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Research Article

Cost-Effectiveness of Intradiscal Methylene Blue Injection as Treatment for Discogenic Low Back Pain

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Abstract

Objective: Although the burden of discogenic chronic low back pain for the individual and for society is high, treatment options are few. Intradiscal methylene blue injection could be a cost-effective intervention.

Design and setting: Cost effectiveness study alongside a multicenter RCT comparing intradiscal injection with methylene blue to intradiscal lidocaine.

Subjects: Patients with, by provocation discography confirmed, discogenic low back pain.

Methods: Pain outcome and Cost information was obtained to assess the costs from a societal- and healthcare perspective with a time horizon of 6 months.

Results: The base case cost analysis showed an incremental cost per QALY of €71,571. Intradiscal methylene blue injection (IMBI) is more effective and more costly. The probability that IMBI is cost-effective ranged between 26% and 42%. Subgroup differences showed that cost-effectiveness of the IMBI treatment could be higher in a selected group of patients with more severe pain (>7 NRS), lower quality of life(<0.45 utility score), and with shorter disease duration (<5 years).

Conclusions: This study found that intradiscal methylene blue is not cost-effective. Costs decreased in both groups and prediction analysis showed a potential for effectiveness in a selected patient group.

Clinical relevance: Based on current evidence IMBI cannot be recommended for discogenic low back pain.

Keywords: *pain treatment, disc, methylene blue, pain intervention costs, cost-effectiveness*

Introduction

Low back pain (LBP) is a common condition with lifetime incidences of up to 80% [1]. In most cases acute LBP does not develop into chronic LBP; the global prevalence of chronic LBP is estimated to be 9% [2]. A presumed source of chronic LBP is lumbar disc degeneration [3]. The prevalence of chronic discogenic low back pain (CD-LBP) in patients with chronic low back pain (CLBP) is estimated to be 18% to 49% [3]. The large variation in prevalence could be caused by variation in diagnostic definition (with or without provocation discography, mixed origin of pain), or by patient selection within the studies [3,4].

The burden for society as well as for the individual patients who suffer CD-LBP is substantial [5]. These patients are often young, in the midst of a working career, and often suffer from severe and disabling pain with subsequent low quality of life. The total annual costs per patient in the Netherlands were calculated to be €8,000 estimated with the

friction costs method (51% healthcare and 49% societal costs) and €18,940 with the human capital cost method (22% healthcare and 78% societal costs) [5]. Societal costs were mainly due to work absence and healthcare costs were caused by patients searching for pain relief in regular health care and in complementary and alternative medicine (CAM) [5].

Treatment options for CD_LBP are limited and the search for optimal treatment is ongoing. In 2010, a study was published [6] concerning a minimal invasive intervention for CD-LBP, intradiscal methylene blue injection, reporting fantastic results (87% responders). The mechanism of action of this intervention was plausible [7,8], and it was decided to repeat this study. First a pilot study was performed in which the results were good for a minimal invasive intervention (40% responding) [9]. Subsequently, a multicenter placebo-controlled randomized controlled trial (RCT) was developed to assess the effectiveness of intradiscal methylene blue injection (IMBI) for CD-LBP compared to a placebo (saline/lidocaine) injection [10]. The economic evaluation presented in this paper was performed alongside this RCT [11].

Patients and Methods

Details of the trial design, study characteristics and outcomes measurements have been published previously [10]. In summary, 81 patients with a by discography confirmed diagnosis of CD-LBP were randomized from 2013 to 2017. The study was performed in three pain centers in the Netherlands, of which one was a university medical center.

Patients were screened for eligibility according to their clinical history, physical examination, and provocation discography. Main inclusion criteria were: a history consistent with lumbar discogenic pain, axial low back pain for at least 6 months, failed conservative management including drug therapy, structured exercise program, physical therapy or occupational therapy, a negative facet blockade, age between 18 and 66 years, neurological exam without motor deficit, pain intensity of at least 5 measured with the Numeric Rating Scale (NRS) 0 to 10 [12]. Main exclusion criteria were discogenic pain confirmed on more than two levels by provocation discography; disk height of >50%; Modified Dallas classification grade 5; extruded or sequestrated herniated discs; previous lumbar surgery or invasive intradiscal procedures on suspected levels; symptomatic lumbar spinal stenosis; grade 1-2 spondylolisthesis. Further exclusions included BMI (Body Mass Index (kg/m^2)) of ≥35, and pregnancy. Following randomization, 40 patients were assigned to the IMBI group and 41 patients to the placebo (control) treatment.

The IMBI treatment is a minimal invasive and safe intervention when performed by an experienced specialist in a specialized pain intervention center. The intervention consisted of an intradiscal injection with a mixture of 1ml methylene blue, 0.5 ml contrast dye (Iohexol-Omnipaque 300), and 0.5 ml lidocaine hydrochloride 2%.In the control treatment the methylene blue was replaced by 1 ml isotonic saline and contained also 0.5 ml contrast dye, and 0.5 ml lidocaine hydrochloride 2%.

This study was approved by European Union Drug Regulating Authorities Clinical Trials (EudraCT), registration number NL325 11.068.10 and the medical ethics committee (METC) of the Maastricht University Medical Centre, registration number 10-2-055. Clinical trials registration number is NTR2547. Patients were enrolled in the study from 2013 to 2017. Written informed consent was obtained from all participants.

Outcome measures

The economic evaluation, comparing effects (quality of life) and costs of IMBI to a placebo injection, was performed from a societal- and healthcare perspective with a time horizon of 6 months and performed according to guidelines for health economic evaluations [13]. All patients were included in the economic evaluation based on the intention-to-treat principle, based on data from health-related quality of life (HRQoL) questionnaires, case report forms, hospital records and cost questionnaires. HRQoL and cost questionnaires were administered at baseline, 3, and 6 months.

For the societal perspective, the quality-adjusted life year (QALY) outcome was used to represent health gain. The QALY is a measure of life expectancy weighted by HRQoL, the latter being presented as utility values. In the present study, HRQoL was measured with the EuroQol five Dimensions (EQ-5D-3L) [14], a questionnaire widely used in

economic evaluations. The EQ-5D-3L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which is rated at three levels (no problems, some problems, major problems), allowing 243 (3^5) potential health states [15]. The EQ-5D-3L scores were converted into a utility value (i.e. HRQoL score) based on health state valuations obtained from the Dutch general population [15,16]. QALYs were calculated according to the following formula: [((utility score at baseline + utility score at 3 months) /2 × 3/12) + ((utility score at 3 months + utility score at 6 months)/2) × 3/12] [13]. In the analysis from the healthcare perspective, a successfully treated patient was used as outcome measure, defined as a patient experiencing ≥30% relief of pain intensity [17] on a weighted numeric rating scale (NRS), for 4 days or a score of ≥6 on a seven point Likert scale (6=much improved; 7=very much improved) of the Patients' global impression of change (PGIC) scale for pain at 6 months [17].

Costs

All health care costs were assessed according to the Dutch guidelines for cost calculations in healthcare [13]. Healthcare costs were costs related to CD-LBP and its treatment. Intervention costs (e.g. diagnostic procedures, treatment procedure, follow-up visits), were retrieved from the hospital information system. Other healthcare costs (e.g. medication, home care, visits to general practitioner, physiotherapist, rehabilitation, complementary and alternative medicine therapies) and non-health care costs (paid domestic help, informal care , productivity loss, loss of daily activities) were determined by means of online patients' filled-in cost questionnaires [13,18]. Cost questionnaires had a recall period of 3 months and were filled out at baseline, 3, and 6 months [18]. The questionnaire consisted of pre-defined resource use categories and patients were asked to complete all categories, regardless of whether or not applicable in that period. Patients were instructed to report low back pain related resources use only. Costs were calculated by multiplying resource use by the cost price per resource unit and were expressed in 2016 euros (€). Integral cost prices for resource use were primarily obtained from the Dutch manual for health care cost analysis [13]. The guideline prices of health care services for 2014 were adjusted to the 2016 price level by using the Dutch Consumer Price Index (CPI) [13]. If a guideline price was not readily available, an assumption was made based on an existing guideline price. Intervention costs consisted of the operation time per patient, general operating room costs, material costs, and radiology assistance. The control group received the same intervention with lidocaine and contrast but without methylene blue. The intervention price was calculated to be €500; this price mainly consisted of resources use like operation theatre, nursing and interventional specialists, as the methylene blue used in the IMBI treatment is inexpensive (about €5 per ampule). Cost prices for medication were derived from the Dutch National Healthcare Institute medication costs database (medicijnkosten.nl), and were calculated for pain medication, and included clawback and taxes. Work absenteeism was measured with the productivity and disease questionnaire (PRODISQ) which was included in the cost questionnaire [19]. The cost of work-absence (productivity losses) was calculated using the friction cost method, which assumes that each worker is replaceable within 85 workdays or 12 weeks [13,20-22].

Statistical analysis

All analyses were based on the 'intention-to-treat' principle. Incomplete- and missing data were imputed, using single imputation in IBM-SPSS 24 (SPSS in, Chicago, Illinois, USA), under the assumption that data was missing at random. Covariates included in the imputation model were all the 23 questions of the cost questionnaire obtained at all-time points, and baseline characteristics like gender and age, baseline pain, and HRQoL. Data analyses were performed with the imputed data. All analyses were performed with a 6 months' time horizon.

To avoid a positive bias in favor for the intervention under study, the base case cost effectiveness analysis was performed with costs and QALYs adjusted for baseline imbalances, i.e. with regression based corrections for baseline differences in costs and utility values between the groups [23,24]. An imbalance, even if not statistically significant, can have a major impact, as the baseline utility score is included in the QALY calculation and baseline costs might influence

subsequent cost outcomes. Furthermore, patients who show a high cost or utility value at baseline can be expected on average to have lower values on subsequent measurements and vice versa [24]. Costs and utility values were therefore corrected for baseline with a regression-based adjustment method that also takes into account regression to the mean effects [24]. Outliers in costs were corrected with the trimmed regression method in which the cutoff point was set to the 90th percentile [24]. All values above the cutoff point were replaced by the 90th percentile cut off value. Utilities were adjusted for baseline differences with the split regression technique, as the dataset showed a bimodal distribution [24]. In this technique two regression models are used for each distribution separately [24]. The adjusted utility values were used for the base-case calculation of QALYs.

To evaluate cost-effectiveness between the IMBI and control group, incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in costs by the difference in effectiveness between the two treatment groups. Cost were not normally distributed and, therefore, for the base case analysis of incremental cost effectiveness, differences between the treatment and control group were compared using non-parametric bootstrapping with 95% confidence intervals (CI) around mean costs and effects of the two treatment groups, using Microsoft Excel for Windows (Microsoft Corp, Redmond, Washington, USA). Results were plotted in an incremental cost-effectiveness plane in which the horizontal axis presents the incremental effect, and the vertical axis represents the incremental cost. The probability that IMBI is cost-effective is graphically displayed in a cost-effectiveness acceptability curve (CEAC). For judging the cost-effectiveness of IMBI, a range of willingness to pay thresholds between €20.000 and €80.000 per QALY gain were used [25,26].

In secondary analyses, an ICER was calculated in which the intervention costs of €500 were included in the IMBI group only. Next, healthcare costs per successfully treated patient were calculated based on the proportions of successfully treated patients for each group at 6 months. Success was defined as at least 30% pain relief on the NRS or at least 'much improved' on the PGIC scale at 6 months. It should be noted that, for the cost-effectiveness analysis from the healthcare perspective based on a successfully treated patient, no willingness to pay threshold exists.

Sensitivity analyses

To assess the robustness of the results of the base-case analysis, sensitivity analyses were performed [13]. First, analyses were performed with unadjusted non-healthcare costs and utility values, i.e., uncorrected for the observed imbalance between the two groups at baseline [24]. Second, an analysis was performed with a QALY calculated with health state valuations obtained from the UK population instead of the Dutch population [16]. Last, information from the baseline cost questionnaires (covering a period of three months before entering the study), baseline pain scores and baseline quality of life, were used as an estimation of costs and effects of care as usual (CAU). CAU was then compared to treatment in an ICER.

Subgroup analyses

We performed subgroup analyses, to explore whether IMBI might be more or less cost-effective in subgroups of patients. Subgroups were based on disease duration (more or less than 5 years), pain severity (more or less than 7 NRS), HRQoL (less than or equal/above median utility value of 0.45), and work status (employed versus unemployed or receiving disability payment). To assess the uncertainty, the differences between the treatment and control group were compared using non-parametric bootstrapping with 95% confidence intervals (CI) around mean costs and effects of the two treatment groups. For all subgroup analyses, for baseline differences adjusted QALYs were used and societal costs were adjusted for baseline imbalances as well.

Results

Patients were recruited from July 2013 up to January 2017. Figure 1 shows the diagram of the participants flow in the RCT. In total 1364 patients with chronic low back pain were eligible for screening (Figure 1). Eighty-one patients

were randomized and completed the study protocol with follow up data of 6 weeks, 3 months and 6 months post intervention. Forty patients received the IMBI and 41 the control treatment. No complications related to the intervention were noted [11]. Data of 81 patients were used for the costs-effectiveness analyses. At 3 and 6 months one patient was lost to follow up. Cost data was missing from 1 patient at baseline, from another patient at 3 months, and another patient did not provide cost information at 6 months. The imputation technique allowed us to keep all patients with missing data in the analyses.

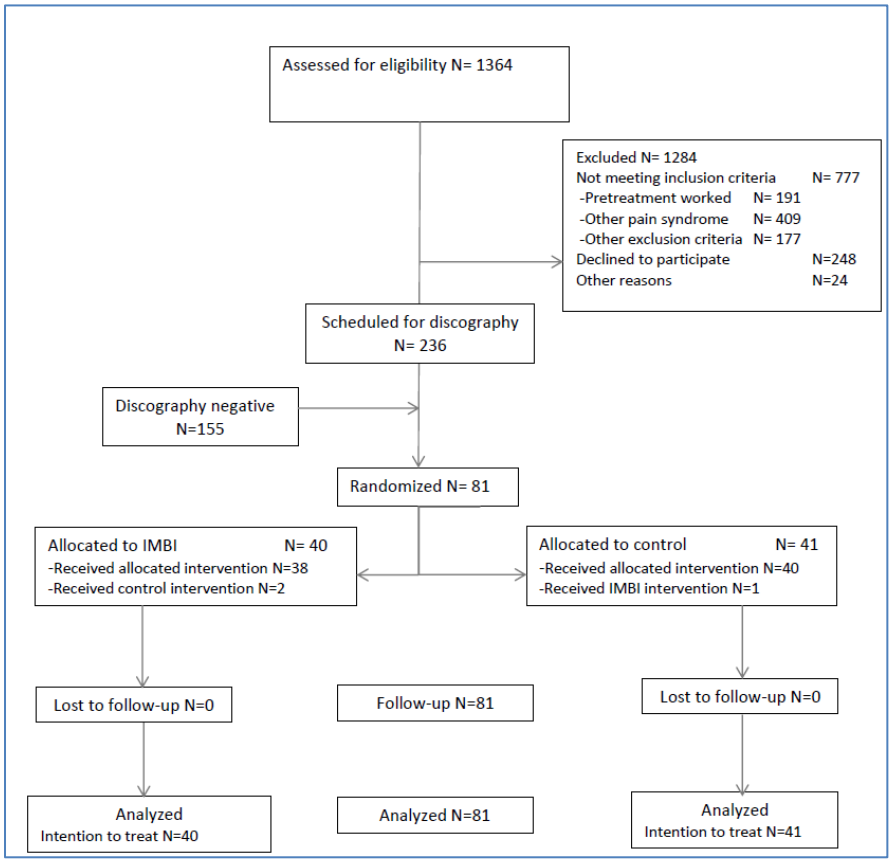

Figure 1. Study flowchart

Outcome

Most baseline characteristics were comparable between the two groups. However, some baseline values essential for the cost-effectiveness analysis, like HRQoL (utility values), work status and costs, were remarkably different between the intervention and control group (Table 1). At baseline, mean utility values were lower in the control group (0.41 *vs.* 0.47). Patients in the control group reported to have more sick days (3 *vs.* 8) over the last 3 months. Mainly as the result of higher productivity losses, mean non-healthcare costs at baseline were remarkably higher in the control group (€3245 *vs.* €2372).

Utility values improved during the 6 months follow-up in both groups. The utility in the IMBI group changed from 0.47 at baseline, to 0.54 (0.53 unadjusted) at 3 months, and continued to improve at 6 months to 0.62 (0.61 unadjusted). In the control group utility at baseline was 0.41 and improved respectively to 0.55 (0.55 unadjusted) and to 0.59 (0.58 unadjusted) at 6 months.

At 6 months, the mean QALY was 0.27 in the IMBI group and 0.26 in the control group. At 6 months, in the IMBI group 35% of patients responded to the treatment (i.e. had at least 30% pain relief) and in the control group response to treatment was successful in 27%.

Table 1. Baseline demographics, work related and cost information

Baseline Characteristics	IMBI (N=40)	Control (N=41)
NRS score, mean (SD)	6.6 (1.4)	6.6 (1.6)
Duration LBP, mean (SD)	10.2 (8.8)	8.5 (7.1)
Age, mean (SD)	41.2 (9.6)	42.6 (10.2)
BMI, mean (SD)	25.8 (3.4)	24.9 (3.8)
Women, N (%)	29 (72.5)	29 (70.7)
Married or living with a partner, N (%)	33 (82.5)	33 (80,5)
Having a paid job, N (%)	28 (70)	29 (70)
Unemployed, N (%)	5 (12.5)	8 (20)
Disability payment (DIA), N (%)	7 (17.5)	4 (10)
Sick from work in days last 3 months, mean (SD)	3 (11)	8 (20)
Utility EQ5DNL, mean (SD)	0.47 (0.28)	0.41 (0.34)
QALY	0.237	0.205
Healthcare costs, mean (SD)	1421 (1710)	1476 (2443)
Non-healthcare costs, mean (SD)	2372 (4737)	3245 (5582)
Societal costs, mean (SD)	3793 (5337)	4720 (7210)
DIA= Disablement Insurance Act		

Costs distribution

As healthcare costs at baseline were fairly balanced between groups, uncorrected healthcare costs over 6 months for each cost type were calculated and shown in Table 2.

Table 2. Societal Costs over 6 months. Mean cost per resource user and mean costs per patient are given for each cost type. Cost types are arranged in health care costs, non-healthcare costs, and total societal costs. Raw costs data are shown and for baseline differences adjusted costs (RBA).

Cost type	N Patients		Mean costs per resource user (SD)		Mean costs per* patient (SD)		%	
	I	C	I	C	I	C	I	C
Cost injection	40	41	500 (0)	500 (0)	500 (0)	500 (0)	22	23
Home care	7	4	2675 (2768)	3118 (2253)	468 (1496)	304 (1121)	22	23
Rehabilitation	2	1	6947 (7204)	8645 (0)	347 (1918)	211 (1350)	16	17
Physical therapy	25	15	534 (437)	495 (507)	334 (431)	181 (385)	16	15
Psychosocial therapy	6	6	1037 (375)	851 (644)	155 (398)	125 (380)	6	6
Daycare clinic	4	9	464 (0)	516 (154)	46 (141)	113 (226)	2	5
Travel costs	35	35	86 (136)	63 (124)	76 (130)	54 (116)	4	3
Medication	40	41	52 (144)	33 (57)	51 (145)	33 (57)	2	2
Pain clinic (outpatient visits)	2	4	367 (129)	343 (328)	18 (84)	34 (136)	1	2
Occupational physician	9	13	74 (43)	69 (37)	17 (37)	22 (38)	1	2
Primary Care	6	6	78 (40)	105 (57)	12 (32)	15 (43)	1	1
Hospital nights	1	1	480 (0)	960 (0)	12 (75)	24 (150)	1	2
CAM therapies	4	1	544 (580)	270 (0)	54 (230)	7 (42)	3	0
Extra requirements	4	2	582 (752)	55 (21)	58 (273)	3 (13)	3	0
Outpatient clinic other	0	1	0 (0)	184 (0)	0 (0)	5 (29)	0	0
Mean total healthcare costs								
Informal care	23	26	86 (73)	152 (198)	49 (70)	96 (172)	3	6
Loss daily activities	28	32	1220 (1189)	1134 (1122)	853 (1140)	885 (1096)	49	39
Productivity loss	6	6	5541 (6017)	8900 (5296)	831 (2942)	1303 (3695)	48	57
Total non-healthcare costs (uncorrected)					1734 (3568)	2283 (4221)		
Mean total non-healthcare costs (corrected*)					1158 (1408)	1260 (1252)		
Total societal costs (uncorrected)					4729 (5298)	4676 (7661)		
Total societal costs (corrected*)					4153 (4275)	3652 (5410)		

I=IMBI intervention; C=control; CAM=Complementary and Alternative Medicine; *regression based adjusted for baseline differences

Health care costs were €2,995 per patients in the IMBI treated group and €2,392 per patient in the control population. Costs for physical therapy were higher in the IMBI group because more patients used this resource type (25 *vs.* 15 patients in the control) and for the same reason the daycare clinic visits costs were higher in the control population (4 patients used this resource type vs. 9 in control).

Uncorrected non-healthcare costs per patient were lower in the IMBI treated group (€1,734 *vs.* €2,283); however, after correction for baseline differences the cost in the IMBI group became slightly higher in the IMBI group (€1,377 *vs.* €1,168). Uncorrected total societal cost was €4,729 in the IMBI group versus €4,676 in the control population. After adjustment for baseline differences in non-healthcare costs, corrected mean societal costs in the IMBI population was calculated to be €4,130 *vs.* €3,580 per patient in the control group. Figure 2 shows the cost type per treatment, i.e. healthcare, non-healthcare, and societal costs over time. In both groups the costs decreased after the baseline assessment.

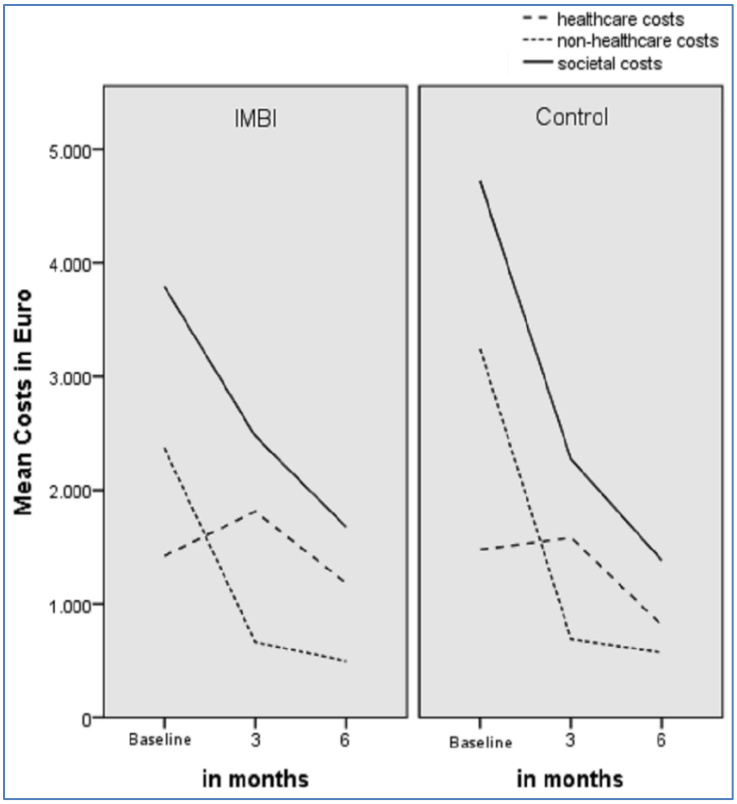

Figure 2. Costs over time between the randomized groups and divided by cost types. At 3 and 6 months, non-healthcare and societal costs are corrected for baseline differences

Cost-effectiveness

The QALY differed in favor of IMBI with 0.007, resulting in an ICER of €71,571 (incremental cost per QALY) (Table 3). Bootstrap analyses showed from a societal perspective, that the majority of cost-effectiveness ratios was situated in the North East quadrant; this means that IMBI is more effective and more costly (Figure 3). The cost-effectiveness acceptability curve (CEAC), Figure 4, showed that from a societal perspective, with a willingness to pay threshold of €20.000 to €80.000/QALY, the probability that IMBI is cost-effective ranged between 26% and 42% respectively.

Table 3. Incremental cost-effectiveness (ICER) for societal costs per QALY at 6 months; base case analysis

Base Case Analysis*	IMBI	Control	Difference	ICER
QALYs (corrected)*	0.271	0.264	0.007	
Societal costs (corrected)*	4153	3652	501	€71,571-/ QALY

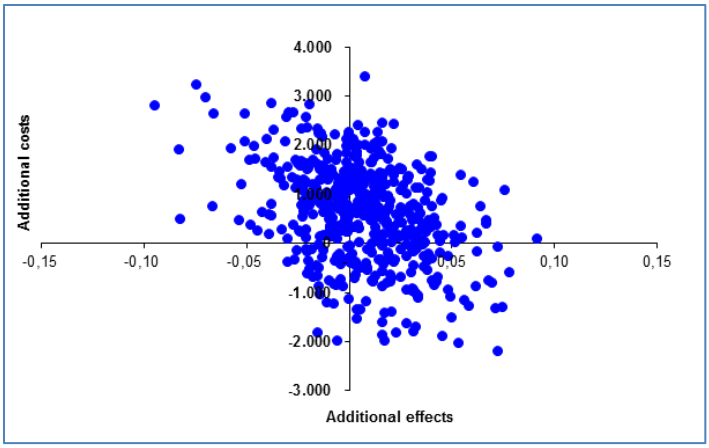

Figure 3. Distribution on the cost-effectiveness plane; 20% south east quadrant (dominant), 33% north west quadrant (inferior),41% north east quadrant (intervention is better but more expensive), 7% is located in the South west quadrant (worse but cheaper)

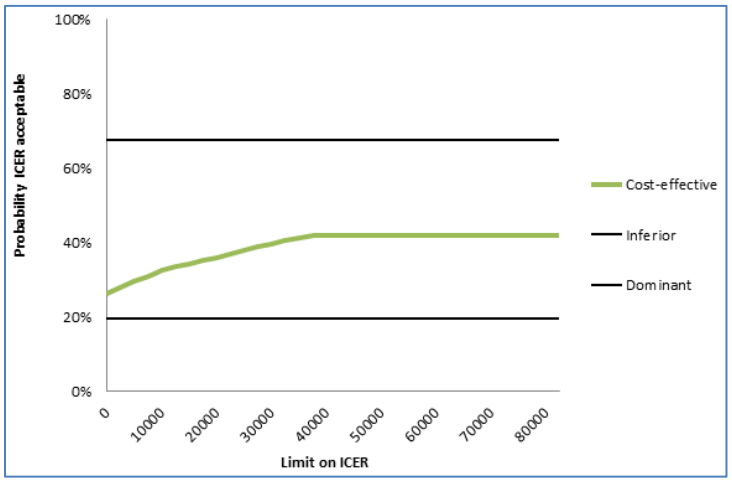

Figure 4. Cost-effectiveness acceptability curve (CEAC)

The ICER for the healthcare costs per responder (Table 4) between IMBI and control was €7,354 per additional respondent.

Table 4. ICER; healthcare cost per responder at 6 months between IMBI and control

	IMBI	Control	Difference	ICER
Responders	0.35	0.268	0.082	
Healthcare costs	2995	2392	603	€7,354/ additional respondent

Sensitivity analyses

Results of the sensitivity analyses are shown Table 5. Analysis of the primary data (not corrected for baseline differences) from a societal perspective showed that IMBI yielded more QALYs and incurred more costs, resulting in an ICER of €4,818 per QALY (Table 5a).

Sensitivity analysis, in which the QALY calculation was performed with the UK Tariff for baseline differences adjusted, showed that the ICER was €41.750 per QALY from the societal perspective (Table 5b). For the intervention versus care as usual (CAU) analysis (Table 5c) the baseline societal cost of the total group were considered as CAU and this resulted in a saving of -€8,745 per QALY, which means that offering patients treatment either with IMBI or placebo is dominant over CAU. Table 5d shows that if intervention costs of €500 were omitted in the control group for the base case analysis the ICER would be €143,000.

Table 5. Sensitivity analyses

5A. ICER analysis performed with primary raw data (not for baseline adjusted costs and utility values)				
Dutch Tariff	**IMBI**	**Control**	**Difference**	**ICER**
QALYs	0.269	0.258	0.011	
Societal costs	4729	4676	53	€4,818/QALY
5B. ICER for societal costs per QALYs calculated with health state valuations from UK population				
UK tariff	**IMBI**	**Control**	**Difference**	**ICER**
QALYs*	0.233	0.221	0.012	
Societal costs*	4153	3652	501	€41,750/QALY
*for baseline adjusted				
5C. ICER; societal costs per QALY in which the control treatment is care as usual (CAU)				
	Treatment	**CAU***	**Difference**	**ICER**
QALYs	0.267	0.22	0.047	
Societal costs	3852	4263	-411	-€8,745/QALY
*Care as usual was calculated by baseline costs and utility values of the total study population (N=81)				
5D. ICER; societal costs per QALY in which for the control treatment the intervention costs are zero.				
Intervention cost IMBI#	**IMBI**	**Control**	**Difference**	**ICER**
QALYs*	0.271	0.264	0.007	
Societal costs*#	4153	3152	1001	€143,000/QALY
#Intervention cost (€500) calculated for the IMBI group only *regression based adjusted for baseline				

Subgroup analyses

The univariate subgroup analyses performed using baseline characteristics (Table 6) showed that the incremental cost-effectiveness differed for subgroups of patients based on their baseline characteristics. The cost per QALY was dominant for the IMBI intervention in patients with high pain severity (≥7). The IMBI treatment was inferior in patients with lower pain severity (<7), or with relative higher HRQoL (utility value ≥0.45), or in employed patients.

Table 6. Subgroup analyses using baseline characteristics

Characteristics	**No. of participants**	**Incremental**	**Incremental**		**Bootstrap results**	
Disease duration	**All (IMBI/control)**	**QALYs**	**costs**	**Cost per QALY**	**Mean (95%CI)**	***Distribution CE-plane**
≤5 years	32 (14/18)	0.09	€2,095.48	€22,168.85	24,837 (23,861;25,812)	NE 1
>5 Years	49 (26/23)	-0.05	- €575.01	€11.951,93 saving/QALY lost	-53,963 (-196,773;88,847)	SW 0.66; SE 0.04; NW 0.3
Pain severity						
<7 NRS	46 (22/24)	-0.02	€867.81	Inferior	-35,202 (-79,670;9,267)	NW 0.82; NE 0.17; SW 0.01
≥7 NRS	35 (18/17)	0.05	- €55.71	Dominant	8.406 (841;15,970)	SE 0.53; NE 0.45; NW 0.02
Quality of life						
<0.45 EQ-5D-3L	39 (18/21)	0.03	€390.53	€11,828.70	5,796 (-14,399;25,990)	NE 0.54; SE 0.38; NW 0.07; SW 0.01
>0.45 EQ-5D-3L	42 (22/20)	-0.03	€923.55	Inferior	-8.351 (-63,630;46,928)	NW 0.96; NE 0.02; SW 0.02
Work status						
Employed	57 (28/29)	-0.01	€11.77	Inferior	-45,542 (-122,408;31,324)	NW 0.45; SW 0.25; NE 0.1; SE 0.2
Unemployed (+WIA)	24 (12/12)	0.05	€1,796.19	€34,213.10	97,731 (19,424;176,039)	NE 0.88; NW 0.01; SE 0.1
*Distribution on the cost-effectiveness plain: NW inferior; SE dominant; NE better & expensive; SW worse & cheaper						

Discussion

In this study, the base case cost-effectiveness analysis from a societal perspective showed that the IMBI intervention is more effective and more costly. The ICER of €71,571 was just below the maximum willingness to pay threshold of €80.000/QALY (Table 3). Even with this high cost-effectiveness threshold however, the probability that IMBI is cost-effective was only 42% (Figure 4), indicating considerable uncertainty. Inclusion of costs for an interventional treatment in the control treatment was hypothesized for the base case analysis to be a naturalistic approach, for in real-life routine practice most included patients would have received a pain intervention. However, this conduct is debatable because the control intervention was designed to be a placebo intervention. Therefore, a secondary analysis was performed in which the intervention costs were excluded for the control group. This analysis (Table 5d) showed that, if the intervention costs were calculated for the IMBI group only the ICER would be inferior, i.e., €143,000.

The sensitivity analysis in which both interventions were compared to CAU showed that either treatment was saving costs at 6 months (Table 5c). Furthermore, Figure 2 depicts that costs decreased in both groups during treatment, IMBI generated 35% responders and the control group 27%. Also, health related quality of life improved during the six months of treatment in both groups; utility values improved from 0.47 to 0.62 for IMBI and from 0.41 to 0.59 for the control group.

To explore whether IMBI might be more or less cost-effective in subgroups of patients, subgroup analyses were performed based on patients' baseline characteristics. We found that IMBI was cost-effective in patients having a more serious pain condition, i.e. with severe (≥7) pain, patients with low HRQoL (utility value <0.45), or those unemployed. It was also shown that IMBI is cost-effective in patients with a lesser disease duration. Because of the limited sample size, a multivariate analysis combining all subgroup characteristics was not performed, therefore, it remains unclear which patient characteristic or combination of patient characteristics adds to the cost-effectiveness of IMBI. However, the subgroup analyses indicate that there is a potential for IMBI being cost-effective in a highly selected group of patients.

To date, little is known about the economic burden of chronic pain and how it affects health care utilization and societal costs [21]. An Irish study showed annual costs for society per patient attending the pain clinic of US$24,043 [27]. Over half of this was attributable to societal costs i.e. wage replacement costs and lost productivity in those unable to work because of pain. These costs outcomes are in line with a Dutch study in discogenic pain patient attending a pain clinic [28]; the annual total costs for society in this study added up to €18,940 per patient of which 78% were societal costs and 22% was attributed to healthcare costs. In both studies the healthcare costs were mainly related to pain treatments. Numerous pain interventions are routinely used, although few are supported by strong evidence. Cost-effectiveness studies regarding societal costs in pain treatments are few, although they can be helpful to inform decision makers [29]. For example, based on an economic evaluation with systematic review of cost-effectiveness studies, the British National Institute for Health and Care Excellence (NICE) recommended the treatment Spinal cord stimulation (SCS)for chronic neuropathic pain conditions [30,31].

A limitation of this study is the fact that we used lidocaine in the control treatment instead of a real placebo. Therefore, if not compared to a potential other effective treatment, cost-effectiveness of the IMBI treatment could be potentially higher. After the start of this study, more evidence became available that lidocaine could also be effective in longer time pain relief [32]. However, this RCT was a direct copy of the RCT performed by Peng et al. and published in 2010 [6]. In this Peng et al. study the control group showed almost no responders and in the treatment group the effect of IMBI treatment was very high. When comparing the patient sample of this former RCT [6] it should be noted that in our patient samples the disease duration was much longer, i.e., mean duration was 3.4 (SD 1.7) in the former RCT

versus in our patient sample 10.2 (SD 8.8) and 8.5 (SD 7.1)in the control group [6]. Indeed, our sub analysis showed that IMBI could be more effective in patients with a lesser disease duration (<5 years). In this lesser disease duration group, the distribution on the cost-effectiveness plain was Northeast 1; showing that the IMBI intervention in this group was for all patients better and more expensive (cost per QALY of €22,168).

Based on current effectiveness evidence, IMBI is not recommended as an intervention for discogenic low back pain. Although, it is important to note that healthcare and societal costs decreased during the 6 months of treatment. Also, 35% of the patients in the IMBI group responded to the treatment and 27% in the control group [11]. We found an indication that cost-effectiveness of the IMBI treatment could be higher in a selected group of patients with shorter disease duration and with serious pain conditions. Therefore, we recommend further research into predictors for (cost-) effectiveness of this intervention.

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