Comparative Effectiveness Review
Number 247

Interventional Treatments for Acute and Chronic Pain: Systematic Review

Evidence Summary

Main Points

- Vertebroplasty is probably more effective than sham or usual care for vertebral compression fractures for reducing pain and improving function in older (Medicare-eligible) populations, but benefits are small. Benefits are smaller in sham compared with usual care controlled trials and larger in trials of patients with more acute symptoms.
- Kyphoplasty is probably more effective than usual care for vertebral compression fractures for reducing pain and improving function in older (Medicare-eligible) populations, but has not been compared against sham.
- Cooled radiofrequency denervation is probably moderately more effective for reducing pain and improving function than sham for sacroiliac pain in younger populations and similarly effective versus conventional radiofrequency for presumed facet joint pain and piriformis corticosteroid injection for piriformis syndrome may be similarly effective versus sham for pain at 1 week, but more effective for reducing pain at 1 month. These interventions were evaluated in younger (non-Medicare-eligible) populations, but findings can probably be applied to older populations.
- Research is needed to determine the benefits and harms of other interventional procedures addressed in this report. Ideally, future trials of interventional procedures should enroll older, Medicare-eligible populations, utilize sham controls, evaluate function as well as pain, include rigorous evaluation of harms, evaluate longer-term outcomes, and evaluate how benefits and harms according to demographic, clinical, and technical factors.

Agency for Healthcare Research and Quality

Background and Purpose

The purpose of this systematic review is to evaluate the effectiveness and harms of selected interventional procedures for acute and chronic pain in the Medicare population. The review focuses on procedures which are not currently covered for by the Centers for Medicare & Medicaid Services (CMS) but are relevant for and have potential utility for use in the Medicare population, or procedures that are covered by CMS but for which there is important uncertainty or controversy regarding use.

Methods

Electronic databases (Ovid® MEDLINE®, PsycINFO®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews) were searched through April 12, 2021 for relevant publications. Searches were supplemented by reviewing reference lists and a Federal Register Notice.

Randomized controlled trials (RCTs) of populations undergoing the designated interventional procedures for the specified conditions versus usual care, no treatment, placebo, or sham were selected using predefined criteria and dual review. Observational studies were eligible for assessment of rare, serious adverse events. This review focused on 10 interventional procedures for specific conditions:

1. Vertebral augmentation procedures (**vertebroplasty** and **kyphoplasty**) for pain due to vertebral compression fracture
2. **Cooled radiofrequency denervation** for degenerative back or hip pain and **pulsed radiofrequency denervation** for degenerative back pain
3. **Intradiscal and facet joint platelet-rich plasma** for presumed discogenic back pain
4. **Intradiscal stem cells** for presumed discogenic back pain
5. **Intradiscal methylene blue** for presumed discogenic back pain
6. **Intradiscal ozone** for radicular low back pain or nonradicular, presumed discogenic back pain (protocol modification to include intradiscal ozone plus corticosteroid)
7. **Sphenopalatine block** for trigeminal neuralgia or headache
8. **Occipital stimulation** for headache
9. **Piriformis injection** (local anesthetic, corticosteroid, and/or botulinum toxin) for piriformis syndrome
10. **Peripheral nerve stimulation** for ulnar, median, or radial neuropathy

The main outcomes were pain and function, and additional outcomes were quality of life, emotional function, global improvement, and harms. Outcomes were analyzed at 1 to 2 weeks, 2 to 4 weeks, 1 to 6 months, 6 to 12 months, and 12 months and longer. Meta-analyses were conducted for vertebroplasty versus no vertebroplasty (sham or usual care) and effects on pain, function, quality of life, and harms; analyses were conducted to assess how the control type, duration of symptoms, and other factors impacted findings. Otherwise, meta-analyses were not conducted due to small number of studies,

methodological limitations, and study heterogeneity. The magnitude of effects was classified as small, moderate or large using previously defined criteria, and strength of evidence was assessed.

Results

The review included 37 RCTs on the comparative effectiveness of interventional therapies for acute and chronic pain. Evidence was most robust for vertebroplasty, followed by kyphoplasty and radiofrequency denervation, and limited for other interventions. Evidence on vertebroplasty and kyphoplasty was highly relevant to populations eligible for Medicare, based on mean age of over 65 years in the trials. For other interventions, patients were younger and populations eligible for Medicare for reasons other than older age were not addressed. Main findings (focusing on effects on pain and function) are summarized by interventional procedure.

Vertebral Augmentation Procedures

Vertebroplasty

- Vertebroplasty for vertebral compression fracture (13 trials, N=1685) was associated with a small reduction in pain intensity versus sham vertebroplasty or usual care at 1 to 2 weeks (10 trials, N=1093), 1 to 6 months (10 trials, N=1094), 6 to 12 months (8 trials, N=993), and 12 months and longer (9 trials, N=965), and a moderate reduction at 2 to 4 weeks (8 trials, N=918) (strength of evidence [SOE]: low at 1 to 2 weeks, moderate at other time points). Restricting to sham vertebroplasty controls (5 trials, N=536) tended to decrease benefits (no difference at 1 to 2 weeks and small at other time points), but the difference between sham and usual care trials was only statistically significant at 2 to 4 weeks (p for interaction=0.01). Benefits also tended to be larger in trials of patients with more acute compared with less acute pain, but differences were not statistically significant.
- There was insufficient evidence to determine effects of vertebroplasty on function at 1 to 2 weeks (7 trials, N=743), due to marked inconsistency between sham trials (no benefit) and usual care trials (small benefit). Vertebroplasty was associated with a small improvement versus sham or usual care in function at 2 to 4 weeks (6 trials, N=708), 1 to 6 months (7 trials, N=637), 6 to 12 months (6 trials, N=690), and ≥12 months (6 trials, N=612). (SOE: insufficient for 1 to 2 weeks, moderate for 1 to 6 months and 12 months and longer, and high for 2 to 4 weeks and 6 to 12 months).
- Vertebroplasty was not associated with increased risk of incident vertebral fracture at 12 months and longer (7 trials, N=826); evidence on serious adverse events was sparse and imprecise but did not indicate increased risk (SOE: moderate for vertebral fracture, low for serious adverse events).
- Three trials that conducted within-study subgroup analyses found no interaction between duration of symptoms and effects of vertebroplasty and one trial found no interaction between sex or prior vertebral fracture and effects of vertebroplasty.

- A stratified analysis of vertebroplasty trials found no interaction between polymethyl methacrylate (PMMA) volume and effects of vertebroplasty.

Kyphoplasty

- Kyphoplasty for vertebral compression fracture (2 trials, N=434) was associated with large reductions in pain and moderate to large improvement in function versus usual care at 1 week and 1 month in patients with or without cancer. No trial compared kyphoplasty against sham (SOE: low for function at 1 week; moderate for pain and for function at 1 month).
    - In 1 trial (N=300) of patients without cancer, effects on pain and function were small to moderate at 3 months to 2 years (SOE: low).
- Evidence on incident or worsening vertebral fracture was inconsistent and imprecise, based on two trials (N=434) (SOE: insufficient).

Cooled Radiofrequency

- Cooled radiofrequency denervation for sacroiliac pain was associated with a moderate to large reduction in pain and small to large improvement in function versus sham radiofrequency at 1 month (2 trials, N=79); improvements in pain and function at 3 months were moderate (1 trial, N=28) (SOE: moderate for pain and function at 3 months; low for function at 1 month).
- Cooled radiofrequency denervation for presumed facet joint pain was associated with a small, nonstatistically significant reduction in pain versus conventional radiofrequency at 6 months and no difference in function (1 trial, N=43); there were no differences at earlier (1- or 3-month) followup (SOE: low).

Pulsed Radiofrequency

- Evidence was insufficient to assess pulsed radiofrequency denervation for presumed facet joint pain versus sham denervation (1 trial, N=40) or continuous radiofrequency denervation (1 trial, N=40) (SOE: insufficient).

Intradiscal Platelet-Rich Plasma

- Evidence was insufficient to assess intradiscal platelet-rich plasma injection for presumed discogenic back pain (1 trial, N=58) (SOE: insufficient).
- There were no differences between intradiscal platelet-rich plasma injection and saline injection in harms, including no serious adverse events, at up to 3 years following treatment (SOE: low).

Intradiscal Stem Cell Injection

- Evidence was insufficient to assess intradiscal stem cell injection for presumed discogenic back pain (1 trial, N=100) (SOE: insufficient).

Intradiscal Methylene Blue

- Intradiscal methylene blue for presumed discogenic back pain (1 trial, N=81) was associated with no difference versus sham at 6 weeks and 3 months. Evidence was insufficient to determine effects of intradiscal methylene blue at 6 months (2 trials, N=153, with conflicting results) and 12 months or longer (1 trial, N=72) (SOE: low for no difference at 6 weeks and 3 months; insufficient for 6, 12, and 24 months).

Intradiscal Oxygen-Ozone

- Evidence was insufficient to assess intradiscal oxygen-ozone for radicular low back pain (1 trial, N=159) (SOE: insufficient).
- No trial evaluated intradiscal oxygen-ozone injection without corticosteroid or oxygen-ozone injection for presumed (nonradicular) discogenic low back pain.

Sphenopalatine Block

- Evidence was insufficient to assess sphenopalatine block versus sham for headache (1 trial, N=41) (SOE: insufficient).

Occipital Nerve Stimulation

- Evidence was insufficient to assess occipital nerve stimulation versus sham stimulation for headache (1 trial, N=157) (SOE: insufficient).
- For headache, occipital nerve stimulation with adjustable parameters versus usual care at 3 months was associated with a small, nonstatistically significant reduction in pain intensity, moderate decrease in headache related disability, and decrease in headache days (1 trial, N=67) (SOE: low for headache related disability and headache days; insufficient for pain).
- Lead migration occurred in 14 to 24 percent of patients (2 trials, N=224), serious device-related complications requiring hospitalization occurred in 5.9 percent of patients (1 trial, N=67), and persistent pain/numbness at implantation site in 13 percent of patients (1 trial, N=157) (SOE: low).
- One trial (N=67) found occipital nerve stimulation with adjustable parameters associated with superior outcomes compared with stimulation using preset parameters.

Piriformis Injection

- One trial (N=50) found piriformis injection with corticosteroid and local anesthetic for piriformis syndrome associated with no difference versus local anesthetic alone in pain at rest at 1 week; piriformis injection was associated with a moderate reduction in pain at rest versus local anesthetic at 1 month (SOE: low for no difference at 1 week and for benefit at 1 month).
- Evidence was insufficient to assess piriformis injection with botulinum toxin.

Peripheral Nerve Stimulation

Evidence was insufficient to assess peripheral nerve stimulation for upper extremity peripheral neuropathic pain (SOE: insufficient).

Limitations

We excluded non-English–language articles and did not search for studies published only as abstracts. We did not conduct statistical and graphical methods for assessing for small sample effects (a potential marker for publication bias) due to small numbers of trials and heterogeneity in study design methods, patient populations, and outcomes.

The evidence base had important limitations. For vertebroplasty, trials varied with regard to patient selection criteria (e.g., duration of pain), technical factors (e.g., volume of PMMA), and sham interventions (e.g., sites of local anesthetic infiltration). In addition, the usual care interventions were not well standardized or defined. Pain and function were the most commonly reported outcomes, with limited evidence on quality of life, health status (e.g., Short-Form 36 Health Survey [SF-36]), mood, analgesic (including opioid) use, and other outcomes. Data on harms were relatively sparse and inconsistently reported. The trials were not designed to evaluate how benefits and harms varied in subgroups defined by demographic, clinical, or technical factors. Data on long-term (≥1 year) outcomes was relatively limited.

For the other interventional procedures evaluated in this report, the major limitation was the small numbers of trials, with important methodological shortcomings (e.g., high attrition, lack of intent-to-treat analysis, baseline group differences, small sample sizes, inadequate or unclear randomization or allocation concealment methods, open-label design, and use of unvalidated outcome measures) in almost all eligible studies.

Implications and Conclusions

Vertebroplasty is probably effective at reducing pain and improving function in older patients with vertebral compression fractures, but benefits were small (**Table A**). Effects of vertebroplasty were reduced in sham versus usual care controlled trials and larger in trials of patients with more acute symptoms. However, it is not possible to attribute differences entirely to the control type used, given substantial other differences across trials with regard to duration of pain, PMMA volume, requirement for bone edema on magnetic resonance imaging (MRI), and other factors. Furthermore, there were not statistically significant interactions between control type and effects on pain intensity at other time points, there was heterogeneity among the sham-controlled trials, and there is controversy regarding potential therapeutic effects associated with different sham procedures. To address outstanding questions regarding vertebroplasty, future trials should ideally include sham as well as usual care control groups and include patients with hyperacute (e.g., <3 weeks) and acute (e.g., 3 to 6 weeks) symptoms. Trials that include sham interventions with and without periosteal local anesthetic could also help clarify

whether the sham treatment itself is associated with therapeutic benefits. Kyphoplasty is probably more effective than usual care for vertebral compression fractures in older patients (**Table A**). However, an important limitation of the evidence is the absence of sham-controlled trials of kyphoplasty. Until such evidence becomes available, kyphoplasty may be considered as an alternative to vertebroplasty, particularly in patients with more vertebral body collapse, as the purpose of kyphoplasty is to help restore vertebral body morphology.

Cooled radiofrequency denervation is probably more effective than sham denervation for sacroiliac pain, cooled radiofrequency may be as effective as conventional radiofrequency for presumed facet joint pain, occipital nerve stimulation may be more effective than usual care for headache, and piriformis corticosteroid injection may be more effective than sham for piriformis syndrome (**Table A**). Evidence on harms was limited, but lead migration was common following occipital nerve stimulation placement. Although evidence on these interventions was limited to younger (below the age for Medicare eligibility) populations, there is no obvious reason that findings would not apply to older patients. Evidence on the other interventions and conditions addressed in this review is sparse and insufficient, and additional research is needed to determine benefits of harms (**Table A**). To ideally inform Medicare coverage decisions, future trials of interventional procedures should enroll older, Medicare-eligible populations, utilize sham controls, evaluate function as well as pain, include rigorous evaluation of harms, evaluate longer-term outcomes, and evaluate how benefits and harms according to demographic (age, sex, race/ethnicity), clinical (pain severity, pain duration, use of opioids, psychiatric or medical comorbidities), or technical (dose, intensity, duration, frequency, techniques) factors.

Table A. Interventional pain therapies for acute and chronic pain*

Intervention	Condition	**Pain** 1 to 2 Weeks Effect Size SOE	**Pain** 2 to 4 Weeks Effect Size SOE	**Pain** 1 to 6 Months Effect Size SOE	**Pain** 6 to 12 Months Effect Size SOE	**Pain** ≥12 months Effect Size SOE	**Function** 1 to 2 Weeks Effect Size SOE	**Function** 2 to 4 Weeks Effect Size SOE	**Function** 1 to 6 Months Effect Size SOE	**Function** 6 to 12 Months Effect Size SOE	**Function** ≥12 Months Effect Size SOE
Vertebroplasty vs. sham or usual care	Vertebral compression fractures	Small† +	Moderate‡ ++	Small ++	Small ++	Small ++	Insufficient§	Small +++	Small ++	Small +++	Small ++
Kyphoplasty vs. usual care	Vertebral compression fractures	Large ++	Large ++	Moderate +	Moderate +	Small +	Moderate +	Moderate to large ++	Moderate +	Moderate +	Small +
Cooled radiofrequency ablation vs. sham	Sacroiliac pain	No evidence	Moderate to large ++	Moderate ++	No evidence	No evidence	No evidence	Small to large +	Moderate ++	No evidence	No evidence
Cooled vs. conventional radiofrequency denervation	Presumed facet joint pain	No evidence	None +	None +	Small +	No evidence	No evidence	None +	None +	None +	No evidence
Pulsed radiofrequency denervation vs. sham‖	Presumed facet joint pain	No evidence	No evidence	No evidence	Insufficient	Insufficient	No evidence	No evidence	No evidence	Insufficient	Insufficient
Pulsed vs. conventional radiofrequency denervation‖	Presumed facet joint pain	No evidence	No evidence	No evidence	Insufficient	Insufficient	No evidence	No evidence	No evidence	Insufficient	Insufficient

Intervention	Condition	**Pain** 1 to 2 Weeks Effect Size SOE	**Pain** 2 to 4 Weeks Effect Size SOE	**Pain** 1 to 6 Months Effect Size SOE	**Pain** 6 to 12 Months Effect Size SOE	**Pain** ≥12 months Effect Size SOE	**Function** 1 to 2 Weeks Effect Size SOE	**Function** 2 to 4 Weeks Effect Size SOE	**Function** 1 to 6 Months Effect Size SOE	**Function** 6 to 12 Months Effect Size SOE	**Function** ≥12 Months Effect Size SOE
Cooled or pulsed radiofrequency denervation vs. sham, usual care, or conventional radiofrequency denervation	Degenerative hip pain	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Facet joint platelet-rich plasma vs. sham or usual care	Presumed facet joint pain	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Intradiscal platelet-rich plasma vs. sham	Discogenic back pain	Insufficient	Insufficient	Insufficient	No evidence	No evidence	Insufficient	Insufficient	Insufficient	No evidence	No evidence
Intradiscal stem cells vs. control*	Discogenic back pain	No evidence	Insufficient	Insufficient	Insufficient	Insufficient	No evidence	Insufficient	Insufficient	Insufficient	Insufficient
Intradiscal methylene blue vs. sham	Discogenic back pain	No evidence	No evidence	None +	None +	Insufficient	No evidence	No evidence	Small +	None +	Insufficient
Intradiscal ozone + corticosteroid vs. corticosteroid	Discogenic back pain	Insufficient	No evidence	Insufficient	Insufficient	No evidence	Insufficient	Insufficient	No evidence	Insufficient	Insufficient
Sphenopalatine block vs. control	Trigeminal neuralgia	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Sphenopalatine block vs. control[‖]	Chronic migraine	No evidence	Insufficient	No evidence	Insufficient	No evidence	No evidence	Insufficient	No evidence	Insufficient	No evidence

Intervention	Condition	**Pain** 1 to 2 Weeks Effect Size SOE	**Pain** 2 to 4 Weeks Effect Size SOE	**Pain** 1 to 6 Months Effect Size SOE	**Pain** 6 to 12 Months Effect Size SOE	**Pain** ≥12 months Effect Size SOE	**Function** 1 to 2 Weeks Effect Size SOE	**Function** 2 to 4 Weeks Effect Size SOE	**Function** 1 to 6 Months Effect Size SOE	**Function** 6 to 12 Months Effect Size SOE	**Function** ≥12 Months Effect Size SOE
Occipital nerve stimulation vs. sham[‖]	Chronic migraine	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence
Occipital nerve stimulation vs. usual care	Chronic migraine	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence
Piriformis injection with corticosteroid plus local anesthetic vs. corticosteroid plus local anesthetic, or sham[‖]	Piriformis syndrome	None +	Moderate +	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Peripheral nerve stimulation vs. sham	Ulnar, median or radial neuropathy pain	No evidence	No evidence	Insufficient	No evidence	No evidence	No evidence	No evidence	Insufficient	No evidence	No evidence

Abbreviations: SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.

* Grey shading indicates insufficient or no evidence

[†]There was no difference in trials with sham control and moderate difference in trials with usual care control, but no statistically significant interaction between control type and effects on pain (p for interaction=0.14)

[‡]There was a small difference in trials with sham control and large difference in trials with usual care control, with a statistically significant interaction between control type and effect on pain (p for interaction <0.01)

[§]There was no difference in trials with sham control and small difference in trials with usual care control, but no statistically significant interaction between control type and effects on pain (p for interaction=0.19)

[‖]Poor-quality trials excluded

Full Report

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