A Metaanalysis of the Effectiveness and Safety of Ozone Treatments for Herniated Lumbar Discs

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PURPOSE: To determine statistically significant effects of oxygen/ozone treatment of herniated discs with respect to pain, function, and complication rate.

MATERIALS AND METHODS: Random-effects metaanalyses were used to estimate outcomes for oxygen/ozone treatment of herniated discs. A literature search provided relevant studies that were weighted by a study quality score. Separate metaanalyses were performed for visual analog scale (VAS), Oswestry Disability Index (ODI), and modified MacNab outcome scales, as well as for complication rate. Institutional review board approval was not required for this retrospective analysis.

RESULTS: Twelve studies were included in the metaanalyses. The inclusion/exclusion criteria, patient demographics, clinical trial rankings, treatment procedures, outcome measures, and complications are summarized. Metaanalyses were performed on the oxygen/ozone treatment results for almost 8,000 patients from multiple centers. The mean improvement was 3.9 for VAS and 25.7 for ODI. The likelihood of showing improvement on the modified MacNab scale was 79.7%. The means for the VAS and ODI outcomes are well above the minimum clinically important difference and the minimum (significant) detectable change. The likelihood of complications was 0.064%.

CONCLUSIONS: Oxygen/ozone treatment of herniated discs is an effective and extremely safe procedure. The estimated improvement in pain and function is impressive in view of the broad inclusion criteria, which included patients ranging in age from 13 to 94 years with all types of disc herniations. Pain and function outcomes are similar to the outcomes for lumbar discs treated with surgical discectomy, but the complication rate is much lower (<0.1%) and the recovery time is significantly shorter.

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Abbreviations: FIO = Italian Oxygen–Ozone Therapy Federation, MCID = minimum clinically important difference, MCD = minimum detectable change, ODI = Oswestry Disability Index, VAS = visual analog scale, SD = standard deviation

THE mechanism of pain in the lumbar region is not fully understood, but it is likely caused by mechanical and/or inflammatory factors. Since 1934 (1), the accepted rationale for surgical treatment of disc herniations is that lumbar back pain is a result of mechanical nerve compression and that partial surgical removal of the disc decreases mechanical compression, which relives the pain. Many common minimally invasive treatments such as percutaneous lumbar discectomy (2), laser discectomy (3), percutaneous plasma disc decompression (ie, nucleoplasty) (4), intradiscal electrothermal therapy (5), and percutaneous intradiscal radiofrequency thermocoagulation (6) rely upon the removal of disc material to reduce pressure on the ganglion nerve root. The proposed mechanism of action for each of these procedures, is that a small change in volume produces a large change in pressure (7).

Oxygen/ozone treatment is a minimally invasive injection for the treatment of disc herniations that is widely practiced in Europe and Asia, as evidenced by the results of our literature search. Intradiscal injection of ozone was first reported in the 1990s by Muto and Avella (8) and other Italian interventional neuroradiologists. Extradiscal injection of ozone into the paravertebral muscle adjacent to a herniated disc was first proposed by Verga in 1989 (9). The technique for oxygen/ozone injection is similar to that used for discography and other percutaneous disc proce-

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Table 1
Study Quality Scoring System

Study Criteria	Base Score
Type of study	
Randomized	0.9
Prospective	0.8
Retrospective	0.7
	Additional Points
Did study use a control arm?	
Yes	+0.1
No	−0.1
Did study present a statistical analysis on the results?	
Yes	+0.1
No	−0.1
Was it a multiple-center study?	
Yes	+0.1
No	−0.1

Note.—The final study quality score (Qs) is the base score ± additional points.

dures. A sterile needle is positioned under image guidance into the nucleus pulposus. Then 1–3 mL of oxygen/ozone from a medical ozone generator is injected into the disc and 7–9 mL is injected into the paravertebral muscle surrounding the disc. After the ozone injection, some physicians may inject pain suppressant (eg, bupivacaine) and/or a corticosteroid. The procedure is minimally invasive, very safe with virtually no adverse events, and completed in less than 30 minutes.

Ozone is a strong oxidizer that quickly reacts and oxidizes the proteoglycans in the nucleus pulposus, which results in a small disc volume reduction and subsequent pain relief. The premise is that a small volume reduction results in a significant pressure reduction. Ozone is also a natural disinfectant. Therefore, the ozone injected outside the disc serves to minimize risk of infection. In addition, ozone has been shown to have antiinflammatory/analgesic effects. Additional discussion of ozone's mechanisms of action can be found elsewhere (10).

There has been controversy regarding the safety and effectiveness of medical ozone (11) and there are no medical ozone generators for this procedure that are currently cleared by the United States Food and Drug Administration. As shown in our literature search, many studies that employed a wide range of inclusion/exclusion criteria, ozone concentrations, and procedures have been performed to determine the efficacy of oxygen/ozone treatment. The purpose of the present study was to use a metaanalysis (a method for statistically combining results of numerous studies to determine an average effect) to estimate the pain, function, and safety outcomes of oxygen/ozone treatment for herniated discs. Institutional review board approval was not required for this retrospective analysis.

MATERIALS AND METHODS

Review Methods

Literature searches were performed using PubMed and the *International Journal of Ozone Therapy* Web site with search

Table 2
Summary of Clinical Trial Patient Information from Literature Search (21–24,27–33)

Study (References)	No. of Pts.	Patient Age (y)		Sex: M/F (%)	Herniation Type	Herniated Disc Treatment Locations
		Range	Mean			
ActiveO Trial (Unpublished data)	50	18–74	45	66/34	Contained	L1–L2 (2.3), L2–L3 (2.3), L3–L4 (9.1), L4–L5 (59.1), L5–S1 (27.3)
Muto et al, 2008 (21)	2,900	19–86	NR	60/40	Contained	Between NR and S1
Oder et al, 2008 (23)	621	22–94	63*	39/61	Bulging, contained, and noncontained	L1–L2 (NR), L2–L3 (NR), L3–L4 (NR), L4–L5 (36.1), L5–S1 (48.3)
Gallucci et al,	82	18–71	41	56/44	NR	L3–L4 (13), L4–L5 (38), L5–S1 (49)
2007 (22)	78	18–71	40	55/45	NR	L3–L4 (16), L4–L5 (35), L5–S1 (49)
Leonardi et al,	37	NR	57	45/55	NR	NR
2006 (28)	52	NR	49	54/46	NR	NR
Buric et al, 2005 (27)	30	19–77	45	53/47	Noncontained	Between L3 and S1
	15	19–77	45	40/60	Noncontained	Between L3 and S1
Qing et al, 2005 (29)	602	17–83	NR	57/43	Contained (protrusion)	NR
Ying et al, 2005 (30)	323	19–76	46	57/43	Contained and noncontained	L2–L3 (2.4), L3–L4 (8.9), L4–L5 (47.0), L5–S1 (41.8)
Muto et al, 2004 (31)	2,200	13–89	NR	NR	Contained	Between L3 and S1
Andreula et al,	300	20–80	NR	NR	Contained	L1–L2 (0.7), L2–L3 (1.2), L3–L4 (8.7),
2004 (32)						L4–L5 (61.8), L5–S1 (27.6)
	300	20–80	NR	NR	Contained	L1–L2 (0.7), L2–L3 (1.2), L3–L4 (8.7), L4–L5 (61.8), L5–S1 (27.6)
Buric et al, 2003 (24)	104	20–60	NR	NR	Noncontained	Between L2 and S1
He et al, 2003 (33)	258	19–62	45	59/41	Bulging (27), protruded (71), extruded (2)	Between L4 and S1

Note.—Values in parentheses are percentages. NA = not applicable; NR = not reported.
* Median.

Table 3
Summary of Clinical Trial Inclusion Criteria from Literature Search (21–24,27–33)

Study (References)	Clinical*	Neuroradiologic†
ActiveO Trial (Unpublished data)	3	Single herniated disc between L1 and S1
Muto et al, 2008 (21)	2	Single (% NR) or multiple (% NR) herniated lumbar disc between NR and S1
Oder et al, 2008 (23)	3	Bulging, contained, and non-contained disc between NR and S1 levels
Gallucci et al, 2007 (22)	Group B: 0.5–1 Group A: 0.5–1	Lumbar disc herniation between L3 and S1
Leonardi et al, 2006 (28)	Group A: <6 Group B: 6–240	Single herniated disc between NR levels
Buric et al, 2005 (27)	Ozone arm 1	Noncontained herniated disc between L3 and S1
	Microdiscectomy arm 1	Noncontained herniated disc between L3 and S2
Qing et al, 2005 (29)	0.25–216	Single (39.5), 2 each (42.0), 3 each (18.0), and 4 each (0.5) contained herniated lumbar discs (level range NR)
Ying et al, 2005 (30)	0.17–264	Single (32.5), 2 each (54.8), and 3 each (12.7) herniated lumbar disc between L2 and S1
Muto et al, 2004 (31)	2	Single (NR) or multiple (NR) herniated lumbar disc between L4 and S1and residues of surgical microdiscectomy with recurrent herniation and/or hypertrophic fibrous scarring
Andreula et al, 2004 (32)	Group A: 3 Group B: 3	Contained disc herniation between L1 and S1 and residues of surgical microdiscectomy with recurrent herniation
Buric et al, 2003 (24)	1	Non-contained disc herniation between L2 and S1
He et al, 2003 (33)	3–204	Bulging (27), protruded (71), extruded (2) discs between L4 and S1

Note.—Values in parentheses are percentages. FBSS = failed back surgery syndrome; NR = not reported.
* Low back pain with or without radicular symptoms that did not improve after conservative therapy for at least a certain number of months.
† CT and/or MR evidence of herniated disc(s) correlating with patients symptoms with or without degenerative disc/vertebra disease.

terms associated with ozone treatment of herniated discs. The following keywords were searched on PubMed: (i) "ozone and discectomy," (ii) "ozone and lumbar and (disc or disk)," (iii) "intradiscal ozone," and (iv) "ozone and herniated and (disc or disk)." The following keywords were searched in the *International Journal of Ozone Therapy*: (i) "discectomy," (ii) "lumbar disc," (iii) "intradiscal," and (iv) "herniated disc." It was not necessary to include "ozone" in the search terms in the *International Journal of Ozone Therapy* because the journal is dedicated to ozone treatment. Any studies that did not perform intradiscal ozone injections or did multiple paravertebral injections were excluded, as these procedures are contrary to the recommended procedure of the Italian Oxygen–Ozone Therapy Federation (FIO) (12). The FIO procedure has been demonstrated to be safe in oxygen/ozone treatments on 15,000 patients (12) with no procedure-related adverse events (ie, no early or late neurologic or infectious complications).

We also excluded any studies that treated the cervical discs, as our primary focus was lumbar discs. Other publications that were excluded were those that did not have English translations, those that we suspected contained results that were published in multiple papers (in which case only the most recent results were used), those that used nonstandard outcome scales that could not be converted to one of the standard scales analyzed, those that did not provide sufficient data or provided data that could not be estimated with a statistically sound method, and those that were discussions of oxygen/ozone treatment without results from clinical studies.

Neurologic	Psychologic	Other
Lower back pain and sciatica exacerbated by sitting and/or standing with recumbent relief	Able and willing to return for follow-up	NR
Paresthesia or hypoesthesia over dermatome involved, slight muscle weakness with congruous myotomal distribution, and signs of root-ganglion irritation	A firm resolve on the part of the patient to recover with a commitment to undergo subsequent physical therapy with postural and motor rehabilitation	NR
Treated disc level determined by comparing morphological data, patient's history, and clinical examination in consensus with a neurologist	NR	Initial ODI >30%
Herniation site congruous with neurologic level	NR	NR
NR	NR	NR
Level of disc herniation corresponding to level of symptoms	NR	NR
Level of disc herniation corresponding to level of symptoms	NR	NR
Classic clinical history, symptoms, and physical signs	NR	Unsatisfactory previous surgery and other minimally invasive interventional treatment
Mild or moderate disc herniation consistent with clinical position assessment	NR	FBSS after surgery
Paresthesia or hypoesthesia over dermatome involved, slight muscle weakness with congruous myotomal distribution, and signs of root-ganglion irritation	Firm resolve on the part of the patient to recover with a commitment to undergo subsequent physical therapy with postural and motor rehabilitation	NR
Low back pain with positive signs of nerve root involvement with or without paraesthesia or hypoesthesia with appropriate dermatome distribution	NR	NR
Level of disc herniation corresponding to level of symptoms	NR	NR
Lasegue sign positive reaction	NR	NR

Outcome Measures

Pain and function improvements and complication rates with oxygen/ozone disc injections were evaluated via meta-analyses. The visual analog scale (VAS) was used as the pain metric and the modified MacNab and Oswestry Disability Index (ODI) were used to assess function. The number of complications reported in each study was used to assess the complication rate. As a result of the linear relationship relating the Roland–Morris Disability Questionnaire to the ODI (13), the results from studies that used the Roland–Morris Disability Questionnaire were converted to ODI with the following equation, which was obtained by performing a linear regression on data comparing the two scales (13):

$$\mathrm{ODI} = 15.72 + 0.56 \cdot \mathrm{RMDQ} \quad (1)$$

Calculating the Treatment Effect for Each Study

Three different types of treatment effects were considered, a pre-/posttreatment mean difference effect, an odds effect, and a proportion (ie, risk) effect (14). The pre-/posttreatment mean difference treatment effect compares the initial mean scores of a sample population versus the mean score of the same population after a procedure. This treatment effect was used for the VAS and ODI scales because these scales produce continuous quantitative data from which means and standard deviations (SDs) were calculated.

A pre-/posttreatment contrast could not be used for the modified MacNab

Table 4
Summary of Clinical Trial Ranking and Treatment Procedures from Literature Search (21–24,27–33)

Study (References)	Relative Rank	Treatment vs Control	Trial Type	No. of Centers	Statistical Analysis	Evaluators Blinded	Addition to Ozone	
							Corticosteroid	Anesthetic
ActiveO Trial (Unpublished data)	0.7	No	Prospective	1	Shapiro-Wilk W, matched-pairs *t*, Wilcoxon	Yes	Yes	Yes
Muto et al, 2008 (21)	0.6	No	Retrospective	2	NR	NR	NR	NR
Oder et al, 2008 (23)	0.6	No	Retrospective	1	*U*, Kruskal-Wallis, Kendall τ, Wilcoxon, Friedman, and χ^2	NR	Yes	Yes
Gallucci et al, 2007 (22)	1	Yes (steroid, anesthetic)	Randomized	1	χ^2	Yes	Yes	Yes
		Yes (Ozone, steroids, anesthetic)	Randomized		χ^2	Yes	Yes	Yes
Leonardi et al, 2006 (28)	0.4	No	Retrospective	1	NR	NR	Yes	Yes
		No	Retrospective		NR	NR	Yes	Yes
Buric et al, 2005 (27)	0.9	Yes (microdiscectomy)	Prospective	1	Wilcoxon signed-rank	NR	No	No
		Yes (Ozone)	Prospective		Wilcoxon signed-rank	NR	No	No
Qing et al, 2005 (29)	0.4	No	Retrospective	1	NR	NR	Yes	Yes
Ying et al, 2005 (30)	0.4	No	Retrospective	1	NR	NR	NR	NR
Muto et al, 2004 (31)	0.6	No	Retrospective	3	NR	NR	NR	NR
Andreula et al, 2004 (32)	1	Yes (ozone, steroids, anesthetic)	Retrospective	2	χ^2	Yes	No	No
		Yes (ozone)	Retrospective		χ^2	Yes	Yes	Yes
Buric et al, 2003 (24)	0.4	No	Retrospective	1	NR	NR	NR	NR
He et al, 2003 (33)	0.4	No	Retrospective	1	NR	NR	Yes	NR

Note.—NR = not reported.
* Epidural or intraforaminal.
† Authors reported volume.

score or complication rate metaanalyses. The proportion treatment effect was used in the complication rate outcome.

For the modified MacNab outcome, an odds treatment effect was used by converting the results from each study into binary data by assigning each of the outcome categories into either a successful or failed category. This allowed the treatment effect to be the odds of a patient showing improvement in the modified MacNab scale. In this analysis, the logit method was used because it has been shown that, when using odds as the treatment effect, the metaanalysis overestimates the degree of heterogeneity across the studies if the logit method is not used (15). The logit method involves using the natural log of the odds as the treatment effect and performing all calculations on this basis.

Weighting the Studies

Each study included in the metaanalyses was weighted by study size and quality score. For the VAS, ODI, and modified MacNab analyses, the initial study weight was a direct inverse of the study variance and was used to give more weight in the metaanalyses to those studies that used larger sample sizes and therefore produced the most statistically accurate results. For the complications rate analysis, the study was weighted by the sample size directly.

A study quality score was included in the VAS, ODI, and modified MacNab analyses in an effort to account for the wide range in the type and quality of studies used in our metaanalyses. The quality score could range from 0.4 to 1.2 based on the components of the study (see **Table 1**) (16). The study quality score was multiplied by the inverse of the study variance plus the inter study treatment effect variation to obtain an adjusted study weight. The adjusted study weight gave more weight in the metaanalyses to studies that were well designed, executed, and analyzed.

Postoperative Medication	Needle Size (gauge)	O_3Conc. (wt %)	Volume (mL)		Second Treatment Included in Results	Image Guidance	Follow-up Time (mo)
			Intradiscal	Extradiscal*			
No	22	2.0 mL†	1–3	7–9	No	CT	1
NR	18–22	2.3–3.0	3–4	10	Yes (% NR)	CT	6 and 12
NR	22	2.3	6	4	NR	Fluoroscopy, CT	2 and 6
NR	22	2.1	5.8	6.5	No	CT	6
NR	22	NA	NA	NA	No	CT	6
NR	22	2.0	4	10	No	Fluoroscopy	1, 6, and 18
NR	22	2.0	4	10	No	18	7.17
No	22	2.3	NR	NR	Yes (20%)	Fluoroscopy	18
Yes	NA	NA	NA	NA	No	NA	18
NR	NR	3.4–4.2	4–9	10	NR	X–ray	3–24
Yes	No. 6	2.6–3.4	6–15	5–10	Yes (a few)	Fluoroscopy	3–12
NR	18–20	2.3	3–4	10	NR	CT	6 and 18
NR	22	2.0	4	8	NR	Fluoroscopy	0.5, 2, and 6
NR	22	2.0	4	8	NR	CT	0.5, 2, and 6
NR	22	3.0	1.5–4	Some (leaked from disc)	Yes (3.8%)	Fluoroscopy	2, 6, 12, and 18
Yes	19–21	2.3–3.0	4–6	15	Yes (60%)	Fluoroscopy (C-arm)	3–28

Calculating the Overall Treatment Effect

A DerSimonian and Laird weighted least-squares random-effects model (17) was used to combine the studies and obtain an overall treatment effect in the VAS, ODI, and modified MacNab analyses. The overall treatment effect was calculated for two different groups of studies: (i) all studies that used ozone and (ii) only those studies that used inclusion/exclusion criteria and treatment procedures similar to those outlined by FIO (12). As a result of the large number of studies that reported zero adverse events, the DerSimonian and Laird random-effects model may not be accurate for determining a combined treatment effect for the complication rate metaanalysis. Therefore, we used an exact method of combining these studies as suggested by Tian et al (18).

Check for Bias

It was important to check if bias was influencing the results of the metaanalyses. Publication bias in particular was a concern because our analyses mainly included published studies. Publication bias occurs because research with statistically significant results is potentially more likely to be submitted, published, or published more rapidly than work with null or nonsignificant results (19). For our case, it was more likely that studies with data for or against oxygen/ozone therapy were published, leaving out studies that may have only marginal results and thereby influencing the estimated effect in one direction or the other.

To assess publication bias, one can use the qualitative funnel plot test; however, we used the quantitative linear regression test (20) to assess for the probability of bias. This method statistically

Table 5
Summary of Outcome Measures from Literature Search (21–24,27–33)

Study (References)	Treatment Arm	VAS	
		VAS Change	Pts. with Improved VAS (%)
ActiveO Trial (Unpublished data)	Single	3.7	75
Muto et al, 2008 (21)	All	>3	85
	Soft disc herniation	NR	NR
	Multiple disc herniations	NR	NR
	FBSS	NR	NR
Oder et al, 2008 (23)	All Arms	3.4	62.5
	Group I: bulging disc	3.5	NR
	Group II: herniated disc	3.5	NR
	Group III: postoperative	3	NR
	Group IV: osteochondrosis	2.5	NR
	Group V: nondiscal	2.7	NR
Gallucci et al, 2007 (22)	Group B: ozone and steroid	NA	NA
	Group A: steroid only	NA	NA
Leonardi et al, 2006 (28)	Group A: symptoms lasting <6 months	NA	NA
	Group B: symptoms lasting >6 months	NA	NA
Buric et al, 2005 (27)	Ozone	4.0	90
	Microdiscectomy	4.1	93
Qing et al, 2005 (29)	Single	NA	NA
Ying et al, 2005 (30)	Single	NA	NA
Muto et al, 2004 (31)	Group 1: degenerative disease complicated by herniation	NA	NA
	Group 2: L4–L5 or L5–S1 herniated discs	NA	NA
	Group 3: multiple disc herniations	NA	NA
	Group 4: FBSS	NA	NA
	Group 5: calcified disc herniations	NA	NA
	Group 6: herniated disc associated with stenosis	NA	NA
Andreula et al, 2004 (32)	Group A: ozone	NA	NA
	Group B: ozone and steroid	NA	NA
Buric et al, 2003 (24)	Single	3.77	NR
He et al, 2003 (33)	Single	NA	NA

Note.—FBSS = failed back surgery syndrome; JOA = Japanese Orthopaedic Association; NA = not applicable; NR = not reported.
* Surgery required.

examines the symmetry of the funnel plot. This is done by first performing a linear regression of the adequate standardized effect (Y_i^*) (see equation 2) versus the precision (P_i) (see equation 3) of each study to obtain the y-intercept. If bias is not affecting the study, the y-intercept will be zero. Therefore, we test whether the y-intercept is zero. It has been recommended that the 90% confidence level (ie, α of 0.1) should be used for this test (20). Therefore, if $P > .1$, there is no adequate evidence to support the existence of bias at the 90% confidence level.

$$\text{Standardized effect} = Y_i^* = \frac{Y_i}{\sqrt{V_i}} \quad (2)$$

$$\text{Precision} = P_i = \frac{1}{\sqrt{V_i}}, \quad (3)$$

where Yi is the study treatment effect and Vi is the study variance.

Estimating Missing Data

In some cases, the literature did not report data that were needed to perform the metaanalyses. If possible, these data were estimated with the use of statistical methods. If there was not a practical way to estimate these data, the study was removed from the metaanalysis. The most common missing piece of data was the SD required for the ODI and VAS metaanalyses. To estimate the missing SDs, the average SD was calculated from those studies that reported SD and used comparable inclusion/exclusion criteria to those outlined in our contemporary unpublished study. Missing SDs from Muto 2008 (21) for both VAS and ODI were calculated from raw data we obtained from the author for 300 of the patients in this study (21). Subsequently, these SDs were used in calculating the estimates for those studies that did not report SDs.

The study of Gallucci et al (22) reported only the percentage of patients who had a posttreatment ODI score less than 20 points. By assuming that the change in ODI score followed a normal distribution, we were able to determine the mean group posttreatment ODI score based on the definition of a normal distribution and the method discussed earlier for determining the SD.

Postprocedure MacNab Outcome (%)					ODI/JOA		
Excellent, Good, or Fair	Excellent	Good or Fair	Poor	Failed*	ODI/JOA	ODI/JOA Change	Patients with Improved ODI/JOA (%)
80	25	55	7	7	ODI	28.4	73
NR	NR	NR	NR	NR	ODI	30	NR
75	40	35	25	NR	ODI	NR	NR
77	32	45	25	NR	ODI	NR	NR
60	25	35	40	NR	ODI	NR	NR
NA	NA	NA	NA	NA	ODI	18	NR
NA	NA	NA	NA	NA	ODI	16.5	NR
NA	NA	NA	NA	NA	ODI	24.5	NR
NA	NA	NA	NA	NA	ODI	5	NR
NA	NA	NA	NA	NA	ODI	8	NR
NA	NA	NA	NA	NA	ODI	12	NR
NA	NA	NA	NA	NA	ODI	38.4	74
NA	NA	NA	NA	NA	ODI	37.5	47
NA	NA	NA	NA	NA	ODI	9.8	54
NA	NA	NA	NA	NA	ODI	10.8	67
NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA
96.5	56	41	3	NR	NA	NA	NA
92.9	39	54	13	NR	NA	NA	NA
78.0	40	38	22	NR	NA	NA	NA
76.0	62	14	24	NR	NA	NA	NA
68.0	56	12	32	NR	NA	NA	NA
62.0	43	19	39	NR	NA	NA	NA
51.0	33	18	49	NR	NA	NA	NA
50.0	25	25	50	NR	NA	NA	NA
70.3	50.3	20.0	25.0	4.7	NA	NA	NA
78.3	53.3	25.0	16.7	5.0	NA	NA	NA
NA	NA	NA	NA	NA	JOA	54.7	NR
77.0	62	15	22.9	NR	NA	NA	NA

Some of the studies (23,24) used median ODI or VAS values instead of the mean. For us to use these studies in the metaanalyses, we assumed that the median was equal to the mean.

Plots

Forest plots were created to summarize the results of each metaanalysis. The forest plots provide a convenient way to compare the overall treatment effect between ozone treatments and other techniques. The study weight was also shown on the forest plots for convenience. The weights shown on the plots were calculated with all the included ozone studies.

The outcome scale plots include the minimum detectable change (MDC) and the minimum clinically important difference (MCID) lines for the respective scale. The MDC is the minimum statistically significant change (95% CI) that indicates improvement (VAS, 1.5 [25]; ODI, 15 [26]). The MCID is the minimum change that a patient perceives as beneficial (VAS, 1.9 [25]; ODI, 10 [25]). The numbers used for the ODI MCID and MDC are conservative. Hagg et al (25) listed the MDC for the ODI as 10, whereas Fritz et al (26) listed the MCID for the ODI as 6. We used the highest values as a worst case condition.

Software

Excel 2003 (Microsoft, Redmond, Washington) was used to perform the calculations and generate the forest plots. All data input was checked by an independent reviewer, and the spreadsheet was validated with metaanalysis input data with known outputs.

RESULTS

Literature Review

The literature search yielded 65 results, of which 11 studies (21–24,27–33) and our unpublished contemporary study were included in the metaanalyses. **Tables 2–6** (21–24,27–33) summarize the patient demographics (**Table 2**), inclusion criteria (**Table 3**), clinical trial relative ranking (ie, study quality score)

Table 6
Summary of Oxygen/Ozone Treatment Complications from Literature Search (21–24,27–33)

Study (References)	No. of Pts.	Complications	Description of Complication(s)	Status
ActiveO Trial (Unpublished data)	50	0	NA	NA
Muto et al, 2008 (21)	2,900	0	NA	NA
Oder et al, 2008 (23)	621	38 (6.1)	Aggravation of symptoms	Transient
Gallucci et al, 2007 (22)	82	0	NA	NA
Leonardi et al,	37	0	NA	NA
2006 (28)	52	0	NA	NA
Buric et al, 2005 (27)	30	0	NA	NA
Qing et al, 2005 (29)	602	3 (0.5)	Severe cardiohypogastric pain and distension; lumbar pain and distension; lower extremities and buttock pain and distension	Symptoms resolved automatically in 24 h; no special treatments required
Ying et al, 2005 (30)	323	8 (2.5)	Mild respiratory impairment, dyspnea and cornea stimulation caused by ozone allergy/reaction	Symptoms alleviated upon leaving ozone environment and inhaling oxygen and calming the patient
Muto et al, 2004 (31)	2,200	0	NA	NA
Andreula et al,	300	0	NA	NA
2004 (32)	300	2 (0.7)	Impaired sensitivity in the lower limb ipsilateral to the treatment	Resolved spontaneously after 2 h presumably because of periganglionic anesthetic injection
Buric et al, 2003 (24)	104	0	NA	NA
He et al, 2003 (33)	258	0	NA	NA
Total	7,859	51 (0.6)	—	—

Note.—Values in parentheses are percentages. NA = not applicable.

and treatment procedures (**Table 4**), outcome measures (**Table 5**), and complications (**Table 6**) of the included studies. There was considerable variation in the treatment procedures (ie, anesthetic agents and drugs used, ozone concentration, volumes injected intradiscally and extradiscally), inclusion/exclusion criteria, herniation type (ie, contained, extruded, and migrated), disc levels treated (ranging from L1–L2 to L5–S1), and patient ages (13–94 years) in the included studies. The included studies were divided into those that had similar and dissimilar inclusion/exclusion criteria and treatment procedures (as indicated in **Figs 1–3**) to our unpublished contemporary study, which used inclusion/exclusion criteria and treatment procedures believed to give the best results when performing oxygen/ozone therapy based on recommendations from FIO (12). A total of 54 studies were excluded for one or more of the following reasons: (i) article was not available, (ii) cervical discs were treated and reported, (iii) discussion with no clinical results, (iv) inadequate details, (v) multiple paravertebral injections were administered, (iv) no English translation was available, (vii) ozone was not injected intradiscally, (viii) article was a response to a literature article, (ix) it was suspected that the same patient population from an included study was reported, or (x) it was an unrelated study.

Metaanalyses

Figures 1–3 show the results of the metaanalyses for VAS, ODI, and modified MacNab score, respectively. The overall treatment effect for study arms with similar inclusion/exclusion criteria as our unpublished contemporary study shows a mean improvement of 3.9 points in VAS and 25.7 points in ODI, whereas the modified MacNab outcome analysis indicates a 79.7% likelihood of improvement. The random-effects model for all included study arms shows a mean improvement of 3.5 points in VAS and 21.0 points in ODI and a 78.2% likelihood of an improvement based on the modified MacNab scale. The 95% CI for the random-effects model of all ozone studies on the ODI scale is just below the MDC at 14.1 points. All other estimated mean treatment effects and 95% CIs are greater than the MCID and MDC values for the respective scale.

Figure 4 shows the results of the metaanalysis for the complication rate. The exact-inferences metaanalysis yielded an estimated 0.064% chance (95% CI, 0.000%–0.136%) of having a procedure-related complication.

Check for Bias

The results of the bias test are shown in **Figures 5–7**. In addition to the bias linear regression line, a second linear regression line that was forced through zero was added to each plot. The slope of the second regression line represents the theoretical unbiased case. The linear regression

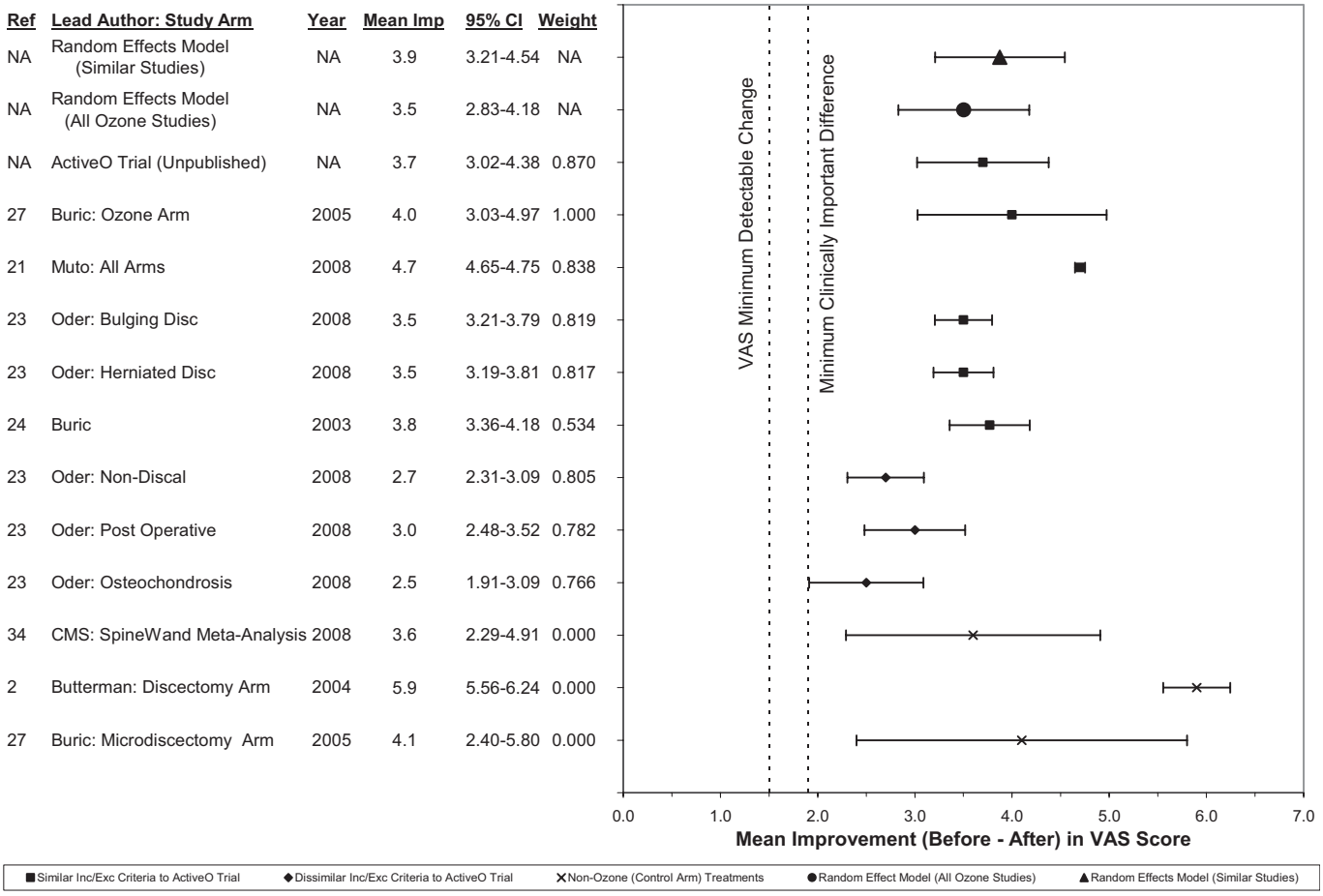

Figure 1. Metaanalysis of improvement in VAS scores after oxygen/ozone treatment of herniated discs.

test detected possible bias at a statistically significant level in the VAS ($P = .001$) and ODI ($P = .03$) metaanalyses but not in the modified MacNab scale metaanalysis ($P = 0.22$). The influence of bias on the predicted outcomes was examined by comparing the bias linear regression line to the unbiased (ie, forced through zero) linear regression line. Bias was found to be small (<10%) for both VAS and ODI. These results as well as potential causes for the bias are discussed later.

DISCUSSION

Our metaanalyses demonstrate the effectiveness and safety of oxygen/ozone therapy for the treatment of herniated discs with data from almost 8,000 patients and from multiple centers in multiple locations. Because the overall treatment effect is greater than the MCID and MDC levels, it is concluded that the treatment has a significant effect that is greater than the sensitivity of the scales being used, and it is beneficial from the patient's perspective. This is impressive in light of the broad inclusion criteria that included patients ranging in age from 13 to 94 years.

Our analyses show that inclusion/exclusion criteria have only a minor influence for Modified MacNab score (1.9%) and VAS (11.4%), but a more significant effect for ODI (22.4%). This shows that the patient selection criteria are important to obtain the best results, but that the oxygen/ozone therapy is still effective even with broad inclusion/exclusion criteria. When compared with studies that used the ArthroCare SpineWand (34,35), discectomy (2), and microdiscectomy (27), the oxygen/ozone treatment is similar for pain and function outcomes. The selected SpineWand and discectomy studies were chosen because they had the largest number of patients of the studies that were identified that used the VAS and ODI outcome scales. The safety of the oxygen/ozone treatment is far superior to that of other treatments for herniated lumbar discs, as it has a very low complication rate of 0.064% (**Fig 4**). In addition, no cases of discitis were reported after oxygen/ozone therapy, unlike all the other methods of disc volume reduction. This is most likely because ozone is a strong oxidizer and an excellent disinfecting agent.

The complications shown in the metaanalysis (**Table 6**) are minor and transient, and are easily avoidable by using a device that is designed to eliminate these types of complications (eg, ozone leakage into the treatment room and high ozone concentrations) during this procedure. The estimated complication rate from the metaanalysis is consistent with the FIO results

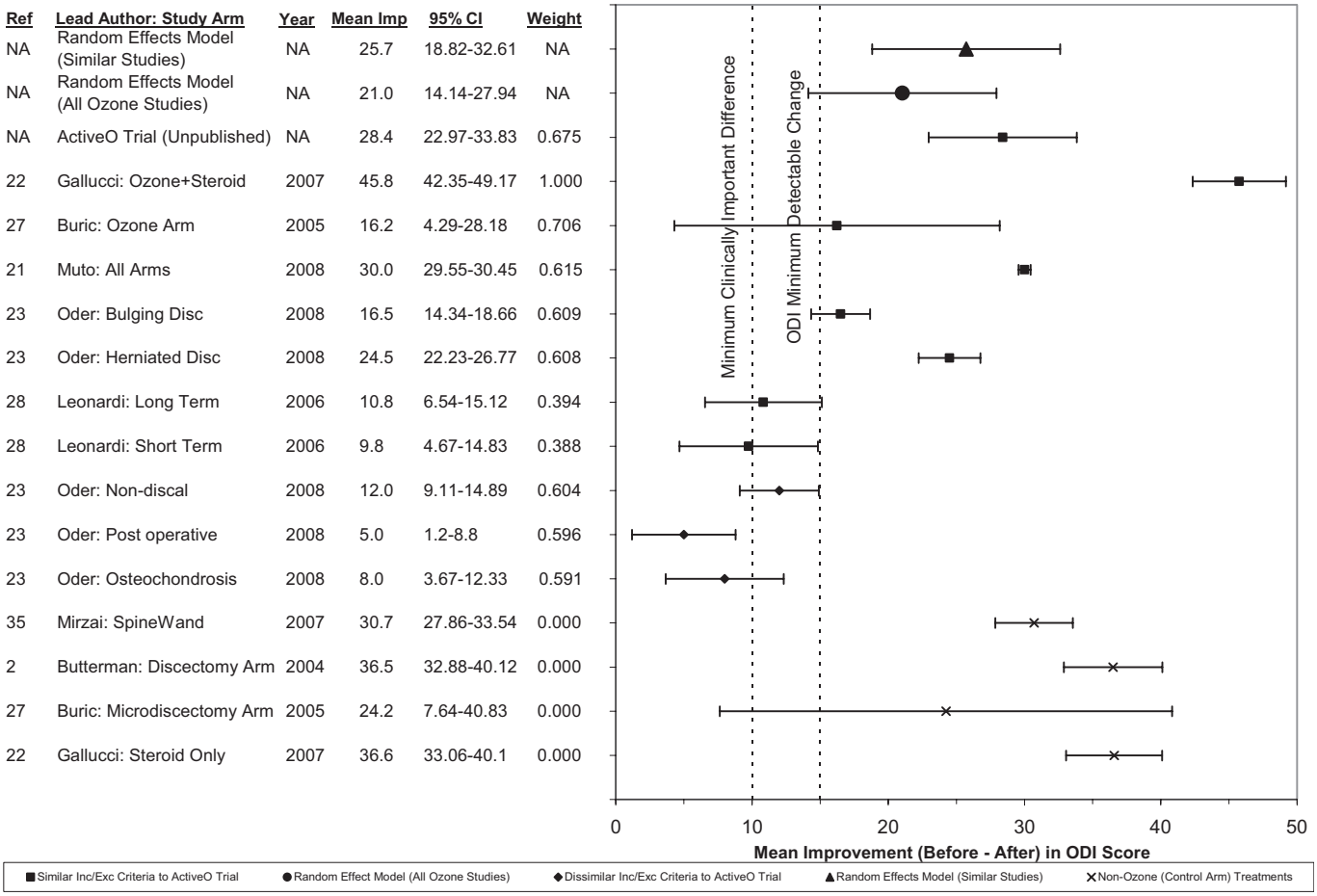

Figure 2. Metaanalysis of improvement in ODI scores after oxygen/ozone treatment of herniated discs.

(ie, no procedure-related adverse events in treatments on 15,000 patients) (12).

In addition to the complications summarized in **Table 6**, there have been a few published case reports documenting complications associated with oxygen/ozone treatment as referenced in the FIO publication (12) and in the study of Oder et al (23). These complications are avoidable if the FIO procedure is followed, which includes image guidance, 2%–3% ozone by weight, small injection volumes, and slow injection rates.

Although quality weighting is often incorporated into metaanalyses, it has been stated that caution should be used when quality weighting a study because quality scores are not direct measures of precision and may lack statistical or empirical justification (36). However, we used quality weighting to account for the large variation of study quality. Sensitivity analyses were performed to determine the influence of quality weighting. Quality weighting had only a small effect, in which the VAS scores were nearly unaffected (0.3% difference), the ODI scores decreased slightly (10% difference), and the MacNab scores increased (2.7% difference).

Missing data, especially SDs, was a problem in multiple studies used in these meta-analyses. We believe our estimate of SDs from comparable studies yields a good approximation for each of the lacking studies. The estimated SDs were based on a large sample size of greater than 350 patients. The SDs reported in studies that used nonsimilar inclusion/exclusion criteria were also similar to this estimate.

As previously discussed, Gallucci et al (22) reported the percentage of patients who had ODI scores less than 20% at the 6-month follow-up instead of the mean difference in ODI score. Therefore, the mean post-treatment ODI score was estimated based on normal distribution definitions and equations. This produced a calculated mean difference that is significantly higher than that of all other studies. This high mean difference value may be a result of differences in the treatment method of Gallucci et al (22). These were the only investigators who performed an intradiscal steroid injection in addition to intradiscal ozone and epidural ozone and epidural steroid injections.

The linear regression test indicated that bias may be a factor in the VAS and ODI metaanalyses. Comparison of the slope of the biased regression line to the unbiased regression shows that they are within 10% of each other in the VAS and ODI cases, suggesting that the effect of the bias on the metaanalyses was small. In addition, most of the studies are below the nonbias regression line, indicat-

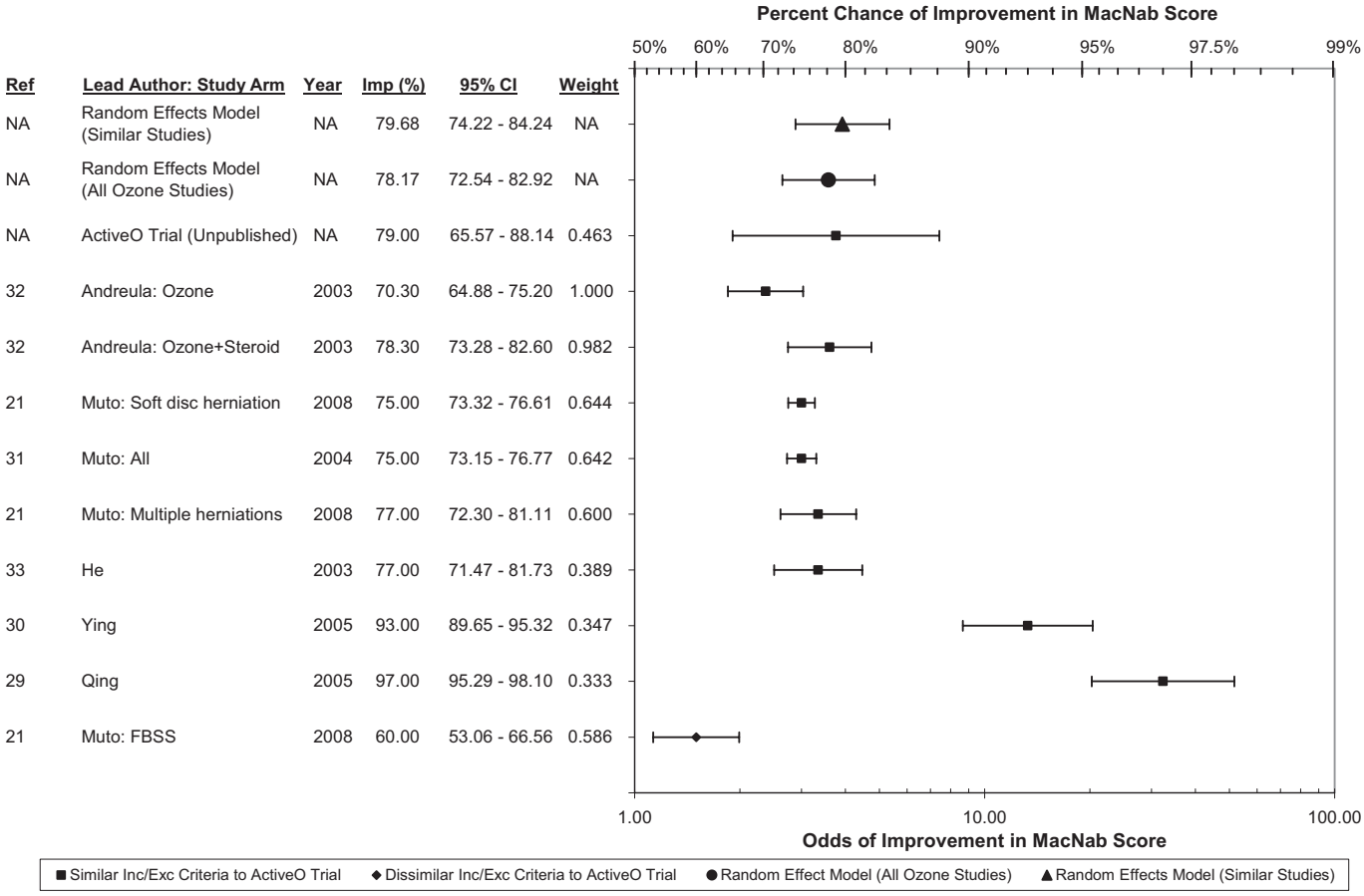

Figure 3. Metaanalysis of improvement in modified MacNab scores after oxygen/ozone treatment of herniated discs.

ing that the smaller studies are underestimating the treatment effect. Therefore, it appears that our metaanalyses are conservative. Sources of the bias may be related to true heterogeneity among studies because of varying technique, varying skill levels and experience among doctors, poor methodologic design of studies, and/or inadequate patient analysis.

Criticism of the quality of studies that have been performed in the treatment of herniated discs with oxygen/ozone has been published (37). We agree that most of the studies performed do not meet the quality of a well designed and executed randomized controlled trial. Therefore, as suggested by Barker and Carter (38), in the event of limited randomized controlled trials, care was taken to include only those studies that included some of the important aspects found in randomized controlled trials such as clear inclusion/exclusion criteria and the use of outcome assessments that have been shown to be effective and objective. Trials that were randomized or prospective were rated higher than retrospective studies in an attempt to minimize bias from lower-quality studies.

Oxygen/ozone therapy for the treatment of herniated discs is an effective and extremely safe procedure. The estimated improvement in pain and function is impressive in view of the broad patient inclusion criteria that included patients ranging in age from 13 to 94 years with all types of disc herniations. In addition, the pain and function results are similar to the results for lumbar discs treated with surgical discectomy, but the complication rate is much lower (<0.1%).

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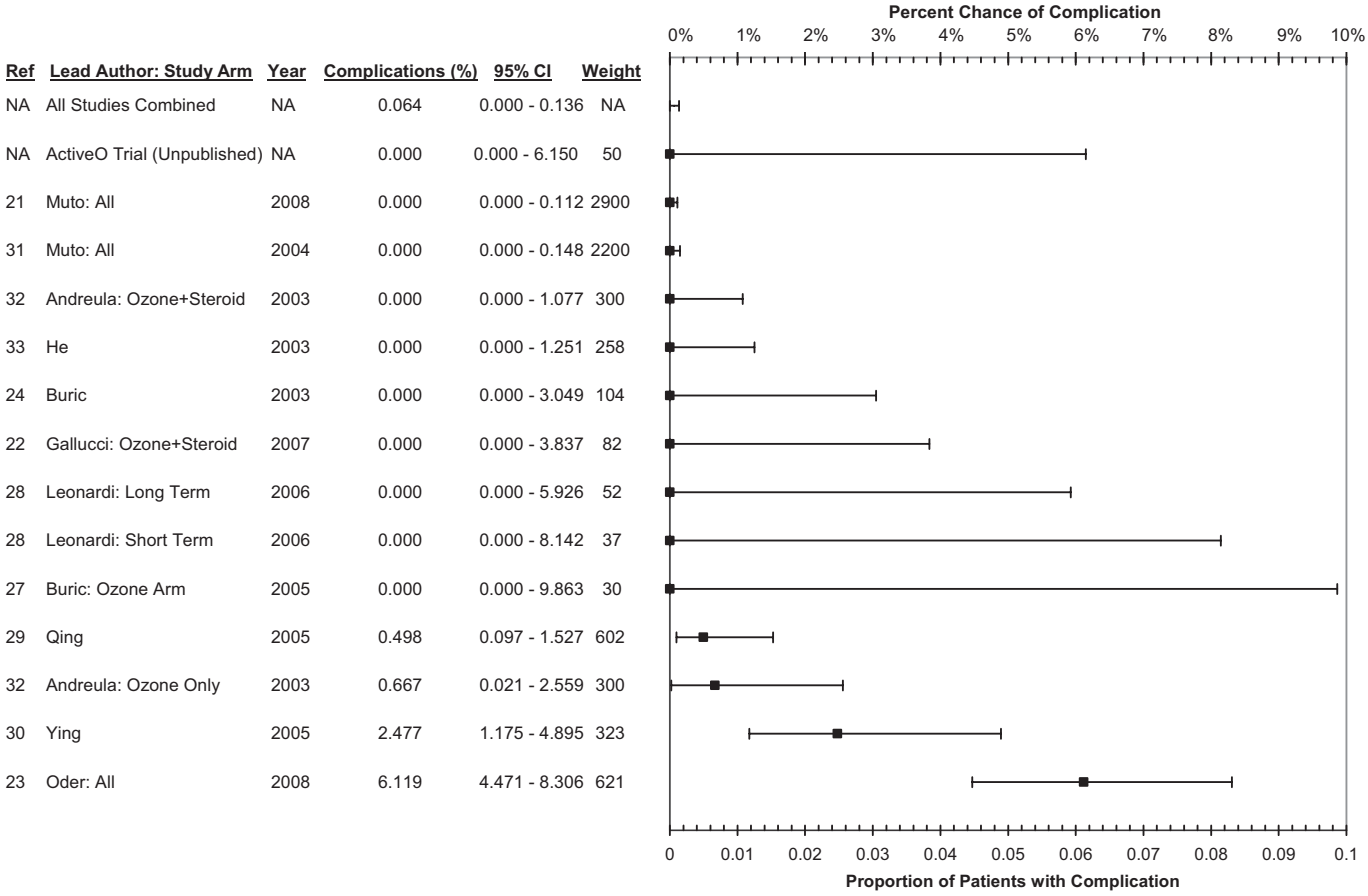

Figure 4. Metaanalysis of complication rate during and/or after oxygen/ozone treatment of herniated discs.

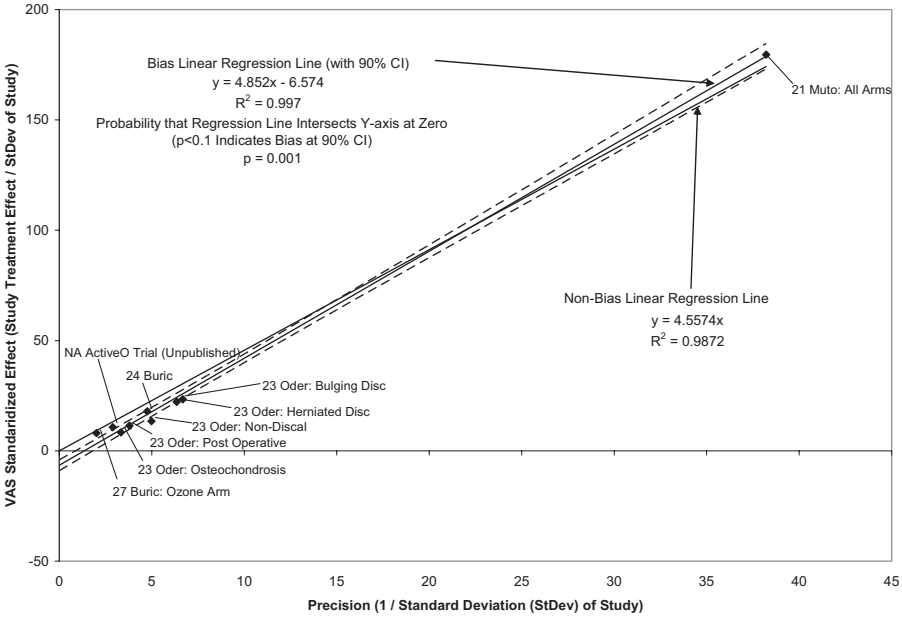

Figure 5. VAS linear regression bias test.

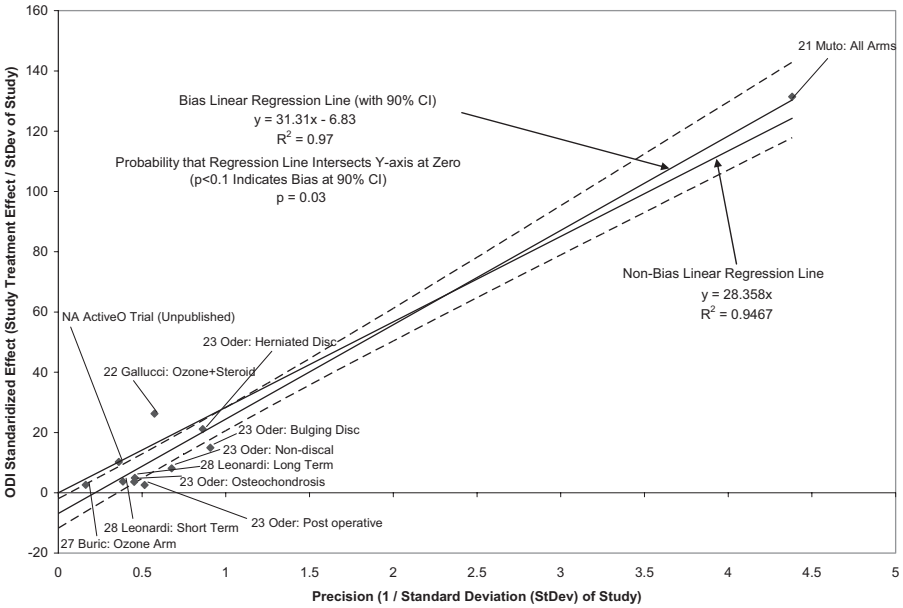

Figure 6. ODI linear regression bias test.

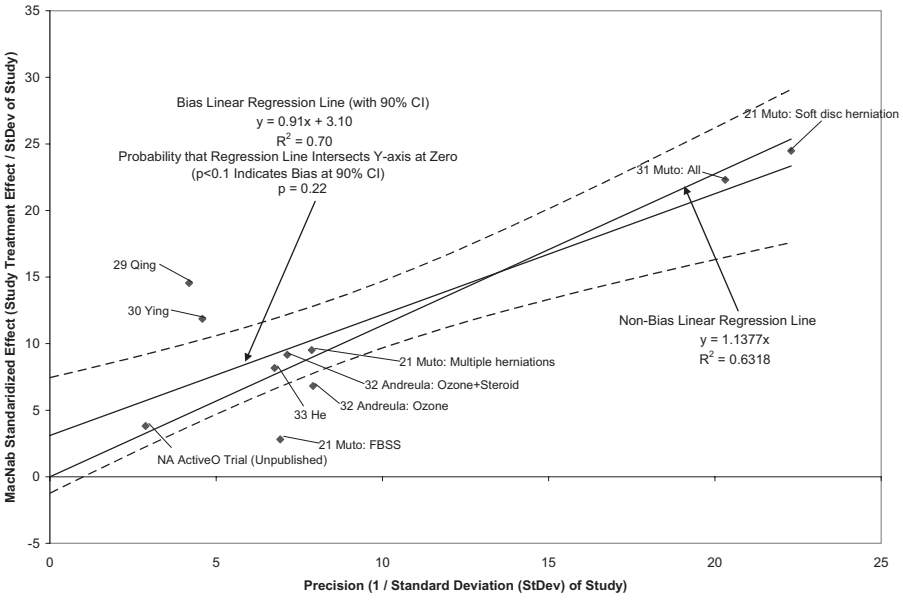

Figure 7. Modified MacNab linear regression bias test.

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