REVIEW

Radiofrequency for Chronic Knee Pain: A Literature Review

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Objective: This review aimed to explore the current applications of radiofrequency (RF) therapy in managing chronic knee pain and to compare different treatment strategies.

Methods: A comprehensive review of recent literature was conducted, concentrating on variations in target selection, guidance techniques, and treatment parameters that influence therapeutic outcomes.

Results: RF therapy is a minimally invasive and effective treatment for chronic knee pain, providing faster recovery compared with traditional interventions. However, differences in treatment options can lead to significant variability in the efficacy and safety.

Conclusion: A thorough understanding of the distinct characteristics of various RF therapy strategies is required for optimizing chronic knee pain management. Future research should emphasize systematic evaluation of these approaches to refine clinical practice and establish evidence-based pain management protocols.

Keywords: radiofrequency, chronic knee pain, pain management, treatment strategies

Introduction

Chronic knee pain is a widespread problem that affects overall health, reduces quality of life, and poses significant socioeconomic challenges. Although there are several conservative and surgical treatment options for chronic knee pain, their limitations and potential side effects complicate the selection of the most appropriate treatment.^{1,2}

Given these challenges, there is a growing interest in exploring innovative treatment options. One promising treatment is radiofrequency (RF) therapy, recognized for its effectiveness, minimally invasive nature, and rapid recovery in managing chronic knee pain.³ As technology advances and understanding of RF deepens, the growing body of literature reflects increasing research interest in the field. However, significant variations among RF therapy protocols, including differences in target selection, guidance techniques, and treatment parameters, may lead to diverse treatment outcomes. With the rising global incidence of chronic knee pain, there is a growing demand for effective, minimally invasive pain management strategies, positioning RF therapy as a promising option.⁴ Thus, it is essential to systematically evaluate and compare these methods. Figure 1 illustrates RF for chronic knee pain. This review aimed to discuss the current status of RF therapy in chronic knee pain and clarify the differences among various RF therapeutic strategies to provide valuable insights for clinical practice.

Search Strategy

A comprehensive literature search was conducted using PubMed, Embase, and the Cochrane Library databases to identify relevant studies on RF therapy for chronic knee pain. The selection process followed predefined inclusion and exclusion criteria. Studies were included if they were clinical trials, systematic reviews, or observational studies, assessing different RF modalities, treatment targets, and efficacy outcomes. Case reports, studies with insufficient data, and those unrelated to knee pain were excluded. Data extraction concentrated on study design, patient population, intervention details, outcome measures, and follow-up duration. To ensure methodological rigor, the quality of the

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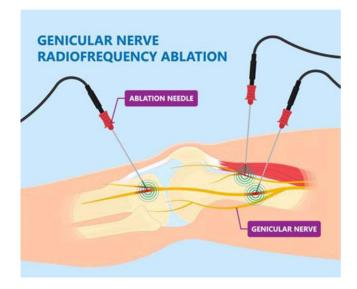


Figure I Schematic diagram of radiofrequency ablation targeting the genicular nerves.

included studies was assessed using validated tools, such as the Cochrane risk-of-bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies.

Basic Principles of RF Therapy

Mechanism of Generation and Transmission of RF Energy

RF therapy is a medical method that uses RF electromagnetic energy to target tissues, mainly through two mechanisms: capacitive coupling or resistive heating. RF energy is typically generated by RF generators, which produce an alternating current that induces high-frequency electromagnetic fields. These waves penetrate the tissue, where they cause oscillations of charged particles (mainly ions), leading to thermal effects that can alter tissue properties. The effectiveness of RF therapy is influenced by various factors, including frequency, power output, and duration of exposure. The penetration depth of different frequencies is different. Lower frequencies generally penetrate deeper structures, while higher frequencies affect shallower layers.⁵ Recent studies have demonstrated that RF therapy exerts non-thermal effects, promoting cell regeneration and modulating inflammatory responses, which may enhance the healing process across various conditions.^{6,7} Furthermore, technological advancements, such as microneedle fractional RF, have improved the precision of RF energy delivery, enabling targeted therapy with minimal impact on surrounding tissue.⁸ The application of RF therapy in pain management has been expanding, demonstrating notable success, especially in the treatment of chronic pain. RF therapy has several advantages over traditional medical or surgical treatments, including being less invasive, faster recovery, and fewer complications, making it a key option for pain management.^{9,10} Figure 2 illustrates how RF energy interacts with tissues.

Effects of RF Therapy on Nerves and Tissues

RF therapy has significant effects on both nerves and soft tissues. When RF energy is applied, it generates local heat, which can cause the tissue to solidify or vaporize, depending on the level of energy used. This heating effect is especially useful for treating pain syndromes because RF therapy can disrupt nerve conduction pathways and provide long-lasting pain relief. Additionally, RF therapy has an anti-fibrotic effect that can promote tissue remodeling and reduce scarring in conditions, such as keloids and hyperplastic scars. The modulation of inflammatory responses is another critical aspect of RF therapy has been explored for its effects on the nervous system, which can potentially improve neuroplasticity and recovery following nerve injuries. Overall, the multifaceted effects of RF therapy on both nerves and tissues highlight its versatility and potential as a therapeutic modality in various clinical applications.^{11,12} RF therapy

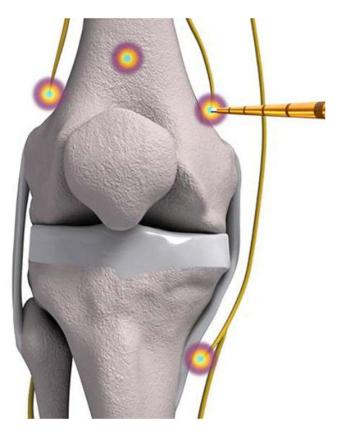


Figure 2 Schematic diagram of radiofrequency (RF) energy mechanisms in targeted tissue modulation.

modulates nociceptive signaling by inducing Wallerian degeneration in sensory nerves, thereby disrupting pain transmission and providing long-term analgesia.¹³ In addition to thermal effects, emerging evidence suggests that pulsed RF exerts neuromodulatory effects by altering gene expression in dorsal root ganglia, potentially contributing to prolonged pain relief.¹⁴

Application Status of RF Therapy in Chronic Knee Pain Clinical Research and Efficacy Evaluation

Recent clinical studies have concentrated on the use of RF to treat chronic knee pain, especially in conditions, such as osteoarthritis. These studies have shown varying degrees of effectiveness in pain relief and functional improvement. However, the results may be influenced by several factors, including the specific RF technology used and follow-up time. It is essential to standardize evaluation metrics across studies to provide a clearer understanding of the effectiveness of treatments. Furthermore, it is necessary to compare RF therapy with traditional pain management strategies, such as corticosteroid injections or physical therapy, to determine the relative benefits of RF interventions. Overall, while current literature supports the potential of RF treatment in managing chronic knee pain, further high-quality randomized controlled trials are needed to validate these findings and refine treatment protocols.^{3,15,16} In addition to thermal effects, emerging evidence suggests that pulsed RF exerts neuromodulatory effects by altering gene expression in dorsal root ganglia, potentially contributing to prolonged pain relief.¹⁷ A recent meta-analysis comparing RF therapy with intra-articular corticosteroid injections reported superior pain relief at six months in patients undergoing RF ablation, highlighting its potential as a longer-lasting intervention.¹⁸

Quantitative data from existing studies indicate that RF therapy achieves significant pain relief, with reported reductions in Visual Analog Scale (VAS) scores ranging from 30% to 70% at 3 to 6 months posttreatment. Additionally, functional improvement has been found, as reflected in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, demonstrating enhanced mobility and daily activities. Comparative analyses suggest that RF therapy provides longer-lasting analgesia than corticosteroid injections, accompanying by a lower incidence of adverse effects.

Most available studies on RF therapy for chronic knee pain have concentrated on short- to mid-term outcomes, with limited data on long-term efficacy. While current evidence supports the effectiveness of RF therapy in providing sustained pain relief for several months, the long-term durability of its effects remains unclear. Future research should incorporate extended follow-up periods to evaluate long-term clinical outcomes, potential pain recurrence, and any late complications associated with RF therapy.

Different RF Therapy Modalities

Various RF treatment modalities have been explored for their effectiveness in alleviating knee pain.¹⁹ Standard RF ablation, pulsed RF, low-temperature plasma RF, and bipolar water-cooled RF are commonly used techniques. Standard RF ablation has been shown to provide immediate pain relief by disrupting nerve conduction pathways, which can be particularly beneficial for patients with local pain. Conversely, pulsed RF operates at lower temperatures and minimizes tissue damage while achieving analgesic effects. This technique has attracted attention due to its safety and lower complication rate. Lowtemperature plasma RF is another innovative approach that utilizes ionized gas to target pain pathways and has shown promise in previous studies. Finally, bipolar water-cooled RF is known for its ability to provide a more consistent and controlled energy distribution, potentially leading to improved outcomes. Each RF modality has distinct advantages and limitations, requiring a tailored approach based on the patient's individual characteristics and pain mechanisms. Modern RF devices have been improved in terms of energy output accuracy and stability, emerging essential for optimizing treatment outcomes. Additionally, advancements in patient safety and comfort have been prioritized. For instance, RF devices with intelligent temperature control systems can continuously monitor and adjust temperature in real time, minimizing the risk of damage to surrounding tissues. This represents a significant advancement in RF-based pain management, enhancing both safety and efficacy. The comparison of these different RF technologies suggests that selecting the right approach should be tailored to the specific clinical needs and patient situation to achieve the best pain management outcomes.^{20–22} Water-cooled RF has gained attention due to its ability to create larger lesion areas with controlled temperature distribution, reducing the risk of thermal damage while ensuring effective nerve ablation.²³ Comparative studies indicate that pulsed RF may be preferable in certain cases due to its lower risk of neurodestruction and ability to preserve nerve function while modulating pain pathways.²⁴ Figure 3 illustrates how water-cooled RF interacts with tissues. Table 1 compares four RF therapy modalities for chronic knee pain management, outlining their mechanisms, operating temperatures ($60-90^{\circ}C$ to $\leq 42^{\circ}C$), clinical advantages, such as nerve preservation and precision control, limitations including tissue damage risk and high cost, and key supporting studies from 2018 to 2024.

Different Target Selection

The selection of RF treatment targets is crucial to determine the efficacy and safety of the procedure. Depending on the specific treatment context, RF therapy can be directed at various anatomical structures, involving nerves, ganglia, or tissues. For instance, in the management of knee osteoarthritis, RF treatment has shown to effectively target the nerves supplying the knee joint, such as the medial superior genicular nerve, medial inferior genicular nerve, lateral superior

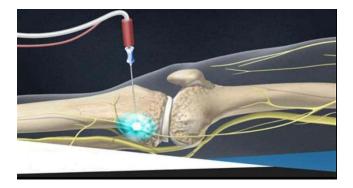


Figure 3 Schematic diagram of water-cooled radiofrequency (RF) system for controlled thermal ablation.

Modality	Mechanism	Temperature (°C)	Advantages	Limitations	Key Studies
Conventional RF ablation	Thermal neurolysis	60–90	Immediate analgesia; long-term effects (6–12 months)	Risk of adjacent tissue damage	Xiao LinShu et al, 2018 ²⁰
Pulsed RF	Non-thermal neuromodulation	≤42	Nerve preservation; lower complications	Shorter analgesia duration (3–6 months)	Huang RY et al, 2017 ²⁵
Low-temperature RF	lonized gas targeting inflammation	40–50	Precision control	Limited clinical data	Kapural et al, 2022 ¹¹
Bipolar water-cooled RF	Uniform energy distribution	50–60	Larger ablation area; reduced thermal injury	Higher equipment costs	Malik K et al, 2011 ²³

Table I Comparison of Radiofrequency Therapy Modalities

genicular nerve, lateral inferior genicular nerve, saphenous nerve, and the intermediate muscular branches of the femoral nerve. Targeting these nerves has been reported to be associated with significant pain relief and functional improvement.¹⁸ The genicular nerves have been identified as optimal targets for RF therapy in knee osteoarthritis, with studies showing significant improvements in pain and function following RF ablation of the superior medial, superior lateral, and inferior medial genicular nerves.²⁶ Emerging techniques, such as intra-articular RF ablation, were explored as alternatives to conventional genicular nerve ablation, providing potential benefits for targeting synovial inflammation.²⁷ The variability in target selection not only influences pain relief, but also is associated with potential complications, emphasizing the need for careful consideration in clinical practice. Overall, the differences in target selection underscore the need for a tailored approach to RF therapy to meet different clinical needs. Figure 4 depicts the specific nerves targeted in knee RFA procedures.

Advances and Applications of Guidance Technologies

Imaging guidance technology plays a critical role in RF treatments by enhancing treatment accuracy and safety and significantly improving patient outcomes.²⁸ Traditionally, RF procedures relied on anatomical markers for localization; however, the integration of advanced imaging methods, such as ultrasound, fluoroscopy, and magnetic resonance imaging (MRI) has changed this situation. Furthermore, robotic magnetic navigation-guided catheter ablation has emerged as a highly effective technique for achieving pulmonary vein isolation in patients with paroxysmal atrial fibrillation, being superior to traditional methods. This advance not only improves the accuracy of catheter placement, but also minimizes the risk of collateral damage to surrounding structures.²⁰ Furthermore, the application of real-time imaging during RF procedures allows for dynamic adjustments based on the patient's anatomy, thereby enhancing the overall safety and efficacy of treatment. The integration of ultrasound and fluoroscopy for RF needle placement has improved the accuracy of nerve targeting, leading to enhanced clinical outcomes and reduced procedural complications.²⁹ Real-time MRI guidance is an emerging modality for RF interventions, enabling detailed visualization of nerve structures and potentially enhancing the safety of RF treatments.³⁰

As these technologies continue to evolve, their integration into clinical practice is expected to further optimize outcomes for various RF applications, including pain management and cosmetic surgery.

Optimization and Individualization of Treatment Parameters

Optimizing the therapeutic parameters of RF therapy is essential to maximize therapeutic benefits and reduce adverse effects. Key parameters, such as power output, duration of application, and electrode type can significantly influence treatment outcomes. Recent studies have emphasized the importance of personalized treatment regimens that take into account patient-specific factors (eg, anatomy, pathology, and pain thresholds).¹⁰ Additionally, the exploration of novel RF technologies, such as IonicRFTM, has demonstrated promising results in enhancing the accuracy of energy delivery, which may improve patient outcomes and shorten recovery time.³¹ As the field of RF therapy continues to evolve, a focus on optimizing and individualizing treatment parameters is crucial to achieve the optimal outcomes for patients across a variety of clinical situations.

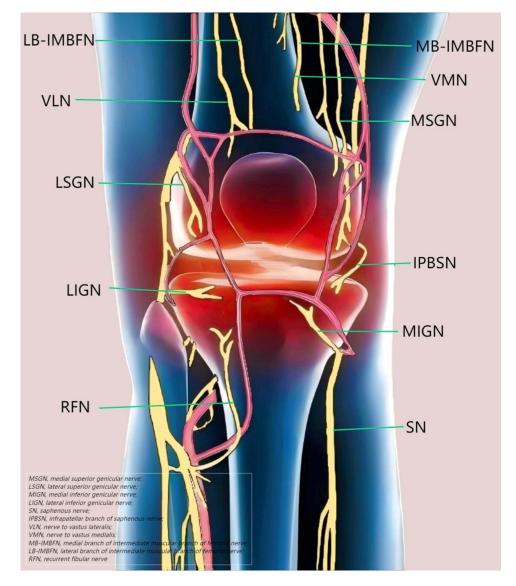


Figure 4 Schematic diagram of genicular nerves anatomy.

Abbreviations: MSGN, Medial superior genicular nerve; LSGN, Lateral superior genicular nerve; MIGN, Medial inferior genicular nerve; LIGN, Lateral inferior genicular nerve; SN, Saphenous nerve; IPBSN, Infrapatellar branch of saphenous nerve; VLN, Nerve to vastus lateralis; VMN, Nerve to vastus medialis; MB-IMBFN, Medial branch of intermediate muscular branch of femoral nerve; LB-IMBFN, Lateral branch of intermediate muscular branch of femoral nerve; RFN, Recurrent fibular nerve.

Indications and Contraindications for RF Therapy

RF therapy is a minimally invasive technique that is widely utilized in various pain management protocols. The prime candidates for this therapy are individuals suffering from chronic pain, particularly those who do not respond well to traditional drug treatments.¹⁰ For instance, patients with chronic knee osteoarthritis, postherpetic neuralgia, and other joint pain conditions may consider undergoing RF therapy. Additionally, this approach may alleviate the pain associated with certain internal diseases. The rationale for utilizing RF therapy in these patient populations lies in its ability to disrupt pain transmission pathways, thereby providing significant relief and improved quality of life for patients with persistent pain.

Despite its wide range of indications, RF therapy has certain contraindications and requires preventive measures. Patients with acute infections, bleeding disorders, malignancies, or allergies to local anesthetics are typically ineligible candidates for this treatment. Additionally, factors, such as pregnancy and implanted cardiac devices may influence the safety and efficacy of RF therapy. Prior to such an intervention, the doctor must conduct a thorough evaluation of the patient's medical history and physical examination results to ensure the safety of the treatment. Finally, careful

consideration of indications and contraindications for RF therapy is essential in clinical practice to achieve the best therapeutic effect.^{32,33}

Efficacy and Safety of RF Therapy

Efficacy Assessment Indicators

The efficacy of RF treatment can be evaluated according to the specific clinical situation using various indicators. Commonly assessed measures include pain relief or functional improvement. For instance, in the management of chronic pain, studies have shown that pain scores significantly reduce after treatment, and numerous patients experience remarkable pain relief that lasts for several months following RF treatment. Patient-reported outcomes, such as quality of life and satisfaction scores, also play a vital role in assessing the overall success of RF treatment, reflecting the importance of a holistic approach to evaluate treatment efficacy. Consequently, combining clinical, radiological, and patient-reported measures provides a comprehensive assessment of RF therapy's efficacy across various applications.^{34,35}

Evaluation of the Safety of RF Therapy

RF therapy is a minimally invasive treatment that has gained popularity due to its efficacy in managing various medical conditions, particularly tumors, heart diseases, and pain management. The assessment of RF safety relies primarily on the outcomes of clinical trials and subsequent observational studies. The current literature indicates that RF has a high overall safety profile; however, it is associated with risks and complications. Therefore, despite the high safety of RF, it is imperative for clinicians to thoroughly evaluate patients prior to treatment and maintain vigilant monitoring to mitigate potential risks and ensure patient safety.³⁶ Prior research indicated that RF therapy maintains analgesic effects for up to 12 months in some patients, although more effective treatments may be required to sustain long-term benefits.³⁷ While RF therapy is generally well tolerated, rare complications, such as neuritis and dysesthesia, have been reported, necessitating careful patient selection and post-procedural monitoring.³⁸

Potential Side Effects and Complications of RF Therapy

Although RF therapy is generally considered safe, it is not without risks. Potential side effects can range from mild to severe, depending on the anatomical location being treated and the patient's underlying condition. Common mild adverse effects include localized pain, swelling, and bruising at the treatment site, which typically resolve within a few days without intervention. More serious complications, though rare, may involve thermal injury to adjacent structures, potentially causing unintended nerve or blood vessel damage. Additionally, there is a risk of infection at the puncture site, necessitating strict adherence to aseptic techniques during the procedure. Long-term complications, such as scar tissue formation or fibrosis, may also occur and impact the function of the treated area. Therefore, clinicians must carefully weigh the benefits and risks of RF therapy and provide patients with thorough preoperative counseling on potential complications.³⁹

Comparison of the Efficacy of RF Therapy with Other Therapeutic Approaches

The comparison between RF therapy and traditional treatment strategies for chronic knee pain has become the focus of recent research. When juxtaposed with traditional drug therapy, RF therapy has exhibited superior results in terms of speed and duration of pain relief. Studies have shown that patients who receive RF therapy have greater improvements in pain and quality of life measures compared with patients who receive standard medical management. In addition, RF therapy has fewer side effects, which is a significant advantage over long-term drug use, which often produces adverse reactions and dependency problems. In addition, RF ablation is less invasive than surgery, resulting in faster recovery time and reduced medical costs due to shorter length of hospitalization and fewer postoperative care requirements. However, it is crucial to recognize that RF therapy may be inappropriate for all patients, as certain pathological conditions may influence its effectiveness. Compared with hyaluronic acid injections, RF therapy provides prolonged pain relief with fewer repeat interventions, making it a cost-effective option for managing chronic knee pain.⁴⁰ In a randomized controlled trial, RF ablation demonstrated superior pain relief and functional improvement over platelet-

rich plasma injections, suggesting its potential as a first-line interventional therapy for knee osteoarthritis.⁴¹ Therefore, the choice of personalized treatment based on the individual patient's situation is crucial to optimize treatment outcomes and improve patient satisfaction.

Combined Application of RF with Other Treatment Methods and Prospects

In the field of pain management, RF technology has been effectively combined with traditional methods, such as drug injections and physical therapy to improve pain relief. Studies have shown that pulsed RF combined with continuous RF can significantly improve the therapeutic effect of patients with refractory diseases, such as orbital neuralgia. In addition, the use of RF technology in nerve blocks and joint injections has shown promising results, particularly in chronic pain management. Combining RF therapy with other treatments has shown to enhance pain relief and improve patients' quality of life, providing a holistic approach for pain relief.

Comprehensive Analysis of the Effectiveness of RF Therapy for Chronic Knee Pain

RF therapy has become an important minimally invasive technique for the treatment of chronic knee pain, especially for patients with osteoarthritis and other degenerative diseases. Several studies have demonstrated the efficacy of RF therapy in reducing pain and enhancing functional outcomes. A systematic review highlighted that patients who underwent RF ablation had significantly lower pain scores after treatment, and several patients maintain pain relief for up to six months.¹⁷ This sustained effect is due to the method's ability to disrupt the transmission of pain signals by targeting specific nerves associated with the knee joint, resulting in long-lasting analgesia. In addition, the safety of RF therapy is commendable and the rate of serious complications is low, making it a viable option for patients who cannot tolerate more invasive surgical interventions. While these findings are promising, additional randomized controlled trials are needed to further confirm the long-term benefits and determine the optimal protocol for RF therapy in managing chronic knee pain.

Future Research Directions for RF

Development and Application of New Technologies

The development of RF technology has greatly promoted its application in various medical fields. Recent advances, including the introduction of new RF devices, such as IonicRFTM, aim to improve the precision and efficacy of the ablation process, indicating a shift toward more complex, targeted treatment modalities. In addition, the development of image-guided RF therapy has improved the accuracy of targeting pathological tissue, thus minimizing damage to surrounding healthy structures. As RF technology continues to advance, research should concentrate on optimizing these new tools to improve patient outcomes, reduce complications, and expand indications for RF therapy in a variety of settings.

Going forward, continuous advancements and innovations in RF technology may facilitate its wider clinical use. As biomedical engineering advances, the performance of RF devices is likely to improve, and research into combined applications will deepen, exploring the integration of RF with emerging therapeutic modalities, such as gene therapy and stem cell therapy. This exploration aims to achieve more personalized and accurate medical services, and more effectively meet patients' individual needs. In addition, as the mechanisms of RF therapy become clearer, more targeted combination treatment protocols are expected to be developed for specific conditions, further improving both efficacy and safety.

Necessity and Prospects of Multicenter Studies

Multicenter studies play a vital role in validating the efficacy and safety of RF therapy in diverse populations and clinical Settings. These studies contribute to the collection of larger datasets, improving statistical power and generalization of the findings. The collaborative nature of multicenter research also promotes an interdisciplinary approach, enabling the integration of various specialties in the management of complex cases, such as those involving coexisting medical conditions. Future research should prioritize multicenter designs to establish robust clinical guidelines and standardized RF therapy protocols, ultimately enhancing patient care and treatment outcomes.

Standardization and Normalization in Clinical Practice

Standardization of RF treatment protocols is essential to ensure consistent and high-quality care in different healthcare settings. Developing clear guidelines based on evidence from clinical trials and multi-center studies will help clinicians make informed decisions about the use of RF therapy in a variety of medical conditions. In addition, the development of "Good clinical practice recommendations" for RF procedures emphasizes the importance of adhering to standardized protocols to improve patient safety and treatment outcomes. As RF technology evolves, these guidelines will need to be constantly updated to incorporate new evidence and technological advances. In addition, training and education initiatives for healthcare providers will be critical to ensure the effective implementation of standardized practices, optimize patient outcomes, and reduce disparities in care.

In conclusion, RF treatment has become a key intervention for chronic knee pain, effectively alleviating symptoms and improving patients' quality of life. This review emphasized the integration of RF techniques with other therapeutic options, including pharmacotherapy, physical therapy, and surgical interventions. Each modality has unique advantages and limitations, and it is thus necessary to assess their relative effectiveness.

RF therapy, recognized for its non-invasive and proven efficacy, continues to expand in clinical applications, allowing for personalized treatment strategies for a variety of knee pain. However, significant differences in RF technologies, such as differences in frequency, application methods, depth of stimulation, and effective duration, can significantly affect patient care outcomes. This highlights the importance of tailoring approaches to optimize treatment outcomes.

Analysis of various treatment strategies reveals complex interactions among patient characteristics, pain mechanisms, and treatment outcomes. While RF ablation provides targeted relief through minimally invasive techniques, factors, such as the duration of pain relief, potential complications, and the patient's overall health must be considered when making clinical decisions. This highlights the need for a personalized treatment approach, where multidisciplinary collaboration can optimize outcomes.

The variability in RF therapy outcomes may be attributed to differences in target selection (eg, genicular nerves vs intraarticular application), energy settings (eg, pulsed RF vs continuous RF ablation), and guidance techniques (eg, fluoroscopy vs ultrasound). Furthermore, inconsistencies in patient selection criteria, follow-up time, and outcome measures contribute to heterogeneity across studies. Standardization of RF treatment protocols and the adoption of uniform efficacy metrics in the future research will be crucial for improving comparability and optimizing clinical recommendations.

Looking ahead, future research should concentrate on several key areas to further clarify the role of RF therapy in the management of chronic knee pain. Longitudinal studies evaluating the long-term efficacy and safety of RF therapy are critical. In addition, exploring potential pain relief mechanisms may yield insights to improve patient selection criteria and treatment options. Studying the synergies of combined RF with other treatment modalities may also enhance pain management strategies.

In summary, while RF treatment is a valuable tool for the management of chronic knee pain, a comprehensive approach that integrates diverse research and treatment strategies is crucial for advancing clinical practice. Ongoing exploration in this field will enhance the understanding and application of RF therapy, ultimately improving patient outcomes and formulating future pain management guidelines.

Disclosure

The authors report no conflicts of interest in this work.

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