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ORIGINAL ARTICLE

Short-term results of intrathecal injection of low-dose bupivacaine in outpatients with chronic low back and lower extremity pain

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Abstract

Purpose To investigate the safety and efficacy of intrathecal injection as an alternative to epidural injection for analgesia.

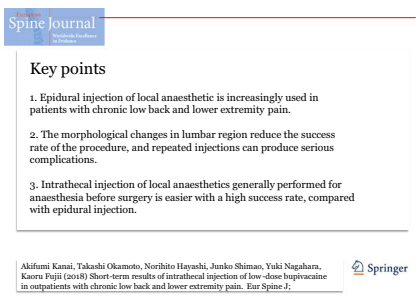
Methods Seventy consecutive outpatients with chronic low back and lower extremity pain received lumbar intrathecal injection of low-dose isobaric bupivacaine using a 25-gauge pencil-point needle. The patients received 0.5, 1.0, and 1.5 mg of bupivacaine at 1-week intervals to determine the optimal dose. Thereafter, they received two more weekly injections with the optimal dose. The safety and efficacy of the treatment were assessed over a 1-year period.

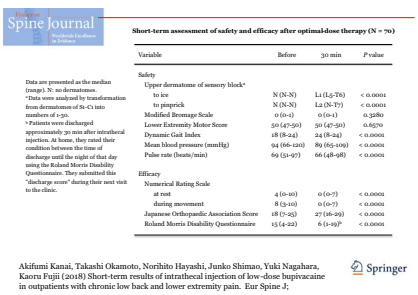
Results No serious adverse events were encountered. The optimal dose of bupivacaine (1.0 mg in 60% of patients) alleviated pain and disability (both, $p < 0.0001$) and provided anesthesia below L1 (L5–T6). Motor block was negligible, and balance impairment improved relative to baseline ($p < 0.0001$).

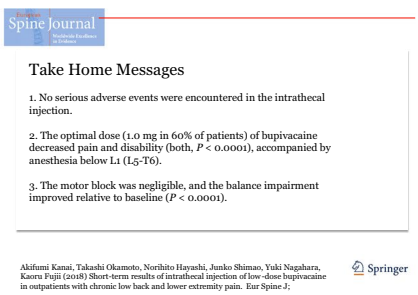
Conclusion Intrathecal injection of low-dose bupivacaine offers a safe and effective treatment for chronic low back and lower extremity pain.

Trial registration The study was approved by the Kitasato University Hospital Ethics Committee, and written informed consent was obtained from all individual participants included in the study. This trial was registered with the University Hospital Medical Information Network (UMIN000008670).

Graphical abstract These slides can be retrieved under electronic supplementary material.







Keywords Intrathecal injection · Bupivacaine · Chronic pain · Low back pain

Introduction

Chronic low back pain with or without lower extremity pain is a common health problem [1]. The use of epidural injection of local anesthetics for chronic pain relief is rapidly increasing [2] and is especially common for patients with lumbar disorders such as disk herniation and sciatica. However, morphological changes in the lumbar spine in these

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disorders reduce the success rate of epidural injection, and repeated injections can produce serious complications [3]. Furthermore, epidural adhesion is typical in these disorders, resulting in insufficient analgesia due to the reduced spread of local anesthetics within the epidural space [4].

Intrathecal injection of local anesthetics, which is not typically used for chronic pain, has a higher success rate than epidural injection [5, 6] and may provide better pain relief in patients with epidural adhesion. One complication associated with intrathecal injection is post-dural puncture headache (PDPH), with a reported incidence of 0.1–2% in patients aged ≥ 65 years [7, 8]; however, the use of a 25-gauge pencil-point needle can reduce the incidence of PDPH [7]. Another potential complication is lower extremity muscle weakness. However, only a small dose of local anesthetic may be required for the treatment of chronic pain disorders, particularly since systemic administration of local anesthetics is effective in alleviating pain [9]. Intrathecal injection may reduce the generation and conduction of peripheral pain impulses in dysfunctional or damaged nerves [10]. Therefore, intrathecal injection of a small dose of local anesthetic around the lumbar nerves may reduce low back and lower extremity pain without producing muscle weakness in the lower extremities.

Methods

Hypothesis

We hypothesized that intrathecal bupivacaine injection would achieve sufficient analgesia with no significant adverse events.

Ethics statement

A trial steering committee and an independent data monitoring and ethics committee oversaw the conduct of the trial. The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants. All procedures were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Participants

Seventy consecutive outpatients who presented with chronic low back and lower extremity pain were enrolled in this study. Patients were eligible for inclusion if they were aged ≥ 20 years, capable of properly assessing their pain severity, had at least moderate pain for ≥ 3 months, and had specific disorders accounting for their pain as determined by medical history, physical examinations, and diagnostic imaging. We excluded patients with high-risk causes of pain (e.g., infection, fracture, malignancy), neurological deficits that disturbed the assessment of sensory loss after spinal anesthesia, a history of previous spinal surgery, severe psychiatric or psychological disorders, serious chronic diseases, any contraindication to or history of intrathecal injection, and/or initiation of other treatments within 1 week prior to the study.

Procedures

Following examination of vital signs, the patients were placed in the lateral decubitus position for intrathecal injection. The L3–L4 intervertebral space was then infiltrated with 1% lidocaine, and the subarachnoid space was accessed at the midline using a 25-gauge pencil-point needle (Uniever®, Unisis Corp., Japan). After observing the reflux of clear CSF, isobaric 0.5% bupivacaine diluted with 0.9% saline was injected slowly into the subarachnoid space through the needle with the bevel-oriented cephalad. Patients were then placed in the supine position for at least 30 min of observation.

We selected bupivacaine in this study because it is available worldwide and is safer for use in neural tissue than lidocaine or tetracaine [11]. Based on preliminary data and actual clinical application, we used an initial bupivacaine dose of 0.5 mg, followed by 1.0 mg and 1.5 mg at 1-week intervals. The optimal dose was selected based on the analgesic effects of these doses and the presence of any adverse physical effects. Thereafter, the optimal dose was administered once a week for 2 weeks. To facilitate blinding, all doses were diluted to 2.0 ml with saline and prepared by an investigator who was not involved in the subsequent patient assessment.

Patients continued to take their other medications during the study to avoid reinforced chronic pain; however, they were not allowed to change medications until 1 month after the final intrathecal injection.

Outcomes

The patients were followed for 1 year after the final intrathecal injection. The primary outcome was the safety of the therapy. Blood pressure and pulse rate were measured every 5 min during the 30-min observation period after the injection. Dermatomal sensory loss to ice and pinprick were checked immediately before and at 30 min and 7 days after each intrathecal injection, as well as at 1, 3, 6, and 12 months after the last intrathecal injection. Motor block was evaluated using the Modified Bromage Scale (MBS, 0–3; 0 indicates no paralysis and full flexion of the knees and feet) and the Lower Extremity Motor Score (LEMS, 0–50; 50 indicates a manual muscle testing grade of 5 for each of

five key bilateral muscles: the iliopsoas, quadriceps, tibialis anterior, extensor hallucis longus, and gastrocnemius) [12]. Spinal anesthesia often causes widespread sensory loss, including loss of deep sensation (position, vibration, and kinesthetic senses), which in turn can affect functional balance. Therefore, we also used the Dynamic Gait Index (DGI, 0–24; 24 indicates the best possible performance) to assess gait [13]. Adverse events were defined as any serious morbidity or events causing distress to the participant that were potentially related to the intrathecal treatment. The severity of these events was estimated with a 4-point Verbal Rating Scale (0: none, 1: slight, 2: moderate, 3: severe). Information on adverse events was gathered by the assessor and from self-completed questionnaires.

The secondary outcome was the efficacy of treatment. Pain intensity at rest and during movement was assessed using the Numerical Rating Scale (NRS, 0–10; 0 indicates no pain, 10 indicates worst pain imaginable). Furthermore, we selected two other outcomes for physical function and disability: the Japanese Orthopedic Association Score (JOAS, 0–29; higher scores indicate milder pain and less disability) [14] and the Roland Morris Disability Questionnaire (RMDQ, 0–24; lower scores indicate less severe disability and better quality of life) [15]. These secondary outcomes were recorded before, on the day of and 7 days after each intrathecal injection, as well as at 1, 3, 6, and 12 months after the final intrathecal injection.

Blinding

The physicians who administered the injection, the assessors, and patients were all blinded to the bupivacaine dose. Additionally, the physicians and assessors were unaware of the details of the patients' background.

Statistical analysis

Continuous parameters are presented as the median (range), categorical data are presented as the number and percentage (of the total number of participants), and adverse events such as PDPH are reported as the number and percentage (of the total number of injections). Safety and efficacy were evaluated using the Wilcoxon signed rank test relative to the baseline values. A mixed-effect model for continuous outcomes adjusted for baseline values, wherein dosage was entered as a fixed factor and patient identification was treated as a random factor, was used to evaluate the effects of treatment on safety and efficacy. Based on preliminary findings, a sample size of 21 patients was needed for a one-arm before-after design to observe a mean change of 2 points in the NRS score from baseline with an intra-group standard deviation of 3 points, a power of 0.9, and an alpha error of 0.01. Due to potential overestimation, we used a Bonferroni correction to the number of comparisons. Analyses were performed using SPSS (version 19.0; SPSS, Inc., Chicago, IL). Two-tailed p values < 0.05 were considered statistically significant.

Results

Clinical, imaging, and *electromyography* findings were used for the diagnosis of disease and pain (Table 1). A total of 332 intrathecal injections were performed in 70 patients during the study period. The reflux of clear CSF was noted in all procedures. The treatment was applied only three and four times in six (9%) patients, respectively, due to either improvement of pain and disability ($n = 10$) or insufficient analgesia, including short-term analgesia ($n = 2$).

Only slight changes in the blood pressure and pulse rate were noted, and no patients required treatment for hypotension or fluid replacement. Although the time to discharge exceeded 60 min in 27 (8%) procedures, the optimal dose of bupivacaine allowed 69 (99%) patients to walk within 30 min. The optimal dose was 0.5, 1.0, and 1.5 mg in 18 (26%), 42 (60%), and 10 (14%) patients, respectively. The DGI score was significantly higher ($p < 0.0001$), but there were no significant differences in the MBS and LEMS scores at 30 min after intrathecal injection of the optimal dose (Table 2). The analgesic effect was prompt and robust,

Table 1 Patients' characteristics

Patient characteristics	Value
N	70
Female sex	41 (59)
Age (years)	62 (27–87)
Height (cm)	158 (140–179)
Body weight (kg)	55 (34–96)
Duration of pain (years)	5 (1–55)
Pain	
Location	
Low back pain	70 (100)
Lower extremity pain	64 (91)
Main type	
Nociceptive pain	8 (11)
Neuropathic pain	53 (76)
Mixed pain	9 (13)
Diagnosis	
Spondylosis deformans	24 (34)
Spinal canal stenosis	20 (29)
Disk herniation	15 (21)
Post-traumatic neuropathy	6 (9)
Spondylolisthesis	5 (7)

Data are presented as numbers (%) or median (range)

Table 2 Short-term assessment of safety and efficacy after optimal-dose therapy ($N=70$)

Variable	Before	30 min	p value
Safety			
Upper dermatome of sensory block[a]			
To ice	*N* (*N*–*N*)	L1 (L5–T6)	<0.0001
To pinprick	*N* (*N*–*N*)	L2 (*N*–T7)	<0.0001
Modified Bromage Scale	0 (0–1)	0 (0–1)	0.3280
Lower Extremity Motor Score	50 (47–50)	50 (47–50)	0.6570
Dynamic Gait Index	18 (8–24)	24 (8–24)	<0.0001
Mean blood pressure (mmHg)	94 (66–120)	89 (65–109)	<0.0001
Pulse rate (beats/min)	69 (51–97)	66 (48–98)	<0.0001
Efficacy			
Numerical Rating Scale			
At rest	4 (0–10)	0 (0–7)	<0.0001
During movement	8 (3–10)	0 (0–7)	<0.0001
Japanese Orthopedic Association Score	18 (7–25)	27 (16–29)	<0.0001
Roland Morris Disability Questionnaire	15 (4–22)	6 (1–19)[b]	<0.0001

Data are presented as the median (range)

N no dermatomes

[a]Data were analyzed by transformation from dermatomes of S1–C1 into numbers of 1–30

[b]Patients were discharged approximately 30 min after intrathecal injection. At home, they rated their condition from the time of discharge until the night of that day using the Roland Morris Disability Questionnaire. They submitted this "discharge score" during their next visit to the clinic

as indicated by changes in the NRS ($p<0.0001$), JOAS ($p<0.0001$), and RMDQ ($p<0.0001$) scores.

There were no significant dose-dependent effects on blood pressure or pulse rate, though higher bupivacaine doses significantly increased dermatomal spread of the sensory block to ice and pinprick (Table 3). Higher bupivacaine doses also significantly increased the motor block scores of the MBS ($p<0.0001$) and LEMS ($p<0.0001$) and led to a prolonged time to discharge ($p<0.0001$). There were significant differences in the DGI scores ($p<0.0001$), with higher scores in the 0.5 mg ($p<0.0001$) and 1.0 mg ($p=0.0211$) groups, and lower scores in the 1.5 mg ($p<0.0001$) group. The NRS, JOAS, and RMDQ scores improved after treatment irrespective of the bupivacaine dose (Table 3).

All patients with available data were assessed for long-term safety and efficacy (Table 4). The anesthesia completely disappeared after each injection, and no additional sensory loss suggestive of neurological disorder was registered. No serious adverse events, including PDPH, were reported. During the study period, seven (10%) patients stopped attending the clinic due to improvement ($n=5$) or insufficient effect ($n=2$) 1–10 months after the final intrathecal injection. Telephone interviews confirmed the lack of any therapy-related complications. As shown in Table 4, significant changes in pain at rest and during movement (NRS), physical activity (JOAS), and quality of life (RMDQ) persisted throughout the 12-month follow-up period. Forty-eight (69%) patients underwent a radiographic inspection following the treatment. No remarkable morphological changes were seen on the radiographic images except in one patient with somewhat worsened spinal canal stenosis and another patient with slightly improved disk herniation. Furthermore, magnetic resonance imaging ($n=33$) indicated no adverse events of the intrathecal injection therapy such as adhesive arachnoiditis, epidermoid cyst, and hematoma. Figure 1 shows the spinal magnetic resonance imaging of a typical patient before and after intrathecal injection. In this case, the 57-year-old female patient with lumbar spinal canal stenosis experienced a significant decrease in her pain scores during movement and at rest. After treatment, her NRS pain score decreased from 10 to 5 during movement and from 8 to 1 at rest; however, magnetic resonance imaging showed no significant change in her spinal canal stenosis. Table 5 presents the short-term efficacy after the last therapy in each disease. Although the sample size was not enough for statistical analysis, the intrathecal injection therapy tended to be less effective for spondylosis deformans and post-traumatic neuropathy in comparison with the other diseases. Eight of nine patients with mixed pain had spondylosis deformans.

Discussion

Our findings suggest that intrathecal injection of low-dose bupivacaine is clinically safe and efficacious. The mechanism underlying reduced chronic pain intensity following

Table 3 Long-term assessment of safety and efficacy after the last therapy ($n=63$)

	Baseline	7 days		1 month		3 months		6 months		12 months	
		Score	*p* value	Score	*p* value	Score	*p* value	Score	*p* value	Score	*p* value
Safety											
Number of segments with decreased sensation to ice	*N* (*N*–5)	*N* (*N*–5)	0.0763	*N* (*N*–5)	0.1161	*N* (*N*–5)	0.1101	*N* (*N*–5)	0.1092	*N* (*N*–5)	0.0427
Modified Bromage Scale	0 (0–1)	0 (0–1)	0.1797	0 (0–1)	0.3280	0 (0–1)	0.3280	0 (0–1)	0.1800	0 (0–1)	0.1092
Lower Extremity Motor Score	50 (47–50)	50 (47–50)	0.3280	50 (47–50)	0.3280	50 (47–50)	0.1780	50 (47–50)	0.1780	50 (48–50)	0.1092
Dynamic Gait Index	17 (9–24)	21 (10–24)	<0.0001	20 (11–24)	<0.0001	21 (10–24)	<0.0001	21 (10–24)	<0.0001	22 (11–24)	<0.0001
Efficacy											
Numerical Rating Scale											
At rest	5 (0–10)	2 (0–10)	<0.0001	2 (0–9)	<0.0001	2 (0–8)	<0.0001	1 (0–7)	<0.0001	1 (0–7)	<0.0001
During movement	8 (4–10)	4 (1–10)	<0.0001	5 (1–10)	<0.0001	4 (1–9)	<0.0001	4 (1–9)	<0.0001	4 (1–9)	<0.0001
Japanese Orthopedic Association Score	17 (7–25)	22 (10–28)	<0.0001	21 (7–28)	<0.0001	22 (7–28)	<0.0001	22 (7–28)	<0.0001	22 (7–28)	<0.0001
Roland Morris Disability Questionnaire	16 (4–22)	8 (2–22)	<0.0001	11 (2–22)	<0.0001	9 (2–22)	<0.0001	8 (1–22)	<0.0001	8 (1–22)	<0.0001

Data were analyzed in 63 patients after excluding patients with missing values at 6 and 12 months

Data are presented as the median (range). Baseline scores indicate data at enrollment

N no segment

Table 4 Dose effect on safety and efficacy ($N = 70$)

	Dose 0.5 mg		Dose 1.0 mg		Dose 1.5 mg		*p* value
	Before	30 min	Before	30 min	Before	30 min	
Safety							
Upper dermatome of sensory block[a]							
To ice	*N* (*N*–*N*)	L2 (L5–T9)	*N* (*N*–*N*)	L1 (L4–T6)	*N* (N–N)	T11 (L4–T5)	< 0.0001
To pinprick	*N* (*N*–*N*)	L4 (*N*–T10)	*N* (*N*–*N*)	L2 (*N*–T6)	*N* (*N*–*N*)	L1 (S1–T6)	< 0.0001
Modified Bromage Scale	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	< 0.0001
Lower Extremity Motor Score	50 (45–50)	50 (45–50)	50 (45–50)	50 (38–50)	50 (45–50)	50 (34–50)	< 0.0001
Dynamic Gait Index	17 (9–24)	24 (11–24)	18 (9–24)	21 (2–24)	20 (10–24)	13 (0–24)	< 0.0001
Mean blood pressure (mmHg)	95 (65–119)	90 (63–109)	92 (66–121)	88 (65–109)	90 (64–122)	88 (66–113)	0.3128
Pulse rate (beats/min)	68 (46–100)	66 (48–92)	68 (43–97)	66 (44–98)	68 (43–97)	66 (42–98)	0.7978
Efficacy							
Numerical Rating Scale							
At rest	5 (0–10)	0 (0–8)	4 (0–10)	0 (0–8)	3 (0–10)	0 (0–7)	0.0687
During movement	8 (3–10)	0 (0–10)	7 (3–10)	0 (0–9)	6 (1–10)	0 (0–7)	0.0149
Japanese Orthopedic Association Score	17 (7–25)	27 (16–29)	18 (7–24)	27 (16–29)	19 (7–26)	27 (16–29)	0.1990
Roland Morris Disability Questionnaire	16 (4–22)	7 (1–19)[b]	14 (4–22)	6 (1–19)[b]	12 (3–22)	6 (1–19)[b]	0.6504

Data are presented as the median (range)

N no dermatomes

[a]Data were analyzed by transformation from dermatomes of S1–C1 into numbers of 1–30

[b]Patients were discharged approximately 30 min after intrathecal injection. At home, they rated their condition from the time of discharge until the night of that day using the Roland Morris Disability Questionnaire. They submitted this "discharge score" during their next visit to the clinic

bupivacaine treatment is unclear. Intrathecal administration may suppress the excitability of the lumbar nerves [10]. Moreover, local anesthesia has anti-inflammatory [16] and vasodilatory effects, which may allow the analgesia to last beyond the duration of the local anesthetic effect. In the present study, morphological changes were not found after treatment despite significant improvements in pain.

PDPH remains one of the most common side effects of central neuraxial blockade and can occur following unintended dural puncture during epidural injections, as well as during uncomplicated intrathecal injections. The reported incidence of accidental dural puncture with a large bore epidural needle is 1–7% [17]. In our study, there were no cases of PDPH.

Intrathecal injection therapy using the optimal dose produced satisfactory sensory anesthesia without impeding motor function, walking balance, or time to discharge. Higher doses of local anesthetic may impair walking ability despite intact motor function, although this effect is transient. There is limited information on the objective assessment of walking balance after intrathecal injection. Imarengiaye and colleagues [18] induced spinal anesthesia with bupivacaine 5 mg (10 times the dose used in the present study) for day surgery and found a disparity between the time to return of gross motor function and time to recovery of postural control and balance for safe ambulation. Taken together, these results suggest that balance impairment should be assessed in addition to gross motor function in patients treated with high-dose bupivacaine. In this dose–effect study, the anesthesia was dose-dependent. Considering that 1.5 mg of bupivacaine generally causes burdensome motor weakness, we recommend an initial dose of 0.5 mg, to be gradually increased in 0.5-mg increments until the optimal analgesic effect and adverse effects on physical activity are balanced. Because higher doses of local anesthetic may produce a more intensive motor block, intrathecal injection might be unsuitable for treating upper body pain.

Previously, intrathecal administration of methylprednisolone acetate was widely used for the treatment of low back pain. However, this treatment was abandoned because of serious neurological complications [19], including adhesive arachnoiditis and meningitis. In contrast, bupivacaine is safe for single or continuous administration into the subarachnoid space [11, 20]. However rare, serious adhesive arachnoiditis and meningitis can occur after epidural and intrathecal injections of local anesthetic. Pleocytosis and proteinosis in the CSF commonly precede adhesive arachnoiditis [21]. One major advantage of intrathecal injection is that periodic assessment of CSF is facilitated, allowing the early identification of such complications.

Treatment of low back pain remains controversial, and the effectiveness of epidural injections is especially controversial [3]. The reported success rate of epidural injection ranges from 50 to 90%, depending on patient selection and

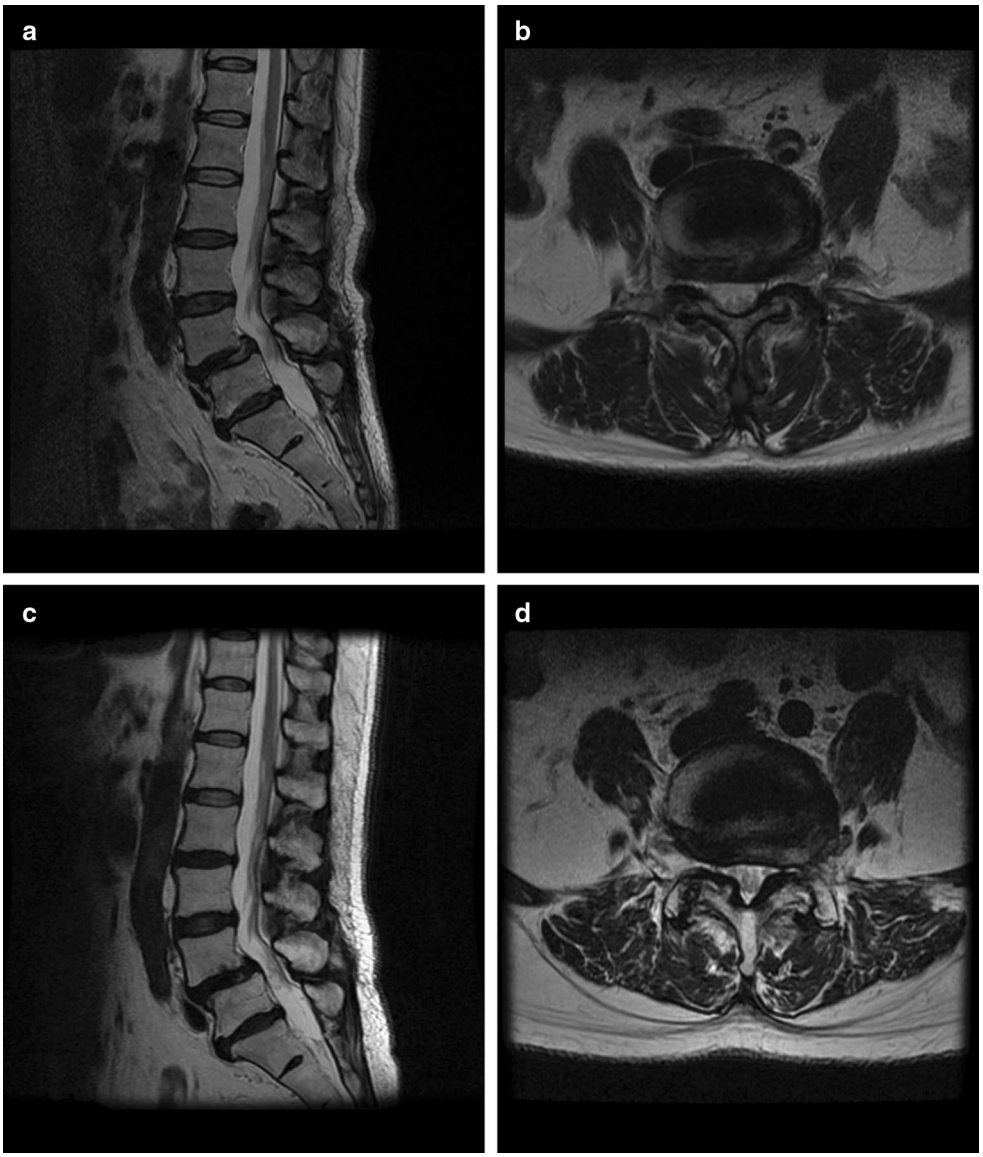

Fig. 1 Spinal magnetic resonance imaging of a 57-year-old female with low back and lower extremity pain due to lumber spinal canal stenosis. T2-weighted sagittal (**a**) and axial (**b**) images at L4–L5 before the treatment, and sagittal (**c**) and axial (**d**) images at L4–L5 after the treatment

Table 5 Comparison of short-term efficacy after the last therapy among diseases ($n=70$)

	NRS during movement			JOAS			RMDQ		
	Baseline	1 month	IC (%)	Baseline	1 month	IC (%)	Baseline	1 month	IC (%)
Spondylosis deformans ($n=24$)	7 (4–10)	5 (2–10)	33 (10–80)	17 (7–23)	20 (7–26)	9 (0–45)	17 (4–22)	12 (3–22)	31 (0–72)
Spinal canal stenosis ($n=20$)	7 (4–10)	5 (2–8)	40 (0–71)	18 (11–23)	21 (12–28)	17 (0–45)	16 (8–21)	9 (2–19)	47 (0–75)
Disk herniation ($n=15$)	8 (6–10)	5 (1–8)	43 (13–88)	14 (10–25)	23 (14–28)	25 (5–48)	16 (6–20)	8 (2–20)	43 (0–81)
Post-traumatic neuropathy ($n=6$)	9 (7–10)	7 (5–9)	33 (22–50)	14 (10–20)	19 (12–22)	13 (0–48)	18 (12–21)	13 (11–17)	34 (13–61)
Spondylolisthesis ($n=5$)	6 (5–8)	3 (3–5)	50 (20–63)	19 (15–21)	22 (20–25)	25 (10–35)	13 (8–22)	8 (4–12)	63 (0–75)

Data are presented as the median (range). Baseline scores indicate data at enrollment

IC improvement rate, *JOAP* Japanese Orthopedic Association Score, *RMDQ* Roland Morris Disability Questionnaire

the technique used [5, 6, 17]. Computed tomography evaluations have demonstrated the presence of common anatomical impediments to epidural injection, particularly at the L5–S1 level [22], which may contribute to the failure of epidural injections in patients with low back pain. Conversely, the success rate of intrathecal injections in our study was 100% with widespread anesthesia, including at the L5–S1 level. Lumbar puncture is frequently performed for anesthesia, chemotherapy, and examination of CSF, and it is less painful than intramuscular and intravenous injections [23]. These factors favor intrathecal injection over epidural injection. Thus, we believe that intrathecal injection therapy is especially useful for patients with subacute severe low back pain. *Intrathecal injection may also facilitate* rehabilitation for patients with *failed back surgery syndrome for whom epidural injection therapy is impossible due to fixed hardware and epidural adhesions*.

Our study has certain limitations. First, patients with various pathologies were included, and it is unclear which specific pain conditions were relieved by intrathecal injection. Second, no controls were included, and the use of other medications was allowed for 1 month after the last intrathecal injection. Therefore, our results may partially be due to the placebo effect and the natural course of illness. Third, the bupivacaine dose was increased in a fixed order, which limits the ability to determine the efficacy of different doses.

Conclusions

Low-dose intrathecal injections of isobaric bupivacaine are safe, tolerable, and effective in improving pain and disability in outpatients with low back and lower extremity pain.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All study procedures performed in human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

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