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The Effectiveness of Intraosseous Basivertebral Nerve Radiofrequency Ablation for the Treatment of Vertebrogenic Low Back Pain: An Updated Systematic Review with Single-Arm Meta-analysis

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Abstract

Objective. To provide an estimate of the effectiveness of basivertebral nerve (BVN) radiofrequency ablation (RFA) to treat vertebrogenic low back pain (LBP). **Design**. Systematic review with single-arm meta-analysis. **Population**. Persons ≥18 years of age with chronic LBP associated with type 1 or 2 Modic changes. **Intervention**. Intraosseous BVN RFA. **Comparison**. Sham, placebo procedure, active standard care treatment, or none. **Outcomes**. The proportion of patients treated with BVN RFA who reported ≥50% pain score improvement on a visual analog scale or numeric rating scale. The main secondary outcome was ≥15-point improvement in Oswestry Disability Index score. **Methods**. Three reviewers independently assessed articles published before December 6, 2021, in MEDLINE and Embase. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework was used to evaluate the overall quality of evidence. **Results**. Of the 856 unique records screened, 12 publications met the inclusion criteria, representing six unique study populations, with 414 participants allocated to receive BVN RFA. Single-arm meta-analysis showed a success rate of 65% (95% confidence interval [CI] 51–78%) and 64% (95% CI 43–82%) for ≥50% pain relief at 6 and 12 months, respectively. Rates of ≥15-point Oswestry Disability Index score improvement were 75% (95% CI 63–86%) and 75% (95% CI 63–85%) at 6 and 12 months, respectively. **Conclusion**. According to GRADE, there is moderate-quality evidence that BVN RFA effectively reduces pain and disability in most patients with vertebrogenic LBP. Further high-quality studies will likely improve our understanding of the effectiveness of this procedure.

Key Words: Endplate; Vertebrogenic, Discogenic; Modic; Ablation

Introduction

Intraosseous basivertebral nerve (BVN) radiofrequency ablation (RFA) has gained attention as a target-specific treatment for pain arising from pathological degeneration

of the vertebral endplates (VEPs) of the lumbosacral spine. At lumbar levels, the BVN is a paired branch of the bilateral sinuvertebral nerves that passes through the basivertebral foramen at the posterior aspect of the vertebral body

to provide sensory innervation to the vertebral body and VEPs. Effective neurotomy of the BVN can be accomplished through careful transpedicular access under either fluoroscopy or computed tomography (CT) guidance, followed by ablation at a location 30–50% of the sagittal plane distance from the posterior cortex of the vertebral body [1, 2]. Since 2017, this treatment has been studied exclusively in populations believed to have pain arising from pathologically degenerated VEPs as evidenced by Modic 1 (MC1) and 2 changes (MC2) on magnetic resonance imaging (MRI) [1, 3–12].

Although BVN RFA is a relatively new treatment, studies investigating the pathological degeneration of the discovertebral complex began in the early 1990s. Initially, scientists postulated that the BVN might be implicated in nociception in some cases of chronic low back pain (LBP) after histological studies demonstrated that the BVN contained numerous neuropeptide Y– and PGP 9.5–positive nerve fibers [13, 14]. The case for VEP-driven pain was further strengthened when immunohistochemical analysis of the BVN demonstrated an abundance of nerve fibers in the BVN that stained positive for substance P, CGRP, and PGP 9.5 [15, 16]. Compared with controls, surgical specimens from patients with a history of chronic LBP and advanced disc degeneration were noted to have increased nociceptor density in the endplate region and adjacent vertebral body. This same pattern was observed in surgical specimens taken from patients with a history of "discogenic" LBP, where greater concentrations of PGP 9.5– and tumor necrosis factor (TNF)–immunoreactive cells near the VEPs were found compared with controls [17]. These histological findings were strongly associated with MC1 and MC2 findings on MRI.

Modic type 1 and 2 marrow changes are a radiographic manifestation of the underlying inflammatory response and fatty infiltration, respectively. These occur in the presence of prolonged mechanical stress and endplate failure, coupled with the ensuing chemical sensitization from leakage of proinflammatory cytokines from the intervertebral disc [25]. The epidemiology and clinical significance of MC1 and MC2 lesions have been discussed and debated ad nauseum [2, 18–24]. Modic changes are observed in the context of advanced disc degeneration or disc herniation [18, 19], but even stronger associations exist with endplate defects in large population-based cohort studies [20, 21]. Endplate injuries can be classified according to their pathoanatomic features: 1) avulsion of annulus fibrosus ("annulus") fibers from their insertion at the cartilage endplate (tidemark avulsion), 2) separation of endplate from the bone (cartilage endplate avulsion), 3) degeneration of the bone–annulus interface (rim degeneration), and 4) traumatic or erosive ingrowth of nucleus pulposis material through the endplate (nodal) [22]. Although of unclear clinical significance, these descriptors help paint a more detailed picture of the disc–endplate relationship. Endplate injuries are likely the predisposing event that, in a subset of individuals, results in chronic inflammation, high bone turnover, and fatty infiltrative changes that can be observed with conventional T1- and T2-weighted MRI sequences [23]. This cascade of events can culminate in what is often referred to as "vertebrogenic" LBP, with nociception transmitted predominantly via the BVN.

Objectives and Rationale

Given the recent increase in studies investigating the treatment of vertebrogenic LBP, the present systematic review was performed to provide an updated estimate of the effectiveness of BVN RFA for the treatment of this condition. We also calculate the aggregate rates of treatment success defined by clinically important pain and functional improvement observed thus far in published clinical trials and cohort studies.

Methods

Protocol and Registration

This systematic review is an update of a prior systematic review for which the protocol was registered with PROSPERO (ID:CRD42020192001) on July 14, 2020. No changes were made to the review methodology, but to avoid redundancy, a ≥15-point Oswestry Disability Index (ODI) threshold was chosen to measure functional improvement [24]. A 15-point ODI improvement is a robust threshold that exceeds the known minimum clinically important difference for chronic LBP [25, 26]. The methods and results are reported in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [27].

Eligibility Criteria
Population
The population of interest was adults 18 years of age or older with chronic LBP associated with MC1 and MC2 changes on MRI.

Intervention
The intervention considered was intraosseous BVN RFA.

Comparison
Sham, placebo procedure, active standard care treatment, or none.

Outcome
The primary outcome considered for this review was the proportion of individuals with ≥50% pain improvement on the visual analog scale (VAS) or numeric rating scale (NRS). Secondary outcomes included ≥15-point improvement in ODI score and ≥2-point improvement in NRS score. Outcomes reported at any time point were included.

Studies

Both randomized controlled trials (RCTs) and observational study designs (nonrandomized comparative studies and single-group observational studies) were included. Non–English language articles and case reports were excluded. No restrictions were placed on the publication date.

Information Sources and Search Strategy

The databases MEDLINE and Embase were searched from inception up through December 6, 2021. MEDLINE was queried with the following terms:

("Basivertebral nerve ablation"[tiab] OR "BVN ablation"[tiab] OR "catheter ablation"[MeSH Terms] OR verteblation[tiab] OR "radiofrequency neurotomy"[tiab] OR "radiofrequency neurotomies" [tiab] OR "radiofrequency ablation"[tiab] OR "radiofrequency ablations" [tiab]) AND ("low back pain"[mesh] OR "low back pain"[tiab] OR CLBP[tiab] OR vertebrogenic[tiab] OR "modic change*"[tw] OR "disc degeneration"[All Fields] OR "endplate degeneration"[tiab] OR "endplate inflammation"[tiab] OR "disc inflammation"[tiab] OR "fatty bone marrow"[tiab] OR "fibrous bone marrow"[tiab] OR "endplate disruption"[tiab]).

Embase was queried with the following terms:

('radiofrequency ablation'/exp OR ('basivertebral nerve ablation':ab,ti,kw OR 'bvn ablation':ab,ti,kw OR 'catheter ablation':ab,ti,kw OR verteblation:ab,ti,kw OR 'radiofrequency neurotomy':ab,ti,kw OR 'radiofrequency neurotomies':ab,ti,kw OR 'radiofrequency ablation':ab,ti,kw OR 'radiofrequency ablations':ab,ti,kw OR 'radio frequency ablation':ab,ti,kw OR 'rfa therapy':ab,ti,kw OR 'rfa therapies':ab,ti,kw)) AND ('low back pain'/exp OR ('low back pain':ab,ti,kw OR clbp:ab,ti,kw OR vertebrogenic:ab,ti,kw OR 'modic change*':ab,ti,kw OR 'disc degeneration':ab,ti,kw OR 'endplate degeneration':ab,ti,kw OR 'endplate inflammation':ab,ti,kw OR 'disc inflammation':ab,ti,kw OR 'fatty bone marrow':ab,ti,kw OR 'fibrous bone marrow':ab,ti,kw OR 'endplate disruption':ab,ti,kw)).

An experienced librarian developed the search strategy. One author (AC) performed the search, and the search was confirmed for accuracy and reproducibility by a second author (TC). Additional eligible records were sought from the cited references of retrieved publications.

Study Selection

Two authors (AC and TC) independently assessed each abstract for eligibility. Any disagreements about inclusion were resolved by a third reviewer (ZM). Publications selected for full-text review were further assessed for inclusion by two authors (AC and TC), with disagreements resolved by a third reviewer (ZM).

Data Items and Collection

The following information was extracted from each study: 1) outcome measures for VAS/NRS and ODI, as well as any information related to pain medication usage or healthcare utilization; 2) bibliographic details; 3) study design; 4) selection criteria; 5) technical details of the procedure; and 6) funding and author disclosures. If data considered critical to the research questions were missing from included studies, attempts were made to contact author groups to obtain this information.

Risk of Bias and Methodological Assessment

The quality of evidence across outcomes was evaluated with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system [32]. Accordingly, risk of bias, imprecision, inconsistency, indirectness, and publication bias were all assessed. Disagreements about determinations of evidence quality according to GRADE were resolved by consensus decision. Our previous systematic review included a GRADE evidence profile based on calculations of between-group success measurements for the included RCTs, and this was again planned for the present review.

Summary Measures and Synthesis of Results

The primary outcome of interest was the percentage of participants reporting ≥50% pain improvement, and the main secondary outcome of interest was ≥15-point ODI improvement after BVN RFA. A between-group comparison of categorical success rates with calculated relative risk and risk difference was planned. Conventional pairwise and single-arm meta-analysis was also planned for this review if the collected data were found to be sufficient for such analysis.

Meta-analyses were planned to examine the following binary outcome variables (yes/no) over time points of 6 months, 12 months, 24 months, and 60 months: 1) proportions of patients reporting ≥15-point ODI improvement and 2) proportions of patients reporting ≥50% NRS/VAS improvement. Proportions and their standard errors of the included studies were used to calculate a pooled effect size (ES) and its 95% confidence interval (CI) in each meta-analysis. A random-effects model was used for all meta-analyses, as heterogeneity was expected in observational studies [28], which was also verified by heterogeneity and I^2 statistics [29]. Specifically, the calculations were performed with (inverse-variance) Freeman-Tukey double arcsine transformation [30, 31] and the exact CIs for the ESs of individual studies [32]. Forest plots were produced for the data at 6 months and 12 months to illustrate the ESs of individual studies, as well as the pooled ES from those studies [28]. Furthermore, line graphs were constructed to visualize ESs over the time points. Publication bias was assessed with Egger's test [33, 34]. Funnel plots were not used, as the number of included studies for each meta-analysis
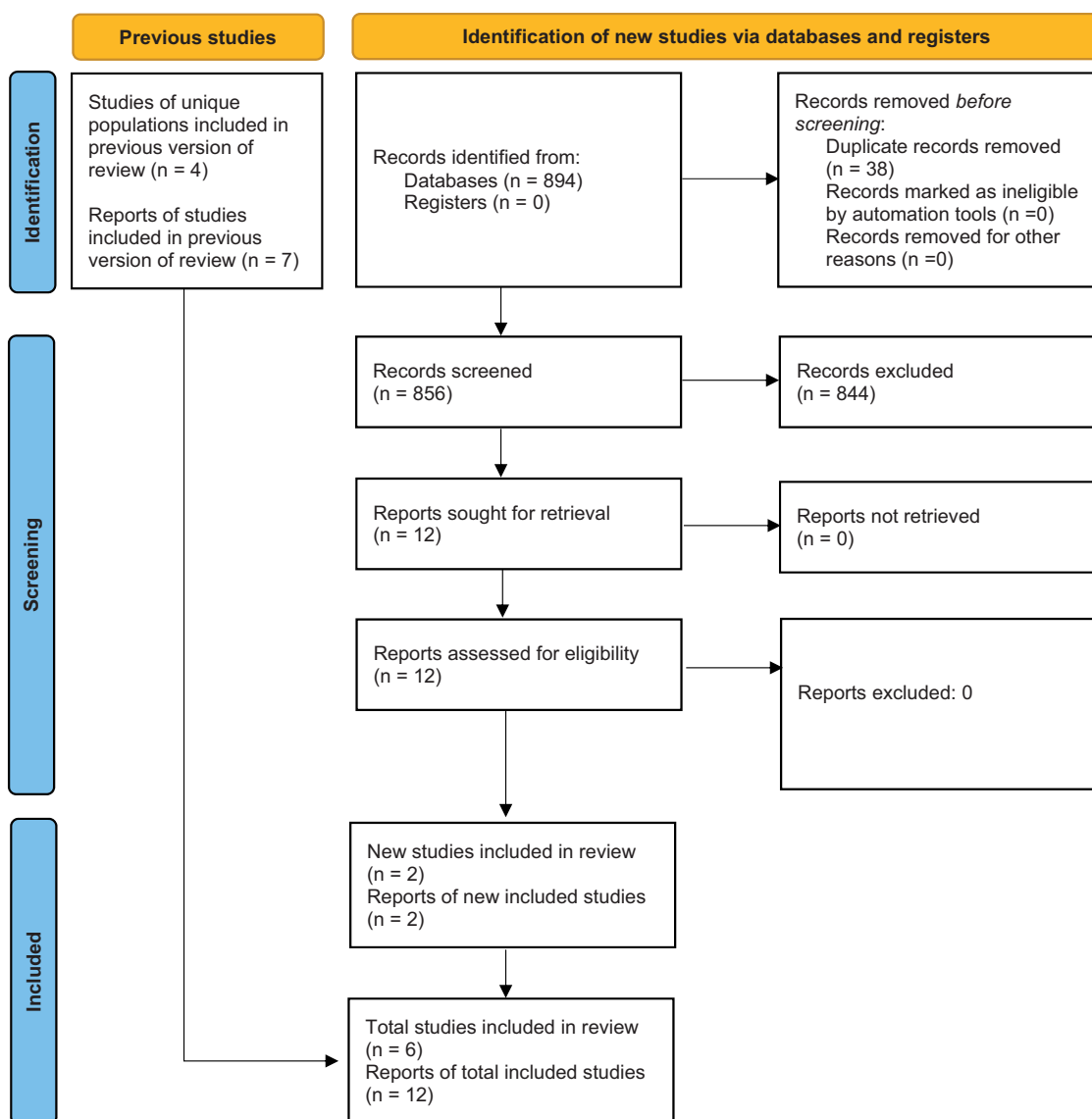
Previous studies	Identification of new studies via databases and registers

Identification

Studies of unique populations included in previous version of review (n = 4)

Reports of studies included in previous version of review (n = 7)

Records identified from:
Databases (n = 894)
Registers (n = 0)

Records removed *before screening*:
Duplicate records removed (n = 38)
Records marked as ineligible by automation tools (n =0)
Records removed for other reasons (n =0)

Screening

Records screened (n = 856)

Records excluded (n = 844)

Reports sought for retrieval (n = 12)

Reports not retrieved (n = 0)

Reports assessed for eligibility (n = 12)

Reports excluded: 0

Included

New studies included in review (n = 2)
Reports of new included studies (n = 2)

Total studies included in review (n = 6)
Reports of total included studies (n = 12)

Figure 1. PRISMA 2020 flow diagram for updated systematic reviews.

was fewer than 10, which is the recommended minimum number of studies for the assessment of publication bias with a funnel plot [35]. Lastly, sensitivity analysis was conducted to assess the between-study heterogeneity and impact of an individual study on the pooled ES; this was done through the leave-one-out approach, which recalculated the pooled ES after a study was omitted, one by one [28, 29]. All of the analyses were performed in Stata 17.0 (StataCorp LLC, College Station, TX, USA).

Results

A total of 856 unique records were identified from the search (Figure 1). After abstract screening for relevant publications, 12 full-text articles were assessed and deemed eligible for inclusion. There were no disagreements among reviewers about study inclusion. These included one RCT comparing BVN RFA with sham, with outcomes reported

at up to 1, 2, and 5 years [4, 7, 9, 10]; one RCT comparing BVN RFA with standard care treatment, with outcomes reported at up to 3, 6, 12, and 24 months [8, 11, 36]; and four single-group cohort studies, with outcomes reported between 3 and 12 months [1, 3, 5, 6, 12].

Study Characteristics

The main characteristics of the included studies are summarized in Table 1. From 2017 to 2021, a total of 414 participants were allocated to receive BVN RFA in two RCTs and four single-group cohort studies [1, 3, 5, 7, 11, 12, 36]. Participants in all reviewed studies were adults with chronic LBP for ≥6 months with MC1 and MC2 changes within at least one of the L3–S1 vertebral bodies. In addition to MC1 and MC2 changes on MRI, participants in the cohort study by De Vivo et al. underwent SPECT/CT and CT-guided medial branch blocks to exclude lumbar facet joint pain [1].

Table 1. Study characteristics

Author, Year	Design	Study Size	Inclusion Criteria	Mean/Median Ages of Participants (Range)	Participant Duration of Pain	Intervention	Targeting Success (Based on Post-Ablation MRI)	Adverse Events	Author Disclosures
Fischgrund 2018*	RCT	225 randomized, 147 received BVN RFA. 128 analyzed in PP population (excluded n = 19 for targeting/access failure or protocol noncompliance).	CLBP ≥6 months despite conservative treatment, Modic 1 or 2 changes from L3–S1, minimum ODI 30, minimum VAS 4 mm	Mean 46.9 (26–69)	6–12 months 4.1%, 1–2 years 10.2%, 2–3 years 6.8%, 3–5 years 12.2%, ≥5 years 66.7%	Fluoroscopically guided BVN RFA, 85°C bipolar ablation for 15 minutes 40–60% from posterior wall	95%	n = 1 nerve root injury (sham group), n = 1 vertebral compression fracture (sham group), n = 7 lumbar radiculitis, retroperitoneal hemorrhage (n = 1), and transient motor or sensory deficits, all resolved with supportive care.	Industry funded
Fischgrund 2019*	SGOS	128 at 18 months and 106 at 24 months	"	"	"	"	"	No delayed adverse events	Industry funded
Fischgrund 2020*	SGOS	100	"	"	"	"	"	No delayed adverse events	Industry funded
Markman 2019*	PSA	224	"	"	"	"	"	No delayed adverse events	Industry funded
Khalil 2019†	RCT	140 randomized, 51 received BVN RFA	CLBP ≥6 months despite conservative treatment, Modic 1 or 2 changes from L3–S1, minimum ODI 30, minimum VAS 4 cm	Mean 50.0 (26–70)	6–12 months 5.8%, 1–2 years 2.9%, 2–3 years 11.5%, 3–5 years 12.5%, ≥5 years 62.7%	Fluoroscopically guided BVN RFA, 85°C bipolar ablation for 15 minutes 30–50% from posterior wall	96%	n = 15, incisional pain, leg pain/paresthesia, back pain in a new location, urinary retention, and lateral femoral cutaneous neurapraxia.	Industry funded
Smuck 2021†	RCT	66 original RFA arm, 61 crossover from standard-care arm treated with BVN RFA at average 6.3 months	"	"	"	"	97%	No delayed adverse events	Industry funded
Koreckij 2021†	SGOS	58 original BVN RFA arm	"	"	"	"	"	No delayed adverse events	Industry funded
Becker 2017	SGOS	16	CLBP ≥6 months, Modic 1 or 2 changes from L3–S1 or positive provocation discography	Mean 48.0 (34–66)	Not reported	Fluoroscopically guided BVN RFA (n = 16), 85°C bipolar ablation for 15 minutes "at least 10 mm anterior to the posterior wall"	91%	n = 4, lumbar pain, buttock pain, dysesthesia, and transient numbness, resolved with pain medications.	Industry funded
Trumees 2019	SGOS	28					97%		

Table 1. continued

Author, Year	Design	Study Size	Inclusion Criteria	Mean/Median Ages of Participants (Range)	Participant Duration of Pain	Intervention	Targeting Success (Based on Post-Ablation MRI)	Adverse Events	Author Disclosures
			CLBP ≥6 months, Modic 1 or 2 changes from L3–S1, minimum ODI 30, minimum VAS 4 cm	Mean 45.2 (SD 8.89)	1–2 years 10.7%, 2–3 years 14.3%, 3–5 years 0%, ≥5 years 75.0%	Fluoroscopically guided BVN RFA (n = 47), 85°C bipolar ablation for 15 minutes 30–50% from posterior wall		n = 3, 1 aborted procedure due to inability to access, 2 leg pain events due to pedicle breach	Industry funded
Macadaeg 2020‡	SGOS	47	"	Median 45.0 (25–66)	1–2 years 14.9%, 2–3 years 10.6%, 3–5 years 2.1%, ≥5 years 72.3%	"	96%	n = 2, potential pedicle breach and associated radiculitis, resolved with oral medications	Industry funded
De Vivo 2021	SGOS	56	CLBP ≥6 months despite conservative treatment ≥6 weeks, Modic 1 or 2 changes from L3–S1	Median 43.0 (38–52)	Not reported	CT-guided BVN RFA (n = 56), core temperature 77°C, automatically stopped when the proximal thermocouple reached 50°C, targeted 50% distance from the posterior wall.	100%	None	None
Fishchenko 2021	SGOS	19	CLBP ≥6 months despite conservative treatment, Modic 1 or 2 changes from L3–S1, minimum ODI 30, minimum VAS 4 mm	Mean 52.6 (SD 6.9)	1–2 years 73.7%, ≥5 years 26.3%	Fluoroscopically guided BVN RFA (n = 19), 85°C ablation for 15 minutes 40–50% distance from posterior wall	Not reported	n = 1, arterial injury of the "lumbalis sinistra" causing a hematoma within the iliopsoas with associated plexitis, treated with endovascular embolization	None

SGOS = single-group observational study; PP = per protocol; PSA = post-hoc secondary analysis; SD = standard deviation; CLBP = chronic low back pain.

Multiple reports from the same population at various time points. Results of the per protocol analysis shown.

[†] Multiple reports from the same population at various time points up to 12 months for the original BVN RFA arm and up to 6 months for the crossover cohort. Results of the per protocol analysis shown.

[‡] Multiple reports from the same population. Truumees et al. reported on the first 28 patients.

Table 2. Pain reduction and functional improvement

Author, Year	NRS/VAS Responder Percentage (95% CI)	ODI Responder Percentage (95% CI)
Fischgrund 2018*	**6 months:** ≥50% VAS reduction 46% (37–55%)§, ≥2.0-cm VAS reduction 62% (53–70%)§	**6 months:** ≥15-point ODI reduction 57% (48–66%)§
	12 months: ≥50% VAS reduction 41% (32–50%)§, ≥2.0-cm VAS reduction 60% (51–69%)§	**12 months:** ≥15-point ODI reduction 58% (49–67%)§
Fischgrund 2019*	**24 months:** ≥50% VAS reduction 46% (37–55%)§, ≥2.0-cm VAS reduction 67% (58–76%)§	**24 months:** ≥15-point ODI reduction 55% (47–64%)§
Fischgrund 2020*	**60 months:** ≥50% VAS reduction 66% (57–75%), ≥2.0-cm VAS reduction 88% (82–94%)	**60 months:** ≥15-point ODI reduction 77/100, 77% (69–85%)
Markman 2019*	Not reported	Not reported
Khalil 2019†	**3 months:** ≥50% VAS reduction 63% (49–76%)§, ≥2.0-cm VAS reduction 73% (60–85%)	**3 months:** ≥20-point ODI reduction 63% (49–76%)
Smuck 2021†	**6 months, BVN RFA arm:** ≥50% VAS reduction 62% (48–74%)§, ≥2.0-cm VAS reduction 75% (64–86%)	**6 months, RFA arm:** ≥15-point ODI reduction 67% (55–79%)
	12 months, RFA arm: ≥50% VAS reduction 64% (51–76%), ≥2.0-cm VAS reduction 79% (68–89%)	**12 months, RFA arm:** ≥15-point ODI reduction 69% (57–80%)
	6 months, crossover arm: ≥50% VAS reduction 66% (52–78%), ≥2.0-cm VAS reduction 74% (63–85%)	**6 months, crossover arm:** ≥15-point ODI reduction 72% (61–84%)
Koreckij 2021†	**24 months:** ≥50% VAS reduction 72% (61–84%)§, ≥2.0-cm VAS reduction 79% (69–90%)	**24 months:** ≥15-point ODI reduction 77% (66–88%)
Becker 2017	**12 months:** ≥50% VAS reduction 38% (15–65%)§, ≥2.0-cm VAS reduction 50% (26–75%)§	**12 months:** ≥15-point ODI reduction 63% (35–85%)§
Macadaeg 2020‡	**12 months:** ≥50% VAS reduction 67% (52–80%)§, ≥2.0-cm VAS reduction 80% (63–89%)	**12 months:** ≥15-point ODI reduction 89% (76–96%)
De Vivo 2021	**12 months:** ≥50% VAS reduction 90% (79–97%)§, ≥2.0-cm VAS reduction 96% (92–100%)	**12 months:** ≥15-point ODI reduction 82% (69–92%)§
Fishchenko 2021	**12 months:** ≥50% VAS reduction 84% (60–97%)	**12 months:** ≥15-point ODI reduction 84% (63–97%)§

SGOS= single group observational study, PSA = post-hoc secondary analysis.

*Multiple reports from the same population at various time points. Results of the per protocol analysis shown.

†Multiple reports from the same population at various time points up to 12 months for the original BVN RFA arm and up to 6 months for the crossover cohort. Results of the per protocol analysis shown.

‡Truumees et al. reported on the first 28 patients from this study in 2019.

§Exact threshold unpublished. Data requested and obtained from the study investigators.

Some studies specifically excluded individuals with disc protrusions >5 mm, spondylolisthesis >2 mm, and significant depression (Beck Depression Inventory >24) [3, 5, 7, 11]. All studies excluded individuals with clinical evidence of symptomatic spinal stenosis or radicular pain. The majority of study participants were Caucasian, nonobese, college educated, and employed [3, 7, 11] and were in their mid-40s to early 50s [1, 3, 5, 7, 11, 12]. Most study participants reported having experienced pain for ≥5 years (62–72%) [3, 7, 11], but in one study, 74% of participants reported a duration of pain between 1 and 2 years [5]. Prior treatment, where described, included opioid use (32–24%), spinal injections (61–70%), lumbosacral or sacroiliac joint RFA (16%), chiropractic care (42%), and physical therapy (70%) [3, 7, 11]. Bipolar RFA was performed in all studies with either fluoroscopic [3, 5, 7, 11, 12] or CT guidance [1] targeting the intraosseous BVN at a point 40–60% from the posterior wall [7] or 30–50% from the posterior wall [1, 3, 5, 11]. Patient-reported outcome measures were reported between 3 and 60 months and included VAS/NRS, ODI, Short Form 36 (SF-36), EuroQuol 5 Dimensions (EQ5D-5L), healthcare utilization, and opioid use.

Synthesis of Results

Responder rates for VAS and ODI at various thresholds are presented in Table 2. As only two RCTs (one sham-controlled trial and one active treatment–controlled trial) have been performed, conventional pairwise meta-analysis was not performed. Instead, a single-arm meta-analysis of outcomes after treatment with BVN RFA was performed to examine the percentage of responders, defined by the ≥50% VAS/NRS and ≥15-point ODI improvement thresholds at 6 and 12 months (Figures 2 and 3). For ≥50% pain improvement at 6 and 12 months, the calculated success rates were 65% (95% CI 51–78%) and 64% (95% CI 43–82%), respectively. Rates of ≥15-point ODI improvement were 75% (95% CI 63–86%) and 75% (95% CI 63–85%) at 6 and 12 months, respectively. Figures 4 and 5 illustrate these same proportions at 6, 12, 24, and 60 months longitudinally. Meta-analysis was also performed to calculate the success rates based on an intention-to-treat analysis (including lost to follow-up, protocol deviations, targeting failure, etc.) for the RCTs and a "worst-case" scenario (unreported patients were categorical failures) for cohort studies, which demonstrated slightly lower success rates for pain and functional
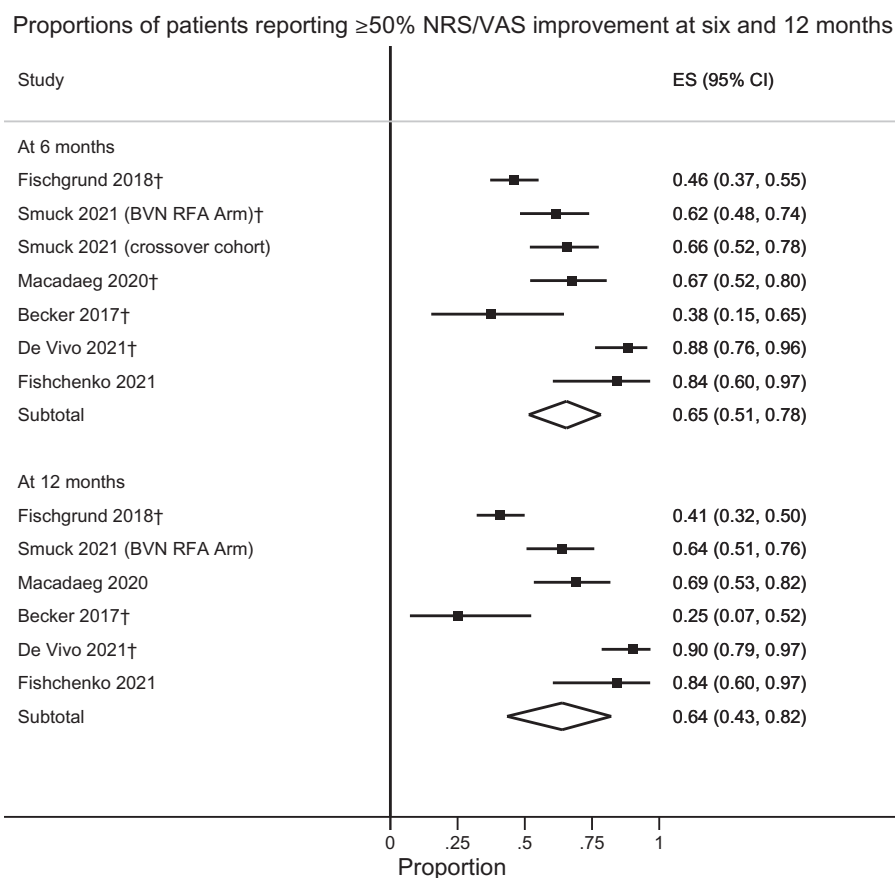
Proportions of patients reporting ≥50% NRS/VAS improvement at six and 12 months

Figure 2. Proportions of patients reporting ≥50% NRS/VAS improvement at 6 and 12 months. †Exact threshold unpublished, data requested and obtained from the study investigators.

improvement: At 6, 12, 24, and 60 months 61% (95% CI 48–74%), 59% (95% CI 40–77%), 49% (95% CI 43–56%), and 50% (95% CI 41–58%) of participants reported ≥50% pain improvement. Rates of ≥15-point ODI improvement at these same time points were 71% (95% CI 59–82%), 70% (95% CI 57–81%), 57% (95% CI 50–64%), and 57% (95% CI 49–65%).

GRADE Quality Assessment

As no new RCTs are included in this updated systematic review, an updated GRADE evidence profile is not presented, but GRADE judgments are described narratively. The evidence from these two RCTs was downgraded from "high quality" because of the risk of bias in the form of selective outcome reporting and the inability to blind participants effectively. The possibility of publication bias was also considered, given that the majority of studies have been industry funded [3, 7, 11, 12]; however, two recently performed independent studies have shown similar results [1, 5]. According to GRADE, there is moderate-quality evidence that intraosseous BVN RFA effectively reduces LBP and related disability in those with vertebrogenic LBP, compared with sham RFA [7] and continued standard care treatment [11].

Publication Bias and Sensitivity Analysis

According to Egger's tests, there was no evidence of serious publication bias in the meta-analysis on the proportions of patients reporting ≥15-point ODI improvement at 6 months or 12 months ($P = 0.802$ and 0.756, respectively) or on the proportions of patients reporting ≥50% NRS/VAS improvement at 6 months or 12 months ($P = 0.409$ and 0.369, respectively). The sensitivity analysis showed that the point estimate and CI of the pooled ES from all meta-analyses did not change substantially after exclusion of any individual study. Omitting the study by Fischgrund (2018) for the analysis on ≥15-point ODI improvement at 6 months and 12 months would have resulted in the pooled ESs of 0.78 (original ES = 0.75) and 0.79 (original ES = 0.75), respectively. Likewise, omitting the study by Macadaeg (2020) at 6 months and 12 months would have resulted in the pooled ESs of 0.70 (original ES = 0.75) and 0.71 (original ES = 0.75), respectively. However, all of the recalculated 95% CIs for the pooled ES largely overlapped with each other. In terms of the analysis for ≥50% NRS/VAS improvement, all of the recalculated point estimates of the ESs (after omission of any individual study) were very close to the original ESs of 0.65 and 0.64 at 6 months and 12 months, respectively, with substantial overlap of CIs.
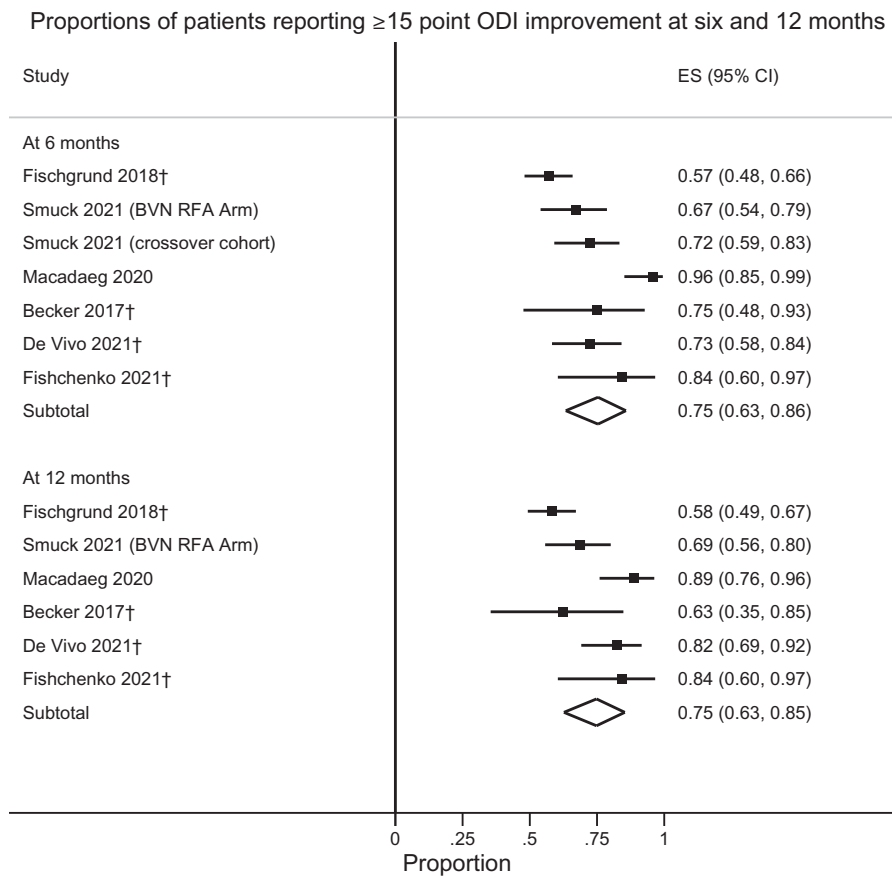
Proportions of patients reporting ≥15 point ODI improvement at six and 12 months

Study	ES (95% CI)
At 6 months	
Fischgrund 2018†	0.57 (0.48, 0.66)
Smuck 2021 (BVN RFA Arm)	0.67 (0.54, 0.79)
Smuck 2021 (crossover cohort)	0.72 (0.59, 0.83)
Macadaeg 2020	0.96 (0.85, 0.99)
Becker 2017†	0.75 (0.48, 0.93)
De Vivo 2021†	0.73 (0.58, 0.84)
Fishchenko 2021†	0.84 (0.60, 0.97)
Subtotal	0.75 (0.63, 0.86)
At 12 months	
Fischgrund 2018†	0.58 (0.49, 0.67)
Smuck 2021 (BVN RFA Arm)	0.69 (0.56, 0.80)
Macadaeg 2020	0.89 (0.76, 0.96)
Becker 2017†	0.63 (0.35, 0.85)
De Vivo 2021†	0.82 (0.69, 0.92)
Fishchenko 2021†	0.84 (0.60, 0.97)
Subtotal	0.75 (0.63, 0.85)

Proportion
0   .25   .5   .75   1

Figure 3. Proportions of patients reporting ≥15-point ODI improvement at 6 and 12 months. †Exact threshold unpublished, data requested and obtained from the study investigators.
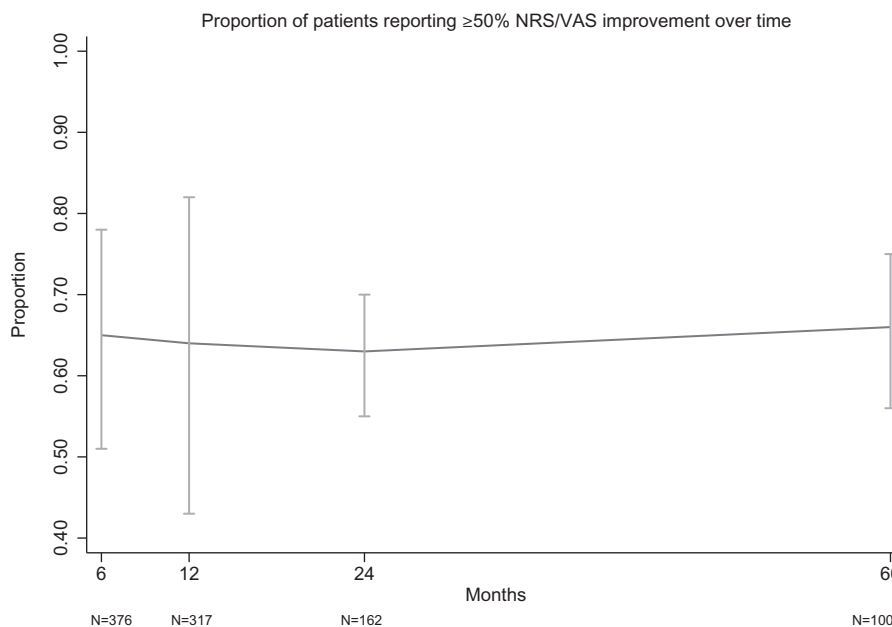
Proportion of patients reporting ≥50% NRS/VAS improvement over time

N=376   N=317   N=162   N=100

Figure 4. Proportion of patients reporting ≥50% NRS/VAS improvement over time.

Discussion

This updated systematic review identified several new publications that reported on the long-term effectiveness of BVN RFA. No new randomized trials were identified; however, substantially more data are now available to describe the short-, medium-, and long-term success rates
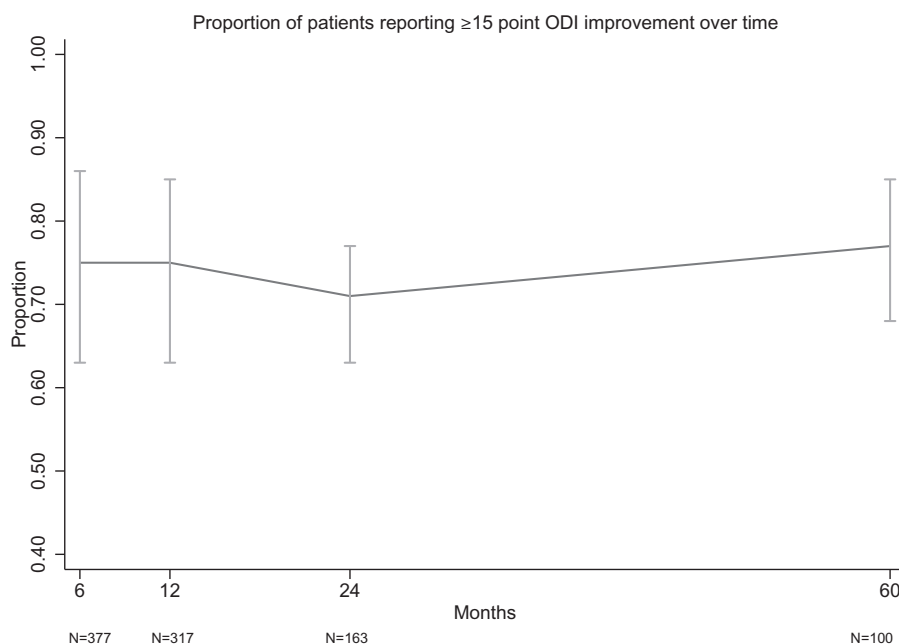
Figure 5. Proportion of patients reporting ≥15-point ODI improvement over time.

of treatment with BVN RFA. Single-arm meta-analysis of these studies demonstrated that approximately 65% and 75% of patients report clinically significant pain and functional improvement at 6 and 12 months after BVN RFA (Figures 2 and 3). The calculated proportions of responders remained remarkably stable at 24 and 60 months, with less than 5% variance in the estimated VAS/ODI responder proportions (see Figures 4 and 5). According to GRADE, the evidence quality was determined to be "moderate." The designation of "moderate quality" suggests that future research will likely improve our understanding of the effectiveness of BVN RFA for vertebrogenic pain [37].

In addition to safety, careful transpedicular access is required to achieve targeting success with BVN RFA. In studies that analyzed post-ablation lesion geometry on MRI, targeting success appeared slightly higher when the BVN was targeted at a point 30–50% from the posterior wall [3, 8, 11] compared with earlier targeting in SMART (40–60% from the posterior wall) [7], though the targeting success rate remained above 90% in all studies (Table 1). DeVivo et al. reported 100% targeting success with the use of CT guidance and an alternative device to that used in other studies [1]. Given that studies after SMART have reported targeting success rates greater than 95%, it appears that successful neurotomy of the BVN is achieved frequently with established techniques.

Because the BVN contains many unmyelinated fibers [14, 15, 38, 39], appropriately targeted thermal ablation can produce a long-lasting neurotomy and durable symptom improvement in those with significant pain and disability due to vertebrogenic LBP. This appears to be supported by the existing literature, in which the vast

majority of study participants observed to initially benefit from BVN RFA continued to report significant pain and functional improvement at 1, 2, and 5 years (Figures 2–5). This pattern appears to be the same in industry-funded [3, 7–10, 36] and independently performed studies [1, 5]. Along with robust improvements in pain and function, healthcare utilization appears to decrease substantially after BVN RFA. In published studies, individuals treated with BVN RFA have seldom required further interventional or surgical treatment. Of the participants who were followed in the SMART trial, only 3% had received a lumbosacral facet joint RFA treatment or spinal injection in the year preceding the 5-year data collection time point [9]. Similarly, 5% of participants from INTRACEPT received an epidural steroid injection at a treated level by the 2-year data collection time point [36]. In both of these studies, a minority of participants progressed to a fusion surgery (8% and 4.5%, respectively). Opioid utilization decreased in participants over time after BVN RFA in most studies but did not differ significantly from the sham or standard-of-care groups at 3–12 months [4, 8, 10]. Despite the lack of significant difference between control arms in the RCTs at 3 months, the 5-year observational data from SMART (which included crossover of sham patients to active treatment) suggested that only 8% of participants were taking opioids at long-term follow-up (compared with 30% at baseline) [9].

No delayed complications were noted in any study report. The most common reported adverse event remains transient leg pain, which is thought to be secondary to pedicle breach (see Table 1). Investigators reported an 11% rate (n = 14) of pedicle breach resulting in "non-serious" leg pain in the 127 participants treated with

BVN RFA from the INTRACEPT study [36]. The median time to resolution for these symptoms was 48.5 days, and most were successfully treated with a single course of oral steroids. Similar transient leg symptoms were observed in the SMART population [7]. Two cases of retroperitoneal hemorrhage have been reported, which may be due to excessive lateral positioning resulting in violation of the lumbar segmental artery [5, 7].

Over the years, many interventional treatments have been used for those with chronic "discogenic" LBP, with varying success. Notable examples have included biaculoplasty, intradiscal RFA, methylene blue, and intradiscal steroid injection [40–45]. More recently, case series of patients treated with extraosseous, epiduroscopic BVN/sinuvertebral nerve (SVN) laser ablation and bipolar RFA have reported positive results [46–48]. Orthobiological treatments are also being adapted to treat vertebrogenic LBP; a technique for intraosseous delivery of plasma-rich growth factor (PRGF-Endoret) has been proposed [49]. Additionally, two recent RCTs investigating the effectiveness of intradiscal steroid in patients with MC1 have been published, but they found only short-term benefit at 1 month compared with intradiscal saline or anesthetic [41, 42]. Although there are no head-to-head trials comparing BVN RFA with any of these interventions in an appropriate population, there are now multiple studies and 5-year outcomes to support the use of BVN RFA for the treatment of vertebrogenic pain. This is not the case for any of these other treatments.

Although the outcomes of BVN RFA reported in the published literature are robust, there could be opportunities to further refine patient selection. Until recently, the characteristic pain patterns for those with vertebrogenic LBP were not directly described; however, analysis of responder characteristics from a large population of patients treated with BVN RFA has been reported [50]. Those with vertebrogenic pain experience predominantly midline LBP without lower leg symptoms, but they also indicated pain in the paramidline and buttock region. Notably, these descriptions are based on a case definition of significant pain relief or functional improvement after BVN RFA (for lack of a superior gold standard of "true" vertebrogenic pain). This is perhaps not surprising given the substantial overlap in the known pain referral patterns from other spinal structures, including the disc, sacroiliac joint, and zygapophyseal facet joint [51–53].

Given the widespread use of diagnostic/prognostic blocks in interventional pain medicine, clinicians might hope for a similar tool to help select patients for BVN RFA. However, although directly anesthetizing the intraosseous BVN seems attractive as a diagnostic test at face value, there are several major issues with this approach. Anesthetic placed at the periosteum of the pedicle before access would almost certainly anesthetize the lumbar medial branch, potentially introducing confounding from relief of lumbar zygapophyseal joint pain. Because of the vascular nature of trabecular bone, local anesthetic injection within the vertebral body might not produce a consistent blockade of the BVN, leading to false-negative tests. Significant procedural pain after transpedicular access might also be a source of false-negative results. Given these challenges, clinicians are encouraged to carefully select patients for BVN RFA on the basis of the clinical and imaging paradigm described in studies published to date.

There are important limitations to this review and for the existing literature related to BVN RFA. RCTs, although not without their own limitations [54, 55], continue to represent the gold-standard study design in medical research [56]. Despite the growing interest in the treatment of vertebrogenic LBP, the present updated review found no new RCTs examining BVN RFA compared with sham or any other treatment. The majority of studies that met the inclusion criteria were supported by industry funding. When the evidence for treatment comes entirely from industry-funded studies, there is an increased risk for bias given the inherent conflict of interest, limiting the publication of negative results [57, 58]. However, it is notable that results from two independently performed studies show similarly high proportions of patients reporting clinically significant pain relief and functional improvement up to 12 months after BVN RFA [1, 5]. The present review was supported by an investigator-initiated research grant from Relievant Medsystems, which produces a device frequently used for BVN RFA. However, the sponsor had no role in the design or conduct of the review or approval of the final manuscript. The protocol, search, data extraction, and statistical analysis were all developed and performed independently without input or oversight from the sponsor.

This review has several strengths. The review was designed, executed, and reported in accordance with quality guidelines for systematic reviews [27, 59]. Although already performed in our prior work, abstract review, full-text review, and data extraction were again performed in duplicate to ensure accuracy. When data considered critical to the review's research question were missing, the authors of included studies were contacted to obtain this information. The single-arm meta-analysis presented provides clinicians with a useful estimate of the effectiveness of BVN RFA when patients are selected on the basis of the published inclusion and exclusion criteria used to date.

Conclusion

According to GRADE, there continues to be "moderate"-quality evidence that BVN RFA effectively reduces chronic LBP and associated disability in individuals with chronic vertebrogenic LBP associated with MC1 and MC2 in the L3 to S1 vertebral bodies. Between 65% and 75% of such patients report clinically significant pain and functional improvement at 6 and 12 months after BVN RFA, with similar success rates up to 5 years.

Further high-quality studies will likely improve our understanding of the effectiveness of this procedure.

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