rhVEGF-A₁₆₅b were assessed in in vivo animal models of traumatic, chemotherapeutic and diabetic neuropathy and chemically-induced osteoarthritis in rats. In some models SRPK1 inhibitors were also tested for efficacy as analgesics. Both rhVEGF-A isoforms and SRPK1 inhibitors were also tested for sensitisation effects in a primary sensory neuronal high-throughput calcium-based assay.

rhVEGF-A₁₆₅a sensitised TRP channel evoked responses in primary sensory neurons in vitro whereas these were blocked by VEGF-A₁₆₅b. SRPK1 inhibitors also blocked TRP channel-evoked responses in primary sensory neurons. rhVEGF-A₁₆₅b ameliorated pain behaviour in traumatic, chemotherapeutic, diabetic and osteoarthritic animal models. SRPK1 inhibition also ameliorated pain behaviour in traumatic and diabetic neuropathic pain models.

Based on these data, control of VEGF-A splicing in favour of VEGF-A_{xxx}b isoforms may be a potential analgesic strategy.

Neuropathic Pain

Leukocyte Elastase Inhibitors for the Treatment of Chronic Pain Conditions involving a Neuropathic Component

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Neuropathic pain remains one of major health problems worldwide and available treatment options are still limited in efficacy or associated with side effects. In the search of novel therapeutic targets for the treatment of neuropathic pain, we recently identified SerpinA3N, a serine protease inhibitor secreted in response to nerve damage by the DRG neurons in a genetic screen. We further showed that SerpinA3N acts against induction of neuropathic pain by inhibiting the T-cell- and neutrophil-derived protease, leukocyte elastase (LE). In the current study, via detailed *in vivo* pharmacology combined with analyses of evoked- and spontaneous pain-related behaviors in mice, we report that upon systemic delivery, a single dose of three independent LE inhibitors can block established nociceptive hypersensitivity in early and late phases in the spared nerve injury model of traumatic neuropathic pain in mice. We further report strong efficacy of systemic LE inhibitors in reversing ongoing pain in two other clinically-relevant mouse models - painful diabetic neuropathy and cancer pain.

Detailed immunohistochemical analyses on the peripheral tissue samples revealed that both T-Lymphocytes and neutrophils are the source of LE upon peripheral nerve injury, whereas neutrophils are the primary source of LE in diabetic neuropathic conditions. In summary, our results provide compelling evidence for a strong therapeutic potential of generic LE inhibitors for the treatment of neuropathic pain and other chronic pain conditions harboring a neuropathic pain component.

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Prediction of Treatment Response

The efficacy of Danggui Shaoyao San to Relieve Periodontal Pain in Orthodontic Treatment

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Objective: To investigate the efficacy of Danggui Shaoyao San (A traditional Chinese medicine prescription) to relieve periodontal pain in orthodontic treatment.

Method: 120 orthodontic patients were randomly assigned to Danggui Shaoyao San, ibuprofen, placebo groups. The orthodontic patient took Danggui Shaoyao San, ibuprofen, placebo randomly for five days. Periodontal pain was recorded and analyzed within 5 days by visualanalogscale.

Results: Pain scores of the groups with Danggui Shaoyao San and ibuprofen groups were less than that of the placebo group, but there is no significant difference between Danggui Shaoyao San and ibuprofen after 12 hours

Conclusion: Danggui Shaoyao San is effective to relieve the periodontal pain following orthodontic treatment

Keywords Orthodontic teeth; Pain; Danggui Shaoyao San; ibuprofen