Twelve-Month Follow-up of a Randomized Clinical Trial Comparing Intradiscal Biacuplasty to Conventional Medical Management for Discogenic Lumbar Back Pain

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Abstract

Objective. This report conveys 12-month outcomes of subjects treated with intradiscal biacuplasty (IDB) and conservative medical management (CMM) for chronic low back pain of discogenic origin, and results for subjects who elected to receive IDB + CMM 6 months after CMM-alone.

Methods. Sixty-three subjects were originally randomized to the IDB + CMM group (N = 29) or CMM-alone (N = 34). Six months following continuous CMM-alone treatment, participants in this study group were permitted to “cross-over” to IDB + CMM (N = 25), and followed for an additional 6 months. The original IDB + CMM study subjects were followed for a total of 12 months (N = 22).

Results. Pain reduction at 12 months was statistically significant and clinically meaningful in the original IDB + CMM group compared to baseline. Functional and disability outcomes were also improved statistically and clinically. Fifty-five percent of the IDB + CMM patients responded to treatment with a mean VAS reduction of 2.2 points at 12 months. Furthermore, 50% and 64% of subjects reported clinically significant improvements in SF36-PF and in ODI, respectively. There was a 1.7-point reduction (improvement) on a 7-point PGIC scale, and a 0.13-point increase (improvement) in the EQ-5D Health Index. Fifty-percent of cross-over subjects responded to IDB + CMM intervention. Mean outcome scores for cross-over subjects were similar to those of the originally-treated subjects, and
Conclusions. The study demonstrated long-term functional and disability endpoints were improved statistically and clinically compared to respective baseline values.

The ethical approval was obtained from the Western Institutional Review Board (IRB) (Puyallup, WA), George Washington University IRB (Washington, DC), JPS Health Network IRB (Fort Worth, TX), and Cleveland Clinic IRB (Cleveland, OH). Each patient was informed about the study in accordance with the Declaration of Helsinki and Good Clinical Practices (21 CFR 50, ICH E2A.4.8), and acknowledged that study participation was voluntary by signing and dating the approved patient informed consent form prior to study entry. A previous publication [19] provided detailed descriptions of the study’s general methods and patient demographics as well as IDB procedure details. Highlights of those study features as applicable to this 12-month follow-up report concerning the original IDB + CMM treatment group, and the cross-over study subjects, are provided below.

Study Design

This was a prospective, randomized, cross-over, open-label, multi-center (nine sites) clinical study that utilized a parallel-group design for comparison of IDB + CMM to CMM-alone for treatment of discogenic LBP. Sixty-three individuals with chronic (symptomatic > 6 months) lumbar discogenic LBP participated in this study. Initially, 29 subjects were randomized to the IDB + CMM treatment group, and 34 to the CMM-alone group. Six months after randomization of the study subjects to respective groups, subjects in the CMM-alone group were allowed to receive IDB, and continue CMM treatment if they requested. At the time of informed consent, patients were explicitly told that the investigators did not know whether or not IDB was more or less effective than CMM, and that CMM-alone may have been sufficiently effective. These “cross-over” study subjects were followed up for additional 6 months.

The physician investigators selected individualized CMM treatment plans for their respective patients. No deliberate pharmacological alterations were made prior to or during the course of the clinical trial. Minimally invasive treatments were allowed for all study subjects during the study to address potential secondary pain generators (e.g., originating from the facet or sacroiliac joints [20]). However, more invasive treatments for back pain, including, but not limited to, intradiscal electrothermal therapy (IDET), spinal fusion, and discectomy, were not permitted.

Study Outcomes

Results of this study comparing IDB + CMM to CMM-alone at 1, 3, and 6 months were previously published [19]. The primary outcome variable was pain level change as measured by means of the visual analog scale (VAS). Secondary outcomes include assessments of function, disability, mental health, and quality of life as indicated by: 1) Short Form 36-Physical Functioning
Comparative Effectiveness Trial of Intradiscal Biacuplasty

Subjects as “treatment responders” [17,21]. Proportions of each study group that had substantial pain relief (≥50% decrease in VAS [21]) were also calculated. Clinically significant differences in SF36-PF (0–100 points) and ODI (0–100 points) were defined as ≥a 10-point decrease and ≥a 10-point decrease, respectively [17]. The PGIC was based on a seven-point scale; “very much improved” (1); “much improved” (2); “minimally improved” (3); “no change” (4); “minimally worse” (5); “much worse” (6); and “very much worse” (7), to express how treatment for their back pain has affected their overall health satisfaction. The responses of “very much improved” (1) or “much improved” (2) were considered clinically significant, which approximates descriptions of clinically significant scores expressed previously [22]. The minimal clinically important difference (MCID) for the EQ-5D Health Index (−0.59–1 point) score change has been defined as an increase by at least 0.074 points [23]. The proportions of subjects in each group that met this outcome benchmark during the first 6 months of the study [19]. The mean VAS score reduction specifically in the treatment responder subgroup (N = 12) was 4.4, which was two points greater than that observed for the entire original IDB + CMM cohort. Furthermore, at 12 months, 41% of subjects had a decrease in the VAS score ≥50% (VAS score reduction range: 56–100%), which is nearly equivalent to the proportion of subjects (42%) in the original IDB + CMM group that met this outcome benchmark during the first 6 months of the study [19].

Results

Study Subject Disposition

Of the originally 297 patients screened, 63 were enrolled as the study subjects, and were consented and randomized into IDB + CMM (N = 29) and CMM-alone (N = 34) groups, respectively.

Figure 1 displays a flowchart of the study subjects until conclusion of this project, after the last patient completed the 12-month follow up. At 12 months following the original IDM + CMM treatment, primary outcome data on 22 of the original 29 (76%) subjects in this cohort were available. Six months after their randomization to CMM-alone treatment, 28 of 34 (82%) subjects in this group remained in the study, and 25 of 28 (89%) elected to cross-over to IDB + CMM treatment. Outcome data on 22 of these 25 (88%) subjects was available after 6-months.

Pain Assessment in Original IDB + CMM Group at 12 Months

The mean 2.2 point decrease in VAS reported at 12 months in the IDB + CMM group was statistically and clinically significant (Table 1). Improvement noted at the 12-month time-point has remained consistent with what was reported at 6 months, where mean improvement of 2.4 points was identified [13] representing a sustainable response to IDB + CMM [17]. Fifty-five percent of subjects in the IDB + CMM group qualified as treatment responders [Figure 2] [17,21], which exceeded the proportion (50%) of treatment responders observed within this group at 6 months [19]. The mean VAS score reduction specifically in the treatment responder subgroup (N = 12) was 4.4, which was two points greater than that observed for the entire original IDB + CMM cohort. Furthermore, at 12 months, 41% of subjects had a decrease in the VAS score ≥50% (VAS score reduction range: 56–100%), which is nearly equivalent to the proportion of subjects (42%) in the original IDB + CMM group that met this outcome benchmark during the first 6 months of the study [19].

Assessment of Secondary Study Outcomes of Original IDB + CMM Group at 12 Months

At 12 months, parameters of function, disability, and quality of life (SF36-PF, ODI, PGIC, and EQ-5D VAS) were statistically improved compared to the respective mean baseline scores (Table 2). Furthermore, the 12-month average IDB + CMM group score-changes for SF36-PF, ODI, and EQ-5D Health Index were clinically significant [17,23] (Table 2). The average BDI and EQ-5D Health Index scores at 12 months were not statistically different from their respective baselines. Figure 3 demonstrates that 50% and 64% of IDB + CMM subjects had clinically significant [17] SF36-PF (A) and ODI (B) score-changes, respectively, at 12 months.

Data Analysis

Analysis of the primary outcome variable (VAS) between visits within each treatment group was conducted by analysis of variance (ANOVA) with visit as fixed effect, and subject and center as block effects, at a 5% level of significance (P < 0.05). For secondary outcome variables between visits within each treatment group, ANOVA was conducted with visit as fixed effect, and subject and center as block effects, at P ≤ 0.0083 to indicate significance. A type I error adjustment for multiplicity was performed on these secondary parameters to preserve the overall 5% level of significance (thus 5%/6 parameters = 0.83%; P ≤ 0.0083).

The number of subjects from which data were collected to make each assessment determination is indicated in the presentation of study results.
Analysis of PGIC outcomes revealed the majority of study subjects in the original IDB + CMM group experienced improvement (Figure 4, A and B), with 46% of subjects (N = 22) achieving a clinically significant benchmark [22] at 12 months (Figure 4A). Approximately 15% of subjects in the IDM + CMM group had no change in PGIC (Figure 4, A and B), while nearly 10% reported worsening of their condition following the treatment (Figure 4B).

Pain Assessment in the Cross-Over Group at 12 Months

The majority (89%) of available CMM-alone subjects opted to receive IDB in addition to CMM 6 months after being originally randomized to the CMM-alone group. These subjects were followed-up for additional 6 months (12 months overall participation in the study). The cross-over group average VAS score improved...
from mean baseline score at 6 months following IDB + CMM treatment (Table 3), and was equivalent to that of the original IDB + CMM cohort at 6 months (−2.4) [19]. Fifty-percent of the subjects in the cross-over group qualified as treatment responders (Figure 5) [17,21], which is consistent with the fraction of treatment responders observed in the original IDB + CMM group at 6 months [19]. Twenty-seven percent of cross-over subjects experienced a reduction in the VAS score ≥ 50% (VAS score reduction range = 80–100%) [19]. The average decline in the VAS score in the treatment responder sub-group (N = 11) was 4.5, which surpassed the point reduction observed in the entire cross-over group by more than two points.

Assessment of Secondary Study Outcomes of Cross-Over Subjects at 12 Months

Twelve-month function, disability, and quality of life variables, as assessed by the average SF36-PF, ODI, PGIC, and EQ-5D Health Index scores at 6-months following IDB + CMM treatment, were each statistically better than their respective average baseline scores (Table 4). Although the average BDI and EQ-5D VAS scores improved, they were not statistically different from their respective mean baselines. The mean functional score-changes for SF36-PF, ODI, and EQ-5D Health Index were clinically significant [17,23] (Table 4). Figure 6 illustrates that 50% and 55% of cross-over subjects had clinically significant [17] SF36-PF (A) and ODI (B) score-changes, respectively, at 6 months. Nearly 70% of study subjects in the cross-over group experienced improvements in PGIC (Figure 7, A and B), with approximately 40% of subjects having clinically significant changes [22] 6 months later (Figure 7A). Less than 15% of subjects in the cross-over group had no

Table 2 Two-month assessments—originally treated IDB + CMM group: physical functioning, disability, mental state, patient impression, and quality of life

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean baseline score (SD) (N)</th>
<th>Mean 12-month score (SD) (N)</th>
<th>Statistically significant difference?*</th>
<th>Mean 12-month score—change from baseline (SD) (N)</th>
<th>Clinically significant score-change?†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF36-PF</td>
<td>48 (27) 62 (28)</td>
<td>Yes</td>
<td>15 (21)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>(29)</td>
<td>(22)</td>
<td>(P = 0.003)</td>
<td>(22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODI</td>
<td>42 (16) 30 (21)</td>
<td>Yes</td>
<td>−14 (18)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>(29)</td>
<td>(22)</td>
<td>(P = 0.002)</td>
<td>(22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>8 (7) 8 (9)</td>
<td>No</td>
<td>−0.24 (6)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>(28)</td>
<td>(22)</td>
<td>(P = 0.86)</td>
<td>(21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC</td>
<td>4.4 (1) 2.9 (1.5)</td>
<td>Yes</td>
<td>−1.7 (1.6)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>(28)</td>
<td>(22)</td>
<td>(P &lt; 0.001)</td>
<td>(21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>56 (27) 76 (16)</td>
<td>Yes</td>
<td>24 (33)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>(29)</td>
<td>(22)</td>
<td>(P = 0.003)</td>
<td>(22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D health index</td>
<td>0.57 (0.21) 0.71 (0.26)</td>
<td>No</td>
<td>0.13 (0.23)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>(29)</td>
<td>(22)</td>
<td>(P = 0.04)</td>
<td>(22)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; N = number of subjects; N/A = not applicable; SF36-PF = short form 36-physical functioning; ODI = Oswestry disability index; BDI = Beck’s depression inventory; PGIC = patient global impression of change; EQ-5D VAS = a visual analog scale-based quality-of-life assessment; EQ-5D Health Index = a quality-of-life assessment.

*P values are based on ANOVA conducted with visit as fixed effect, and subject and center as block effects, at P ≤ 0.0083 to indicate significance.

†A clinically significant score change for SF36-PF is ≥ a 15-point increase, and ≥ a 10-point decrease for ODI [17].
Figure 3 Twelve-month SF36-PF and ODI outcomes: Original IDB + CMM study group SF36-PF (A) and ODI (B) score changes, and proportions of subjects with clinically significant score changes in group, at 12 months. A clinically significant score-change for SF36-PF is \( \geq 15 \)-point increase, and \( \geq 10 \)-point decrease for ODI [17]. Each bar indicates the score change from baseline to 12 months for each subject. The "(0)" notation indicates the score change of a study subject.

Figure 4 Twelve-month PGIC outcomes: Original IDB + CMM study group scores (A) and score changes (B), and proportions of subjects with clinically significant, no changes, or worsened changes in scores, at 12 months. The PGIC scale is: score of 1, "very much improved" (overall health satisfaction); 2, "much improved"; 3, "minimally improved"; 4, "no change"; 5, "minimally worse"; 6, "much worse"; 7, "very much worse." The responses of "very much improved" (1) or "much improved" (2) were considered clinically significant [22]. The "(0)" notation indicates that no study subject met the designated outcome.
Table 3  Six-month assessment—cross-over group: pain

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean baseline score (SD) (N)</th>
<th>Mean 6-month score (SD) (N)</th>
<th>Statistically significant difference?*</th>
<th>Mean 6-month score—change from baseline (SD) (N)</th>
<th>Did group respond to treatment?†</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>7 (2) (23)</td>
<td>4.7 (3) (22)</td>
<td>Yes (P &lt; 0.001)</td>
<td>-2.4 (3) (22)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VAS = visual analog scale; SD = standard deviation; N = number of subjects.
*P values are based on ANOVA conducted with visit as fixed effect, and subject and center as block effects, at a 5% level of significance (P < 0.05).
†A treatment response is defined as at least a two-point or 30% decrease from baseline in the VAS score [17,21].

Figure 5  Six-month VAS outcomes: Cross-over study group VAS score changes, and proportion of treatment responders in group, at 6 months. A treatment responder had at least a two-point or 30% decrease from baseline in the VAS score [17,21]. Number of subjects that reported data = 22. Each bar indicates the score change from baseline to 6 months for each subject. *Score changes met 30% decrease from baseline criterion to qualify respective subjects as treatment responders.

PGIC score change (Figure 7, A and B), while nearly 15% reported worsening of their condition (Figure 7B).

Comparison of CMM-Alone Group Outcomes to the Cross-Over Group

Several independent indicators demonstrated the cross-over group results at 6 months were more favorable than those observed in the CMM-alone group at 6 months, and were similar to the 6-month recorded outcomes in the originally-treated IDB + CMM group. First, the VAS-conditioned treatment response rate of the CMM-alone cohort at 6 months was 18% [19], while this rate for the cross-over group was 50% (Figure 5). Next, the proportions of cross-over group subjects with clinically significant functional changes in SF36-PF and ODI scores were 50% and 55% (Figure 6) respectively, while only 22% and 11% of the CMM-alone group reported such changes at their 6-month visit. The EQ-5D Health Index score at 6 months was significantly different from the baseline in the cross-over group only (Table 5). Finally, while none of the CMM-alone group average outcome scores were significantly different compared to respective baseline values at 6 months, mean scores for the VAS, SF36-PF, ODI, and PGIC were significantly different at this time-period for both the cross-over and original IDB + CMM cohorts (Table 5).

Opioid Use

Daily opioid intake at baseline was 22.3 milligrams (mg) in the original IDB + CMM group (N = 28). There was a mean 11 mg dose reduction in opioid use in this group (N = 21) at 12 months. In the cross-over group, daily opioid usage at baseline was 27 mg (N = 23). Six months after IDB + CMM treatment, the average daily opioid use in this group (N = 22) was reduced by 3.4 mg.

Adverse Events in Original IDB + CMM and Cross-Over Groups

There were no IDB-related AEs in the original IDB + CMM or cross-over group from 6 to 12 months of the study, and 6 months of IDB + CMM treatments, respectively.

Discussion

This report of 12 month results for the original IDB + CMM cohort, as well as 6-month outcomes of the cross-over group, demonstrated long-lasting benefits, and strengthens the results reported previously at 6 months [19].

The public healthcare burden of treatments for chronic LBP, from routine conservative care to spinal surgery, has been steadily increasing. However, the outcomes of these treatments have become a subject of criticism and scrutiny of leading epidemiologists and proponents...
of value-based healthcare [24–26]. As clinicians, patients, and payers search for long-term efficacious therapies for patients that bridge the gap between current options that are often unsuitable or lack efficacy, the role of IDB may become indispensable.

The current results demonstrate statistically significant, clinically relevant, and durable improvements in pain (VAS), function and disability (SF36-PF, and ODI), and satisfaction (PGIC). The VAS-based pain scores continued to improve past 6 months given that 55% of

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**Table 4** Six-month assessments—cross-over group: physical functioning, disability, mental state, patient impression, and quality of life

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean baseline score (SD) (N)</th>
<th>Mean 6-month score (SD) (N)</th>
<th>Statistically significant difference?*</th>
<th>Mean 6-month score—change from baseline (SD) (N)</th>
<th>Clinically significant score-change?†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF36-PF</td>
<td>42 (25) (23)</td>
<td>56 (27) (22)</td>
<td>Yes (P &lt; 0.001)</td>
<td>17 (19) (22)</td>
<td>Yes</td>
</tr>
<tr>
<td>ODI</td>
<td>42 (15) (23)</td>
<td>29 (16) (22)</td>
<td>Yes (P &lt; 0.001)</td>
<td>−13 (14) (22)</td>
<td>Yes</td>
</tr>
<tr>
<td>BDI</td>
<td>8 (5) (23)</td>
<td>7 (5) (22)</td>
<td>No (P = 0.18)</td>
<td>−1.6 (5) (22)</td>
<td>N/A</td>
</tr>
<tr>
<td>PGIC</td>
<td>4.7 (1) (23)</td>
<td>3 (1.5) (22)</td>
<td>Yes (P &lt; 0.001)</td>
<td>−1.8 (2) (22)</td>
<td>N/A</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>58 (26) (23)</td>
<td>68 (24) (22)</td>
<td>No (P = 0.15)</td>
<td>10 (32) (22)</td>
<td>N/A</td>
</tr>
<tr>
<td>EQ-5D health index</td>
<td>0.54 (0.2) (23)</td>
<td>0.71 (0.2) (22)</td>
<td>Yes (P = 0.005)</td>
<td>0.17 (0.2) (22)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

SD = standard deviation; N = number of subjects; N/A = not applicable; SF36-PF = short form 36-physical functioning; ODI = Oswestry disability index; BDI = Beck’s depression inventory; PGIC = patient global impression of change; EQ-5D VAS = a visual analog scale-based quality-of-life assessment; EQ-5D Health Index = a quality-of-life assessment.

*P values are based on ANOVA conducted with visit as fixed effect, and subject and center as block effects, at $P \leq 0.0083$ to indicate significance.

†A clinically significant score-change for SF36-PF is $\geq$ a 15-point increase, and $\geq$ a 10-point decrease for ODI [17].

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**Figure 6** Six-month SF36-PF and ODI outcomes: Cross-over study group SF36-PF (A) and ODI (B) score changes, and proportions of subjects with clinically significant score changes in group, at 6 months. A clinically significant score-change for SF36-PF is $\geq$ a 15-point increase, and $\geq$ a 10-point decrease for ODI [17]. Each bar indicates the score change from baseline to 6 months for each subject. The “(0)” notation indicates the score change of a study subject.
subjects in the original IDB + CMM group qualified as treatment responders (Figure 2) [17,21] compared to 50% having been treatment responders within this group at 6 months [19]. Results for six of the same subjects in the original IDB + CMM group did not meet the “treatment responder” and “clinically significant” criteria set for the VAS or SF-36 and ODI at 12 months, while results for others in this group met at least one qualification criterion. The original IDB + CMM group had a clinically relevant mean score change in the EQ-5D Health Index at 12 months, indicating a trend towards overall improvement in health status. Although BDI mean improvement did not reach statistical significance, this was not unexpected because subjects entering the trial were not clinically depressed (mean baseline score of 8), further decreasing the likelihood of large changes. Overall, the beneficial effects on pain of IDB + CMM were ongoing at 12 months, which was congruent with previously published results (mean point reduction of 2.9 on the numerical rating scale [NRS]) in a randomized sham-controlled efficacy trial at 12 months by Kapural et al. [17].

The cross-over group reported a statistically significant mean pain score at 6 months following IDB + CMM treatment. Furthermore, 50% of subjects in the cross-over group qualified as treatment responders, which is equivalent to the proportion of treatment responders in the original IDB + CMM group at 6 months [19], demonstrating consistency of the procedure. Secondary outcome measures including SF36-PF, ODI, PGIC, EQ-5D Health Index demonstrated significant improvement at 6 months following cross-over to IDB + CMM. Results for seven of the same subjects in the cross-over group did not meet the “treatment responder” and “clinically significant” criteria set for the VAS or SF-36 and ODI at 6 months, while results for others in this group met at least one qualification criterion. Both the BDI and EQ-5D VAS showed improvement, but did not reach statistical significance. Clinically meaningful improvements were noted in the functional, disability, satisfaction, and quality of life metrics, as assessed by SF36-PF, ODI, PGIC, and EQ-5D Health Index, respectively, in this group. At 6 months, the pain outcome of the cross-over cohort in this current study was statistically improved, while that reported for a cross-over group elsewhere at 6-months was not [17].

The study demonstrated that 55% of study subjects in the original IDB + CMM group qualified as treatment responders. However, 64% reported significant functional benefit. Therefore, functional outcome was better than subjective perception of pain, and this is remarkable. Perhaps patients experienced more dramatic pain relief.
and increased their physical activity, and it might have resulted in more pain. Although 50% success in the primary outcome may be perceived as somewhat disappointing, it has to be weighed against available alternative options. The CMM did not result in significant changes in the primary and secondary outcomes. Results of spinal surgery for treatment of discogenic pain have been disappointing with an even less composite success rate of 33% [27], and significant risk of peri-operative and post-operative complications, including 20% risk of the failed back surgery syndrome [28]. The surgical options are more expensive and consume more resources. Moreover, post-operatively, surgical patients have more disability and require prolonged rehabilitation. On the contrary, IDB has been safe and only minimal morbidity reported in the present and other studies [13–17,19,29,30]. The post-IDB period is essentially similar to that which follows any image-guided injection, and the physical therapy program is tailored to functional restoration within 6 weeks.

It is important to note that this study was not statistically powered to evaluate reduction in opioid use, because the sample size was not adequate to detect statistically different changes between study groups. At the 12-month time-point, the original IDB + CMM group experienced a mean 11 mg dose-reduction in daily opioid usage (morphine equivalents), while mean daily opioid use of the cross-over group was reduced by 3.4 mg 6 months after IDB + CMM initiation. Thus, in addition to long-term analgesia afforded by IDB + CMM, these outcomes show the potential for diminished opioid use in clinical setting in which IDB + CMM would be implemented to treat discogenic LBP.

The number of AEs was nominal and consistent with a trial of this magnitude. There were no new procedure-related AEs identified as a result of biacuplasty in the cross-over group. No procedure-related SAEs were reported in this study. This absence of SAEs should not be taken lightly. Intradiscal biacuplasty has a much better risk-benefit ratio compared with other minimally-invasive and surgical methods. Intradiscal electrothermal therapy trials reported transient, but serious complications, such as foot drop, increased radicular pain, and incontinence [31]. Spinal fusion may be successful in only 33% of cases [27]. Moreover, it carries a significant risk of peri-operative and post-operative complications [32]. Similarly, disc replacement has been reported as effective with pain reduction and Oswestry Index by approximately 70% and 60%, respectively. However, the device-related serious complications may occur in about 20% [33].

The conceptual principles of IDB appeared to be robust, durable and actual. Utilizing thermal energy in a bipolar

Table 5  Cross-over group vs. CMM-alone group or original IDB + CMM group—mean outcome scores by statistical significance at 6 months

<table>
<thead>
<tr>
<th></th>
<th>CMM-alone*†</th>
<th>Cross-over*‡</th>
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<td>VAS</td>
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<td>Yes</td>
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<td></td>
<td>(P = 0.081)</td>
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</tr>
<tr>
<td>SF36-PF</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(P = 0.6)</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>ODI</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(P = 0.87)</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>BDI</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(P = 0.8)</td>
<td>(P = 0.18)</td>
<td>(P = 0.81)</td>
</tr>
<tr>
<td>PGIC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(P = 0.32)</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(P = 0.32)</td>
<td>(P = 0.15)</td>
<td>(P = 0.1)</td>
</tr>
<tr>
<td>EQ-5D health index</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(P = 0.79)</td>
<td>(P = 0.005)</td>
<td>(P = 0.021)</td>
</tr>
</tbody>
</table>

VAS = visual analog scale; SF36-PF = short form 36-physical functioning; ODI = Oswestry disability index; BDI = Beck’s depression inventory; PGIC = patient global impression of change; EQ-5D VAS = a visual analog scale-based quality-of-life assessment; EQ-5D health index = a quality-of-life assessment.

*P values for VAS is based on ANOVA conducted with treatment as fixed effect and center as block effect at a 5% level of significance (P ≤ 0.05) [19].
†P values for secondary parameters are based on ANOVA conducted with treatment as fixed effect and center as block effect, at P < 0.001 to indicate significance [19].
‡P values for secondary parameters are based on ANOVA conducted with visit as fixed effect, and subject and center as block effect.
fashion to ablate nociceptive nerve fibers for pain relief are now supported by two large randomized controlled efficacy and effectiveness trials which contain greater than 120 patients collectively [17,19]. Lasting and consistent improvements in pain, function, disability, satisfaction, and quality of life across multiple parameters (both general and specific) were documented. Additionally, the procedure has shown to be reproducible in a multi-center scenario as noted by similarities in the previously reported single-center results [16,17]. The IDB + CMM strategy appeared to deliver consistent outcomes, particularly in this multi-center scenario. The results were comparable across subjects originally randomized to IDB + CMM to those who crossed-over at 6-months from CMM-alone to IDB + CMM. However, the subjects in the cross-over group demonstrated more modest improvement in pain scores. Only 27% of cross-over subjects achieved at least 50% improvement of pain, compared with 41% of subjects in the original IDB + CMM group. It is possible that delay in the anticipated IDB resulted in less dramatic responses in the cross-over group. It has been demonstrated that a waiting time of 12 weeks or more after waitlist enrollment for lumbar surgery was associated with a modest likelihood of experiencing worse pain at 6 months postoperatively [34]. Nevertheless, the responders in both groups had very significant pain reduction of more than four points. This result lasted, and appeared to improve during the study period.

It is unclear how long past the study period the analgesia afforded by IDB + CMM can last for the subjects in this investigation. It is possible that, similar to the return of facet pain following RF ablation of the medial branch nerves, patients suffering from discogenic LBP could experience pain again following IDB + CMM, and like facet RF ablation patients, need successive treatments at predictable intervals. The phenomenon of peripheral nerve regeneration has been noted [35,36], including the likelihood of its occurrence following RF ablation [37], and thus it is possible that regeneration of discal nerves targeted by biacuplasty could reconstitute nociceptive pathways responsible for pain signal transmission post-procedure. However, it is unclear if: 1) discal nerve regeneration alone is sufficient to produce pain again; and 2) if it is, the period of time for such regeneration to occur, and its variability among treated patients, is not known. Consequently, it is not clear how often repeat biacuplasty procedures, as attributable to the putative effect of nerve regeneration to produce pain again, would need to be performed, if at all.

This study suggests that although neo-innervation is accountable for nociception, usually a constellation of numerous factors is needed to be expressed to produce the phenotypical picture of chronic LBP. As indicated by Battilo and colleagues, “disc degeneration may be explained primarily by genetic influences and by unidentified factors, which may include complex unpredictable interactions” [38]. We may speculate that temporary interruption of the sensory input may suffice for long-term results.

The results reported here strongly suggest that IDB is safe and effective, and indicate that IDB fills an important niche as a minimally-invasive therapy to treat discogenic LBP in carefully selected patients.

Limitations

The sample size of this study was insufficient to constitute a statistically powered CMM-alone group after the first 6 months, and thus outcome comparisons between IDB + CMM and CMM-alone treatments could not be completed beyond this time-frame. The loss of study subjects in the CMM-alone group was indirectly related to an ethical concern that it was not in the best interest of patients to continue ineffective CMM and suffer from back pain. Therefore, they were offered an opportunity to cross over to IDB + CMM as a rescue treatment, which had already demonstrated its effectiveness [19]. Finally, not every eligible member of the IDB + CMM and cross-over study groups provided data at each respective follow-up time-point.

Medication diaries were not utilized within the trial and instead, medication intake data reflected the prescription practice of the investigators as prescribed doses of medications were captured. It is common practice to prescribe opioids on an “as needed” basis. For the purpose of analysis, the maximum allowable daily dose for that opioid was calculated and utilized. As a result, specific daily dose changes for “as needed” medications were harder to identify. Additionally, there are multiple psychosocial influences on the use, misuse, and prescribing habits of opioid medications that could have affected the ability to accurately reflect this variable.

Conservative medical management (CMM) was not standardized and the physicians were permitted to treat their patients based on personal clinical preferences. These practices vary from clinic to clinic and patient to patient, which reflects real-world application, and even in a research setting it is challenging to maintain standardized protocols. Additionally, the assessment tools in the study are externally-validated instruments and the internal validity related to reporting is unknown; however, the multi-variable indicators, both general and back pain specific, were implemented to counterbalance this drawback, and the outcome data demonstrated consistent improvements in pain, function, and quality of life, which lend credibility to the results. Moreover, the results of the treatment in terms of effect and duration replicated what has been previously shown in other studies [16,17,19].

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Comparative Effectiveness Trial of Intradiscal Biacuplasty


