

Recent trends in chronic pain medicine

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Submitted: 11-Jan-2023

Revised: 12-Jan-2023

Accepted: 12-Jan-2023

Published: 21-Jan-2023

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/ija.ija_31_23

Quick response code



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ABSTRACT

Chronic pain presents as an unequalled challenge for physicians, owing to the complexity of biochemical and biological pathways involved in pain transmission and high variability of pain perception among individuals. Often, there is an inadequate response to conservative treatment, and opioid treatment has its own drawbacks, such as side effects and opioid dependence. Hence, novel strategies have evolved for the effective and safe management of chronic pain. Radiofrequency technique, regenerative biomaterial, platelet-rich plasma, mesenchymal stem cells, reactive oxygen species scavenger nanomaterial, ultrasound-guided interventional pain management procedures, endoscopic spinal procedures, vertebral augmentation therapy, and neuromodulation are some of the promising and upcoming modalities in the armamentarium of pain physicians.

Key words: Chronic pain, neuropathic pain, opioid analgesics, pain management, radiofrequency therapy, spinal cord stimulation

INTRODUCTION

Chronic pain presents as an unequalled challenge for physicians, owing to the complexity of biochemical and biological pathways involved in pain transmission and high variability of pain perception among individuals. Due to the side effects associated with opioids and the growing concern around increased dependence on opioid use, there is a need for definitive and safe strategies to treat chronic pain. Inadequate response to conservative treatment prompts the use of minimally invasive pain and spine interventions (MIPSI).^[1,2] Keeping in mind the various newer management strategies that are coming up in the field of chronic pain medicine, we conducted a literature search in various databases. The information thus compiled, along with the clinical experience of the authors is presented in this article.

NEWER MODALITIES IN THE MANAGEMENT OF NEUROPATHIC PAIN

Common neuropathic pain (NeUP) syndromes include painful polyneuropathy (e.g., due to diabetes),

post-herpetic neuralgia, peripheral nerve injury, radiculopathy, cancer-related neuropathic pain, central post-stroke pain, and trauma or entrapment neuropathy. Pharmacological treatment fails to provide adequate pain relief in many patients; hence, there is an unmet need for newer approaches, especially interventional techniques like neuromodulation.

NeuP management has been traditionally done by pharmacotherapy and its main focus is on treating symptoms. A recent meta-analysis and the Special Interest Group on Neuropathic Pain proposed gabapentinoids, tricyclic antidepressants (TCAs), and selective serotonin and norepinephrine reuptake

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How to cite this article: Malhotra N, Joshi M, Dey S, Sahoo R, Verma S, Asish K. Recent trends in chronic pain medicine. Indian J Anaesth 2023;67:123-9.

inhibitors as first-line drugs for neuropathic pain. Lidocaine, capsaicin, and tramadol were proposed as the second-line treatment, while strong opioids (morphine and oxycodone) and botulinum toxin A (BTX-A) were included as third-line treatments for peripheral neuropathic pain.^[3,4] Although not included in many NeuP treatment guidelines, interventional pain management (IPM) modalities such as pulsed radiofrequency (RF), cryoneurolysis, peripheral neurostimulation (PNS), and spinal cord stimulation (SCS) hold a lot of promise, as reported in recent literature.^[4,5]

In the pharmacological treatment of NeuP, when single-agent treatment fails, then combination treatment, especially opioid or TCA with gabapentin, has been shown to be effective and can be considered.^[6] BTX-A when given intradermally at multiple locations over the affected dermatome is another novel treatment approach that has been shown to relieve focal painful neuropathy and painful diabetic polyneuropathy with pain relief lasting for up to 12 weeks.^[7] Infusion therapy of ketamine and lidocaine can be considered as a fourth-line treatment option in complex regional pain syndrome (CRPS), fibromyalgia, and traumatic spinal cord injury.^[5]

Advanced neuromodulation techniques like PNS and SCS have shown significant pain relief and better quality of life in failed back surgery syndrome, CRPS, or other neuropathic pain conditions.^[3,6] Furthermore, another new minimally-invasive ultrasound-guided hydrodissection technique has shown significant improvement in entrapment neuropathies like carpal tunnel syndrome and similar conditions.^[8]

RADIOFREQUENCY TECHNIQUE

Pain impulses are mediated through the nerves to reach their destination in the brain. Many techniques have been used to selectively destroy pain transmitting sensory nerves. Of the many techniques used, RF has proven itself as the most effective and is the most widely used. The last 70 years have witnessed the refining of the RF technique to avoid tissue charring, boiling, and uncontrolled tissue lesions.^[9] With the advent of thermocouple electrodes, temperature monitoring has become very accurate, and hence the RF lesion size can be planned precisely. Recently, there have been several advancements in electrode designs including curved and spring-type electrode

tips for specific purposes. Electrode systems have been refined so that accurate control of temperature and lesion size can be achieved.^[10] In fact, there are newer applications like pulsed RF, pulse-dose RF, and bipolar RF that appear to bring in newer options of lesioning.

It is appropriate to produce RF lesions when the pain is primarily nociceptive. Usually, they are found in facet joint arthralgia, chronic knee pain, sacroiliac joint pain, headache disorders and facial pain, and the intervertebral discs as in discogenic low back pain.^[11,12] Other indications for the application of RF are cancer-related pain, sympathetic mediated pain, and mixed pain of both nociceptive and sympathetic variety. RF techniques form a distinct arm in the management of intractable benign and malignant pain syndromes. They need to be performed with good background knowledge of anatomy, radiological imaging, and an appreciation of their place amongst a large armoury of interventions for treating chronic pain.

Several limitations are associated with singular RF lesioning. The RF lesion when done at a single point or done as a singular lesion can fail because of the following reasons: afferent fibres being in ventral root, the finite RF lesion being more localised than the local anaesthetic in a selective nerve root block, heat loss to nearby blood vessels, ectopic sprouting of ganglion cells, intersegmental nervous connections, sympathetic maintenance of pain, and placebo effects of prognostic blocks.

REGENERATIVE MEDICINE

Regenerative medicine in pain management is gaining importance as it has the potential to treat pain without the continuous use of analgesics. Regenerative therapies have been used to manage various chronic pain conditions like low backache due to degenerative intervertebral discs, pain arising from knee osteoarthritis, shoulder pain, neuropathic pain, etc. Biologically active materials, engineered tissues, and natural polymers provide a non-pharmacological alternative to managing chronic and inflammatory pain. With advancements in molecular biology, novel regenerative biomaterials have been designed to augment the healing process naturally and to reduce the adverse effects associated with conventional analgesic use.^[1]

Regenerative biomaterials

Biomaterials used for promoting tissue regeneration include natural polymers like hyaluronic acid, collagen, chitosan, and synthetic polymers such as polycaprolactone and polylactic-co-glycolic acid. They specifically act in bone and cartilage repair and in nerve repair. Scaffold pore design like collagen peptide (Pro-Hyp-Gly)-presenting hydrogels and adipose mesenchymal stem cell-derived tissue-engineered constructs are being used successfully for degenerative intervertebral discs that cause low backache.^[1]

Another promising therapy in regenerative medicine is the use of bioactive agents such as platelet-rich plasma (PRP) and growth factors like mesenchymal stem cells (MSCs). The ability to activate the intrinsic regenerative pathways and exert an anti-inflammatory effect has made PRP and MSCs one of the main pillars of regenerative medicine. Evidence from well-designed case-control or cohort studies on the use of PRP and MSCs in the lumbar facet joint and lumbar epidural and sacroiliac joint injections is currently described as level IV evidence.

Platelet-rich plasma

Autologous PRP is a processed liquid fraction of autologous peripheral blood with a platelet concentration above baseline. Platelets are the source of α -, δ -, and λ -granules, which are storage units for a wide range of components consisting of biologically active factors like growth factors, cytokines, lysosomes, chemokines, microparticles, and adhesion proteins that augment the synthesis of new connective tissue and aid in revascularisation. The main advantage of PRP includes its safety and indigenous preparation.^[13]

There are various techniques for harvesting PRP. Commonly, through an aseptic venipuncture, 20–60 mL of autologous blood is drawn and centrifuged. The resultant blood is divided into platelet-poor plasma, PRP, red blood cells, and white blood cells. After concentrating the resultant blood further, 3–6 mL of PRP is obtained. The recommended PRP concentration is 2.5–6 times higher than the plasma concentration.^[14]

The use of PRP has been shown to be effective in musculoskeletal disorders of the back, shoulder and spinal disorders, osteoarthritis, and patients with chronic complex and recalcitrant wounds.

Mesenchymal stem cells

MSCs are multipotent stem cells, multipotent progenitor cells, or marrow stromal cells found in the

bone marrow, lungs, adipose tissue, and other body tissues. MSCs have the ability to differentiate into osteogenic, chondrogenic, and adipogenic lineage. Recent studies have shown the use of MSCs in immunomodulation with low immunogenic potential.

MSC is harvested from the bone marrow and adipose tissue and is then expanded in cell cultures *in vitro*. Culture expansion is performed to reduce the heterogeneous MSC population. MSCs are then collected from the tissue culture flasks, trypsinised, centrifuged, pelleted, and resuspended in liquid ice-cold collagen fibronectin gel. The collagen fibronectin gel forms a soft gel at body temperature. This MSC mixture is then injected in the target tissue.^[14]

MSCs can alleviate discogenic lower back pain by modulating primary nociceptive pain and regenerating disc tissue. However, the survival of MSCs is a limiting factor for long lasting results.

Regenerative therapy using natural and synthetic biomaterials is a prudent alternative for chronic pain management. Studies comparing PRP and MSC with steroid injections have shown the former to be favourable and safer. Robust data and research on the efficacy of bioactive materials in regenerative medicine can help to incorporate their use in routine clinical practice.

REACTIVE OXYGEN SPECIES SCAVENGERS

Cellular functions such as oxidative phosphorylation result in reactive oxygen species (ROS) as byproducts. ROS when produced in excess causes tissue damage, inflammation, and pain. This has been postulated as a cause of development of neuropathic pain. A fairly new technique, ROS scavenging nanomaterials facilitates the elimination of pro-inflammatory cytokines and ROS in microglia and ameliorates allodynia.^[15]

NEWER APPLICATIONS OF ULTRASOUND IN CHRONIC PAIN INTERVENTIONS

Traditionally, MIPSI was taught and performed under fluoroscopy and computed tomography scan guidance. In fact, many pain physicians still solely rely on fluoroscopy for performing various MIPSI. However, in recent times, ultrasound has emerged as an alternative and excellent imaging tool for performing MIPSI. Furthermore, it also aids in the diagnosis of many musculoskeletal and neuropathic pain conditions that

we encounter in our daily practice. Ultrasound helps to avoid the radiation exposure that is associated with fluoroscopy and also allows to visualise the target structures, perform procedures in real-time, and avoid unintended damage to the surrounding structures.^[16] Another important aspect of ultrasound is that it has improved the safety, accuracy, and performance of various MIPSIs.^[17] Ultrasound application in MIPSIs can be briefly discussed in three parts: peripheral nerve, spine, and musculoskeletal interventions.

Ultrasound has revolutionised the management of peripheral neuropathy, be it post-traumatic, post-surgical, or even entrapment neuropathy. The morphology of the nerves, entrapment site, and neuroma, if any, can be precisely identified and targeted for interventional treatment including hydrodissection, pulsed RF neuromodulation, cryoablation, chemical ablation, or even PNS implantation.^[16,18,19] Ultrasound has emerged as an alternative tool in entrapment neuropathies like carpal tunnel syndrome. It has the added benefit of identifying other possible aetiologies like cyst, tenosynovitis, or others in case of entrapment neuropathy, whereas an electrodiagnostic study can only identify the neuropathy and not the cause. Another classic example of safety and accuracy in MIPSIs with ultrasound is stellate ganglion block. Ultrasound helps in the deposition of medication just below the prevertebral fascia, and avoids damage to the surrounding blood vessels, nerves, and oesophagus.^[16] Various other bedside procedures like peripheral nerve blocks, and coeliac plexus block are the added benefits of ultrasound in MIPSIs.

For spine interventions, fluoroscopy is still the imaging modality of choice. However, facet joint and sacroiliac joint procedures have been increasingly and accurately performed with ultrasound guidance.^[16] MIPSIs like cervical root blocks that reported catastrophic complications in the past have now re-emerged again only because of ultrasound which can detect radicular blood vessels and avoid intravascular injection.^[20]

Finally, coming to the musculoskeletal interventions like joints, bursa, tendon or ligaments, ultrasound undoubtedly is the imaging modality of choice. Dynamic examination, comparison with contralateral side, subsequent scanning, and comparison in the follow-up period following regenerative therapy are some very important and pertinent aspects in modern-day pain practice. The diagnostic utility of ultrasound in rotator cuff disorders, other joint

pathology, and even in inflammatory arthropathy plays a great role in early identification, and the avoidance of costly imaging modalities. Accurate needle placement for various joint interventions with real-time ultrasound, performing barbotage procedure in calcific tendinosis, or even precise regenerative medicine therapy in tendinosis are examples of some MIPSIs which can be performed safely, accurately, and quickly in the office setting, thereby saving time, money, and admission in the hospital.

ENDOSCOPIC SPINAL PROCEDURES

Endoscopic spinal procedures provide safe, direct, and targeted access to the pathology with less soft tissue disruption. The most common level for endoscopic spinal intervention is at the lumbosacral level, followed by the cervical and thoracic levels. There are two major indications for endoscopic spine surgery: disc herniation and stenosis.^[21]

The approach can vary:

Transforaminal lumbar/thoracic: This method refers to a posterolateral percutaneous approach to the disc or epidural space through the neural foraminal window. The most critical advantage of this approach is that it provides direct access to the pathology without requiring a large skin incision, wide muscle retraction, unnecessary bone resection, and general anaesthesia.^[22] With the 'inside-out' technique, the tip of the working cannula rests anterior and directly underneath the dural sac. With the 'outside-in' technique, the tip of the working cannula sits directly posterolateral to the dural sac in the neuroforamen.^[23]

Interlaminar approach: This refers to the percutaneous posterior or interlaminar approach to the epidural space or disc pathology. The approach is similar to that of open microscopic lumbar/thoracic decompression.

Anterior and posterior approaches for cervical spine: Targeting and disc decompression are relatively easier without thecal sac retraction in the anterior approach. In the case of foraminal disc herniation or foraminal stenosis in the cervical spine, the posterior percutaneous endoscopic cervical foraminotomy and disc decompression can be more effective.^[24]

Caudal/Trans-sacral approach: It involves insertion of the small fiberoptic endoscope or epiduroscope.

The last and most critical factor for categorisation is the property of endoscope used: percutaneous endoscope, microendoscope, biportal endoscope, and epiduroscope. The most commonly used system is full or percutaneous endoscopic system, which is characterised by (1) the use of a working channel and the optics in the same tubular device, (2) complete percutaneous approach with a small skin incision, and (3) utilisation of a monoportal approach with continuous saline irrigation.

Some endoscopic spine interventions have been commonly studied and applied in real practice. These include percutaneous endoscopic lumbar discectomy, percutaneous endoscopic decompression (PED) for lumbar lateral recess/foraminal stenosis, interlaminar PED for lumbar central/lateral recess stenosis, and percutaneous endoscopic cervical discectomy.^[22,23]

The levels of evidence vary according to the history of each endoscopic procedure. As far as evidence is concerned, only transforaminal endoscopic lumbar discectomy technique has been proven by some randomised trials.^[4,24] Incidental durotomy, increased cerebrospinal fluid pressure, and haematoma are the few common complications noted in endoscopic spinal procedures.^[21]

VERTEBRAL AUGMENTATION THERAPY

Vertebral augmentation therapy is an umbrella term that includes vertebroplasty and kyphoplasty. It is an established intervention for painful vertebral compression fractures of the spinal column, resulting in rapid onset of pain relief along with improvement in mobility and reduced disability.^[25]

These interventions are percutaneous image-guided invasive procedures in which acrylic bone cement is injected into the damaged vertebral body. The current indication for vertebroplasty is intractable non-radicular pain resulting from compression fractures due to osteoporosis, myeloma, vertebral metastases, and aggressive painful vertebral haemangioma, while the contraindications include bleeding disorder, unstable fracture, and lack of definable vertebral collapse.^[25]

Magnetic resonance imaging must be performed prior to vertebroplasty and focus is placed on persistent oedema or presence of a linear intracorporeal cavity containing gas or liquid, indicating a fracture non-

union, which is an indication for the absence of fracture healing.^[26]

The patient is in the prone position and the skin is incised under local anaesthesia, allowing the passage of a trocar to the anterior part of the vertebra. The targeted vertebra can be approached posteriorly in a transpedicular or parapedicular way, either unilaterally or bilaterally. Thereafter, polymethylmethacrylate (PMMA) cement is injected under fluoroscopic guidance. Possible mechanism of pain relief includes stabilisation of the fractured component and the destruction of nociceptive fibres during the exothermic reaction produced by polymerisation of PMMA.^[26]

Complications associated with percutaneous vertebroplasty include cement leakage, which can seep into the veins, paravertebral soft tissue, the intervertebral disc, or into the spinal canal.^[10] Other risks include increased risk of fractures of adjacent vertebrae, postoperative infections, fat embolism, and pulmonary embolism.^[27]

NEUROMODULATION

The International Neuromodulation Society defines neuromodulation as ‘the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.’^[28]

Neuromodulation can be invasive and non-invasive. Non-invasive techniques include (but are not limited to) transcranial magnetic stimulation, transcranial direct current stimulation, and vagus nerve stimulation. Common invasive technologies are SCS, dorsal root ganglion (DRG) stimulation, PNS, and deep brain stimulation [Table 1].

Although neuromodulation modalities act through different mechanisms, they share functional convergence by promoting neuroplasticity.^[29] This might involve both synaptic plasticity and functional modifications (e.g., ion channels) that can alter neuronal excitability.^[29,30]

SCS is the most common implantable neuromodulation therapy, and its use has substantially increased over the past two decades. The global market size of SCS devices is expected to reach US\$2.8 billion by 2025.^[31] SCS involves the placement of a subcutaneous implantable pulse generator connected to two electrodes with leads

Table 1: Various invasive neuromodulation technologies and their major applications

Invasive neuromodulation technology	Major indications
Spinal cord stimulation (SCS)	Failed back surgery syndrome Complex regional pain syndrome (CRPS) Neuropathic pain (including diabetic neuropathy) Vascular pain and peripheral vascular disease
Dorsal root ganglion (DRG) stimulation	Focal CRPS Neuropathic pain for hand, chest, abdomen, foot, knee, or groin (difficult to treat with SCS)
Peripheral nerve stimulation (PNS)	Peripheral neuropathies Headache
Deep brain stimulation (DBS)	CRPS Phantom limb pain Peripheral neuropathies Neurological disorders like Parkinson's disease
Restorative neurostimulation	Chronic mechanical low back pain
Intrathecal drug delivery (pump)	Cancer-related pain Spasticity

that travel into the epidural space posterior to the spinal cord dorsal columns. After trying the therapy for about a week (known as a 'trial'), a patient who has experienced a reduction in pain by at least half may choose to continue treatment with a permanent system. Many modes of stimulation are available with specific indications and distinct features like higher frequency stimulation, burst stimulation, closed loop stimulation, etc. Issues like funding, placebo effect, and reduced efficacy with time are the limiting factors.

Encouraging results with newer techniques like DRG stimulation and restorative neurostimulation^[32] indicate a bright future for the technologies ahead.

CONTROVERSIES IN THE INTERVENTIONAL SPINE PROCEDURES

Controversies exist with regard to the selection and preparation of patients, pharmacological agents used, the optimal time, threshold, and frequency of interventions. This does demand standardisation.

Among the route of approaches in interventional spine procedures for lumbar radiculopathy; interlaminar (IL), caudal, and transforaminal (TF) approaches are in practice. Controlled trials showed TF approach as the most effective for the radicular pain. Interlaminar epidural steroid injections with better anteriorly placed target specificity, gains the upper hand in many studies^[33-35] through literature reveals a few with contradictory data. There is no compelling evidence to use lumbar epidural steroid injections for the treatment of symptomatic spinal stenosis. Facet-mediated pain from the lumbar spine, is treated by medial branch blocks and subsequent radiofrequency ablation.^[36-38]

At the cervical spine, some studies favour transforaminal epidural injection as a safe approach, while others favour approaching the spine via at an angle of 70 degrees. Further randomised controlled trials are warranted to reveal the safety of selective nerve root block and transforaminal epidural steroid injection at the cervical spine. Another area of ongoing controversy is the use of particulate steroids in spinal interventional drug medication mixture. This does carry the risk of neurological deficits. Although specialised centres have replaced it with the non-particulate substitute, many centres still opt for it.

The optimal time, investigations, especially the coagulation profile, is a grey area from an interventional pain specialist's perspective, as universally accepted national protocols are yet to be developed. The practice of blending or cocktailing and compounding drugs for intrathecal delivery is not under the approval of any agency in India or outside. Alarming there are no medications currently marketed in India with the label 'for intrathecal use only'! Many of these off-label drug combinations and their dilutions need to be standardised for the safety of patients and practitioners.

SUMMARY

The field of pain medicine is rapidly evolving. RF technique, regenerative biomaterial, reactive oxygen species scavenger nanomaterial, PRP, MSCs, ultrasound-guided MIPS, endoscopic spinal procedures, vertebral augmentation therapy, and neuromodulation are some promising and upcoming modalities in chronic pain management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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