Received: 20 February 2018 | Revised: 30 October 2018 | Accepted: 31 October 2018

DOI: 10.1111/aas.13305

ORIGINAL ARTICLE

acta Anaesthesiologica Scandinavica

Intrathecal betamethasone for cancer pain: A study of its analgesic efficacy and safety

Hitoshi Taguchi[1] | Keiko Oishi[1] | Koh Shingu[2] | Hideo Matsumoto[1] | Munehiro Masuzawa[1]

[1]Department of Anesthesiology, Kansai Medical University Medical Center, Moriguchi, Japan

[2]Department of Anesthesiology, Kansai Medical University, Hirakata, Japan

Correspondence
Hitoshi Taguchi, Department of Anesthesiology, Kansai Medical University Medical Center, Osaka, Japan.
Email: taguchidoc@outlook.jp

Abstract

Background: A preliminary study has shown effective cancer pain relief by intrathecal betamethasone (ITB). However, further evidence is needed to support this new approach.

Methods: Cancer patients with opioid-resistant pain received lumbar intrathecal administration of betamethasone 2 or 3 mg once a week for 28 days. Immediate and short-term analgesia (using a percentage pain reduction scale and a numerical rating scale, NRS) and long-term analgesia (using NRS) were assessed. Patients were classified into two groups according to the most painful site of metastasis: vertebral column and/or surrounding nerve plexus metastases (group A) and other metastases distal from the vertebral column (group B).

Results: A total of 104 patients received ITB. Pain relief was observed not only in the lower half but also in the upper half of the body. The proportion of group A patients who experienced immediate analgesia was 81% (47/58), which was significantly greater than that of group B ($P < 0.001$). A decrease in NRS scores 1 day after ITB administration was observed in significantly more patients in group A than in group B ($P < 0.001$). Long-term analgesia was also recorded in a greater proportion of patients in group A than in group B in the 7-day (59%, 38/64 vs 6%, 2/33) and 28-day periods (71%, 40/56 vs 31%, 8/26) ($P < 0.001$). No adverse effects related to neurotoxicity were recorded.

Conclusion: Intrathecal injection of betamethasone produced analgesia for opioid-resistant cancer pain, and may be a potent therapeutic option for intolerable pain from vertebral column and/or surrounding nerve plexus metastases.

KEYWORDS
analgesic techniques, cancer, glucocorticoid, intrathecal, pain

1 | INTRODUCTION

In patients with cancer pain, systemic opioid therapies occasionally produce insufficient analgesia and have adverse effects (AEs),[1] especially in terminally ill patients with bone and nerve plexus metastases.[2,3] Moreover, administration of opioids via invasive procedures, such as epidural and intrathecal injection, may entail technical difficulties, have limited indications, and occasionally lead to

serious complications.[4] Glucocorticoids are given systemically to reduce pain and to treat anorexia and malaise[5] but are rarely given topically.

In January 1999, we treated a terminally ill patient with advanced uterine cancer who had intolerable pain.[6] Intravenous morphine had been ineffective, and other analgesic options were difficult to administer. Considering the difficulty of conventional treatments and on compassionate grounds, we chose intrathecal glucocorticoid treatment so as to alleviate cancer pain and other symptoms. The package insert of Rinderon® (betamethasone) injection, which has been approved by the Ministry of Health, Labor and Welfare in Japan, indicates that it can be intrathecally administered for meningeal leukemia, cerebrospinal meningitis, and malignant tumors (malignant lymphoma and similar diseases).[7] Rinderon® injection is usually administrated together with anticancer drugs, such as cytarabine, intrathecally to enhance the anticancer action for meningeal cancers. The patient accepted the uncertainty and potential risks associated with this treatment approach (ie, topical glucocorticoid administration), which were fully explained to her, therefore we administered the first intrathecal injection of betamethasone (4 mg). Potent analgesic effects were observed, and her physical and mental condition improved markedly. This motivated us to further investigate intrathecal betamethasone (ITB) for cancer pain treatment.

In our previous case report, betamethasone 1-4 mg injected into the lumbar intrathecal space was shown to produce unexpected long-lasting analgesia in cancer patients with intractable pain.[6] Subsequently, we conducted a preliminary study, in which betamethasone 1 mg was injected intrathecally in 10 cancer patients[8]; in almost all patients, not only pain but also uncomfortable symptoms were improved, and no safety concerns related to neurotoxicity of ITB were noted. Based on these results, we investigated the analgesic efficacy and safety of ITB in cancer patients with opioid-resistant intolerable pain in a clinical setting.

2 | METHODS

2.1 | Study design

The study was carried out from 1999 to 2013 at Kansai Medical University, Takii Hospital (current Medical Center), Osaka, in accordance with the Declaration of Helsinki. It was approved in 2001 by the Research Ethics Committee of Kansai Medical University (approval number: 104), Osaka, Japan.

Approval was given retrospectively, because at the start of the study (1999), there was no official committee in the university that approves and monitors clinical studies. Between 1999 and 2001, having fully examined the ethical issues in our department, we carried out the study after providing patients and their families with a detailed explanation (through discussion and in writing) of the procedure for ITB administration and its potential risks and benefits, and obtaining informed consent for participation.

Because the study began in 1999, it is not registered with a public trials registry.

Editorial Comment

Achieving pain relief in metastatic cancer pain can be challenging, particularly if the pain is opioid-unresponsive. Unconventional treatments must often times be attempted. In the current study, intrathecal betamethasone, labeled in Japan, was administered to patients with intractable metastasizing cancer pain. Comparing patients with vertebral (and juxta-vertebral) to non-vertebral metastasis supplied a control condition. Pain relief was observed with the intervention, and signs of neurological toxicity were not noted.

The inclusion criterion was the presence of severe cancer pain not controlled by conventional opioid therapies at the referral visit to our department. Patients with cranial cancer or whose general health was in critical condition were excluded.

Cancer pain was assessed in terms of site, intensity, and characteristics; vital signs and the results of physical examination, including neurological findings, were also recorded. Primary cancer site and metastases were identified by plain radiography, computerized tomography, and magnetic resonance imaging.

The most painful site of metastasis was categorized as the vertebral column, the nerve plexus surrounding the vertebral column, and sites distal from the vertebral column. Patients were classified into two groups: group A, patients with pain primarily from vertebral column and/or surrounding nerve plexus metastases; and group B, patients with pain primarily from other metastases distal from the vertebral column.

After obtaining written informed consent, the procedure for ITB administration was carried out.

2.2 | Procedure

Following measurement of the vital signs, the patient was placed in the lateral decubitus position. A pencil-point spinal needle (27 or 25 gauge) was inserted into the subarachnoid space through the interlaminar space of the lumbar vertebrae (at L2-S1 level), avoiding the metastatic region. After confirmation of backflow of cerebrospinal fluid (CSF), a betamethasone solution, total volume 2 mL (Rinderon injection® 1A: betamethasone 2 mg in 0.5 mL plus saline 1.5 mL; Shionogi & Co., Ltd, Osaka, Japan) or 3 mL (Rinderon® injection 1.5 A: betamethasone 3 mg in 0.75 mL plus saline 2.25 mL) was injected into the lumbar intrathecal space for about 30 seconds.

For cancer pain in the lower and upper half of the body, betamethasone was administered at a dose of 2 mg (2 mL) and 3 mg (3 mL), respectively. ITB administration was scheduled to be conducted once a week during the 28-day study period (ie, four times).

Doses of regularly administered opioids (prescribed by the patients' physicians before referral) were unchanged. However, changes in rescue doses of opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) were permitted, depending on patient needs.

2.3 | Observation after the procedure

Vital signs, and neurological symptoms and signs, were monitored in the 1 hour after administration of ITB.

Potential AEs related to the neurotoxicity of ITB (eg, sensory, motor, recto-bladder, and cerebrospinal dysfunction) were recorded, in addition to technical problems with the ITB administration procedure. AEs were assessed through weekly medical examinations by a physician and patient reports (from their 28-day diaries).

2.4 | Assessment of pain relief

Pain was assessed in the following order: immediate pain relief after the first procedure; short-term pain relief (1 day before *vs* after the first procedure); long-term pain relief (7 days and 28 days).

2.4.1 | Immediate pain relief after the first procedure

We used a percentage pain reduction scale (PPRS, 0-100) score for the assessment of immediate pain relief after the first procedure. A starting reference point (indicating pain just before ITB administration) was determined as PPRS100, and we asked patients to rate their pain reduction score immediately after ITB administration (30-minute period). Pain relief was defined as >50% reduction in PPRS score. We chose this method because halving of the intensity of pain that the patient had experienced immediately before ITB administration indicates sufficient pain relief, based on patients' statements.

2.4.2 | Short-term pain relief after the first procedure

The degree of pain 1 day after ITB administration was assessed using a numerical rating scale (NRS, 0-10) score, and compared with that 1 day before ITB administration.

2.4.3 | Long-term pain relief for 7 days and 28 days

A mean NRS score over 7 and 28 days was then calculated for each patient. Long-term analgesia was defined as NRS score ≤5. The cut-off for NRS score was selected based on the opinion of the majority of the patients who felt that halving of pain intensity would provide satisfactory pain relief.

NRS was used to enable patients to easily rate their pain on a daily basis. Before going to sleep each night, patients used a pain diary to record an NRS score representing an average of the pain intensity they experienced throughout the day, doses of analgesics, and unpleasant symptoms.

For ethical reasons, control data (ie, NRS scores for pain experienced over the 7 days before ITB administration) were not collected; because of severe cancer pain, patients enrolled in the present study were willing to receive treatment immediately rather than defer for 7 days to allow control data to be collected.

2.5 | Statistical analyses

The Wilcoxon signed rank sum test was used to compare the analgesic effects before and after ITB in terms of immediate percentage pain reduction and pain relief 1 day before and after. The Mann-Whitney U test was used to compare the analgesic effects between groups A and B in terms of immediate and short-term pain relief.

The chi-square test of independence was used to compare the long-lasting analgesic effects for a 7- and 28-day period after ITB administration in groups A and B.

3 | RESULTS

3.1 | Patient flow and characteristics

A total of 117 patients were enrolled. After exclusion of 13 patients with marked deterioration in physical and mental condition, who found visiting our hospital inconvenient, or who declined to participate in the study, ITB was administered to 104 patients (Figure 1).

A total of 78 inpatients and 26 outpatients attended the first visit. During the study period, nine inpatients were discharged because of sufficient analgesia, and three outpatients were admitted to hospitals, because of deterioration in general health. Almost all the patients had recorded the most severe pain during the course of the disease in the 4 weeks before the first administration of ITB.

Data on the analgesic efficacy of ITB during the 28-day study period were obtained from 78.8% (82/104) of patients; 45.2% (47/104) of patients completed the protocol (ie, ITB administered four times) and 54.8% (57/104) of patients underwent the procedure between three and one times (three times, 45 patients; twice, 6 patients; once, 6 patients).

Table 1 shows the primary cancer sites in the 104 patients who received ITB. Opioids, NSAIDs, and glucocorticoids had been previously administered to 87 (83.7%), 72 (69.2%), and 11 (10.6%) patients, respectively. Table 2 shows regular and rescue use of opioids and NSAIDs.

3.2 | Sites and characteristics of cancer pain

Most patients (68.3%, 71/104) had metastasis of the vertebral column, and 32.7% (34/104) had metastasis of another bone (eg, rib and coxal bone). Metastasis of the nerve plexus surrounding the vertebral column was present in 64.4% (67/104).

The most painful site was in the upper half of the body in 45 patients and in the lower half of the body in 59 patients. The pain was in one site in 36 patients, two sites in 64 patients, and three sites in 4 patients.

Group A and group B comprised 67 and 37 patients, respectively (Figure 1). Continuous pain, behavioral pain, and breakthrough pain were recorded in 99.0% (103/104), 98.1% (102/104), and 87.5% (91/104), respectively. Allodynia was experienced by 16.3% (17/104).

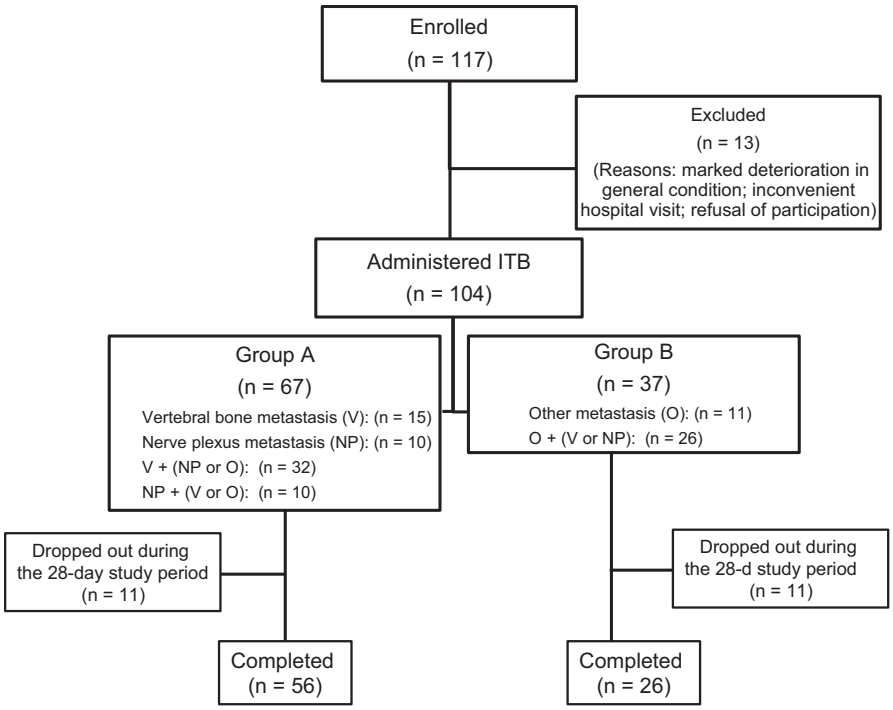

FIGURE 1 Patient flowchart. Patients were classified into two groups according to the most painful site of metastasis: vertebral column and/or surrounding nerve plexus metastases (group A) and other metastases distal from the vertebral column (group B). Second most painful sites are shown in parentheses

TABLE 1 Patient characteristics by primary cancer site (n = 104)

Primary cancer site	n (%)	Male:female, n	Median age (interquartile range), y
Colorectal	27 (26.0)	18:9	63 (55-70)
Rectum	17 (16.3)		
Colon	10 (9.6)		
Lung	13 (12.5)	11:2	63 (55-70)
Liver	13 (12.5)	12:1	64 (59-71)
Breast	8 (7.7)	0:8	61 (55-73)
Pancreas	7 (6.7)	2:5	62 (61-72)
Esophagus	4 (3.8)	4:0	56
Stomach	4 (3.8)	1:3	67
Kidney	4 (3.8)	4:0	61
Thyroid gland	3 (2.9)	1:2	68
Prostate	3 (2.9)	3:0	65
Uterus	3 (2.9)	0:3	40
Others	15 (14.4)	9:6	61 (53-70)
Total	104	65:39	62 (56-70)

TABLE 2 Regular and rescue use of opioids and NSAIDs during the study period

	Regular[a] n[c]	Rescue[b] n[c]
Opioids	106	35
Sustained-release morphine	54 (dose: 20-1200 mg/day)	
Rapid-release morphine	16 (dose: 20-90 mg/day)	23
Morphine suppository	9 (dose: 10-40 mg/day)	6
Morphine injection	8 (dose: 30-1200 mg/day)	2
Transdermal fentanyl	16 (dose: 2.5-40 mg/day)	
Buprenorphine suppository	3 (dose: 0.4 mg/day)	4
NSAIDs	72	74
Oral NSAIDs	58	50
NSAID suppository	14	24

NSAID, nonsteroidal anti-inflammatory drug.
[a]Drugs were prescribed by the patients' physicians before referral and continued to be used after administration of intrathecal betamethasone without dose change.
[b]Doses could be increased depending on patient needs.
[c]Some patients were administered several opioids.

3.3 | Immediate pain relief

After exclusion of 13 patients who reported somnolence or reduced pain following opioid administration, immediate pain relief was evaluated in 91 patients. Figure 2 shows box plots of change in PPRS scores after ITB administration. About two-thirds of patients (64%, 58/91) reported pain relief within 10-30 minutes of the first ITB administration. The proportion of patients who reported immediate pain relief was significantly greater in group A than in group B (81%, 47/58, vs 33%, 11/33; $P < 0.001$). The onset of analgesia in the lower half of the body was quicker than that in the upper half of the body.

3.4 | Short-term pain relief (1 day after ITB administration)

Figure 3 shows box plots indicating NRS scores on 1 day before and after ITB administration. A decrease in NRS scores after ITB

administration was observed in significantly more patients in group A than in group B ($P < 0.001$).

3.5 | Long-term analgesic efficacy

Data from 97 and 82 patients (excluding 7 and 22 patients, respectively, whose pain diaries were incomplete) were analyzed to investigate the analgesic efficacy in the 7-day and 28-day periods, respectively. The analgesic efficacy (mean NRS score ≤5) was observed in 40 of the 97 patients (7-day period) and 48 of the 82 patients (28-day period). A significantly greater proportion of patients in group A had analgesic efficacy compared with those in group B at the 7-day period (59%, 38/64, vs 6%, 2/33; $P < 0.001$) and at the 28-day period (71%, 40/56, vs 31%, 8/26; $P < 0.001$) (Table 3).

ITB did not produce pain relief in patients with painful sites far from the vertebral column, such as the rib or the limb, and in patients with both vertebral and rib metastases, it was effective for the vertebral pain but not the rib pain.

Relief from cancer pain in the lower half and upper half of the body was experienced by 74% (20/27) and 69% (20/29) of group A patients, respectively. Most group A patients who experienced pain relief over the 28-day study period did not need their dose of analgesics to be increased (83%, 33/40); moreover, decrease of the analgesics was seen in 20 (61%) of the patients (Table 4). For these patients, ITB treatment was continued after the study period, depending on the individual need.

3.6 | Adverse effects

In the hour immediately after injection of ITB, there were no major problems such as technical failures and complications in any patients. No abnormal symptoms or signs related to sensory and motor nerve dysfunction were seen nor AEs such as remarkable hypotension, bradycardia, headache, or other unpleasant symptoms.

No clinically significant AEs related to ITB neurotoxicity, such as back pain, limb numbness, perineal dysesthesia, recto-bladder dysfunction, and mental disorder, were observed in any patient during the 28-day study period (Table 5).

No general AEs of glucocorticoids, such as gastric ulcer, infection, and moon face, were observed. Conversely, improvements in unpleasant symptoms such as gait disturbance, sleeplessness, and bad mood were observed in almost all group A patients. No problems related to the procedure for ITB administration, such as bleeding, infection, post-spinal headache, and failure of drug injection, occurred.

In three patients, the following worsened or newly developed symptoms related to cancer progression were observed: compression caused by thoracic vertebral metastasis, pathological fracture of the femur and newly occurring cervical vertebral metastasis.

4 | DISCUSSION

4.1 | Site of action of intrathecal betamethasone

ITB, administered once a week, produced long-lasting analgesia without neurotoxic AEs. Of note, pain relief was achieved in most patients with vertebral column and/or surrounding nerve plexus metastases, the pain of which is difficult to treat,[9] and the effect was found even when the pain was located in the upper half of the body, far from the site of the lumbar intrathecal injection. In contrast, ITB did not produce pain relief for sites far from the vertebral column such as rib and limb metastases, even in patients having both thoracic vertebral and rib metastases for which the innervation was from the same spinal segment. These results suggest that the pharmacokinetics and pharmacodynamics of ITB differ from those of intrathecal opioids and local anesthetics, which block specific nerve pathways.

We believe that the isobaric nature of the Rinderon injection® preparation mixed with saline (the specific gravity of the solutions used in this study was almost the same as that of CSF) allowed it to spread widely throughout the CSF. Once betamethasone has spread throughout the CSF, its high lipophilicity allows it to penetrate the meninges, such as the dura mater, and thereby reach other structures associated with the vertebral column. Penetration was likely to have been facilitated by histological disruption caused by the invasive cancer tissue.

4.2 | Comparison with conventional treatments

Oral or intravenous opioids occasionally induce intolerable AEs as well as insufficient analgesia. Long-term opioid therapy may lead to

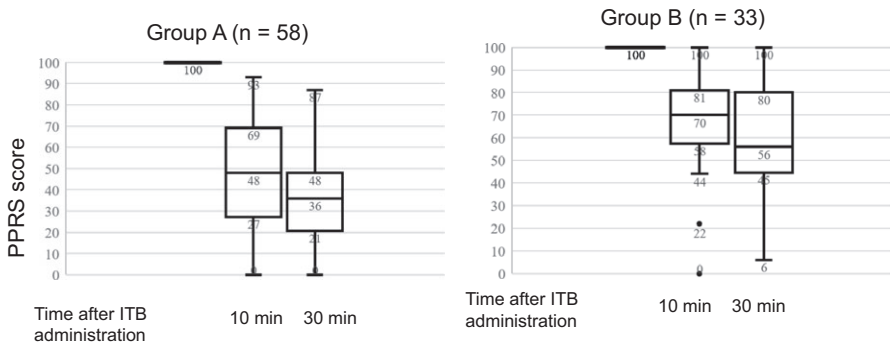

FIGURE 2 Box plots of change in percentage pain reduction scale scores to assess immediate pain relief in group A (left) and group B (right). ITB, intrathecal betamethasone; PPRS, percentage pain reduction scale

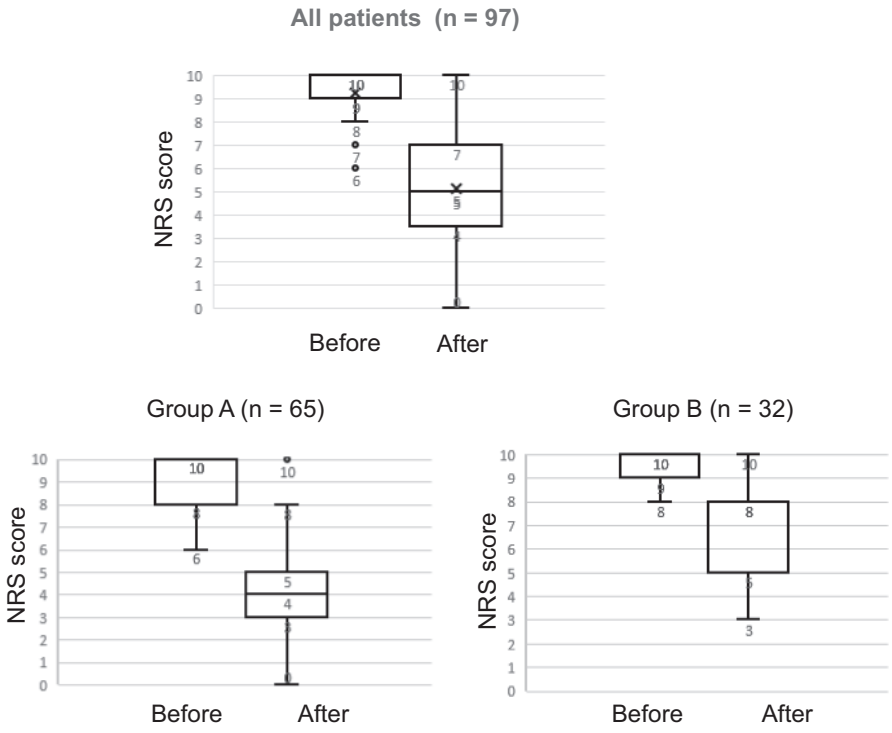

FIGURE 3 Box plots indicating NRS scores on 1 day before and after ITB administration in all patients (upper) and group A (lower left) and group B (lower right)

TABLE 3 Long-term analgesic efficacy assessed by NRS

	Group A	Group B	*P*[a]
7-day period (n = 97)			
n	64	33	
Mean NRS score ≤5	38 (59)	2 (6)	<0.001
Mean NRS score >5	26 (41)	31 (94)	
28-day period (n = 82)[b]			
n	38/56	9/26	
Mean NRS score ≤5	28 (74)/40 (71)	3 (33)/8 (31)	<0.001/<0.001
Mean NRS score >5	10 (26)/16 (29)	6 (67)/18 (69)	

NRS, numerical rating scale. Data are expressed as n (%).
[a]Group A *vs* group B.
[b]Patients who completed the study protocol (four times ITB)/total patients (1-4 times ITB).

TABLE 4 Dose of analgesics in patients who experienced pain relief induced by ITB in the 28-day study period (n = 48)

	Patients who completed the protocol (four times of ITB)/Total patients (1-4 times of ITB)		
Dose of analgesics	Group A (n = 40), n (%)	Group B (n = 8), n (%)	*P*[a]
Not increased	21 (84)/33 (83)	3 (50)/4 (50)	0.083/0.046
Decreased	16/20	2/3	
Unchanged	5/13	1/1	
Increased	4 (16)/7 (18)	3 (50)/4 (50)	

ITB, intrathecal betamethasone.
[a]Group A vs group B.

analgesic tolerance, especially when administered intrathecally.[10] In the present study, opioids were not administered in some patients because of unpleasant symptoms. Epidural and intrathecal opioids often have unpleasant and potentially harmful AEs[11] and sometimes they cause complications associated with the use of implanted catheters.[12]

Epidural or intrathecal injection of local anesthetics can induce sensory, motor, and autonomic nerve dysfunction, causing reduced activities of daily living. Intrathecal injection of neurolytic agents may entail technical difficulties and the risk of neural complications.[13]

A single betamethasone injection into the lumbar intrathecal space can be performed easily and safely at an outpatient clinic, using a small pencil-point needle. ITB may be a minimally invasive and practically potent option for the management of uncontrollable cancer pain.

4.3 | Glucocorticoids in management of cancer pain

The use of glucocorticoids is a multiple therapy, improving not only pain but also the unpleasant symptoms experienced by patients with advanced cancer.[14,15] In the present study, however, oral glucocorticoids were administered in some patients but they had little effect.

Oral dexamethasone and betamethasone are generally used at a dose of 2-4 mg/day for nerve compression caused by cancer invasion or metastasis.[16] Similarly, these drugs are used at a dose of 8-20 mg/day for spinal cord compression and increased intracranial pressure.[17] In the present study, a smaller dose of betamethasone (2 or 3 mg/week) was administered intrathecally rather than orally.

TABLE 5 Incidence of adverse effects related to ITB in the 28-day study period (n = 104)[a]

	With symptoms before ITB[b], n	Symptoms after ITB[c], n			Without symptoms before ITB[b], n	Symptoms after ITB[c], n		Data unavailable
		Worsened	Unchanged	Improved		Newly developed	None	
Sensory nerve disturbance in the lower limbs								
Pain	35	1	4	30	43	1	42	26
Numbness	31	1	7	23	47	0	47	26
Sensory weakness	15	1	9	5	63	0	63	26
Dysesthesia	1	0	0	1	76	0	76	26
Perineal dysesthesia	11	0	6	5	67	0	67	26
Motor nerve disturbance in the lower limbs								
Weakness	14	1	4	9	64	0	64	26
Standing up disturbance	26	0	10	16	52	0	52	26
Gait disturbance	53	1	21	31	25	1	24	26
Cerebrospinal neuro-disturbance								
Headache	5	0	0	5	73	0	73	26
Back pain	26	0	3	23	52	0	52	26
Excitement	1	0	1	0	77	0	77	26
Bad mood	51	0	14	37	27	0	27	26
Recto-bladder disturbance								
Rectal dysfunction	22	0	17	5	44	0	44	38
Urinary dysfunction	21	0	17	4	45	0	45	38
Circulatory disturbance								
Hypotension	3	0	3	0	75	0	75	26
Edema	4	0	4	0	74	1	73	26
Adverse effects of glucocorticoids								
Peptic ulcer	0	0	0	0	78	0	78	26
Present or deterioration of infection	0	0	0	0	78	0	78	26
Muscle	0	0	0	0	78	0	78	26
Glaucoma	0	0	0	0	78	0	78	26
Skin	0	0	0	0	78	0	78	26
Other	0	0	0	0	78	1	77	26

ITB, intrathecal betamethasone.

[a]No adverse effects associated with ITB neurotoxicity were recorded in any of the patients.

[b]Symptoms observed before the first ITB administration (recorded because symptoms associated with cancer progress and metastasis and symptoms of complications of ITB administration are similar).

[c]Symptoms observed after the first ITB administration during the 28-day study period.

Glucocorticoids seem to induce analgesia via reduction of algogenic substances, such as prostaglandins. Analgesia induced by ITB may help decrease the inflammatory reaction via inhibition of cytokines and inflammatory cells[18] and suppression of spinal glial activation[19] including neuroimmune enhancement[20] in the invasive cancer tissue.

4.4 | Mechanism of analgesia induced by intrathecal betamethasone

Betamethasone injected into the CSF is likely to spread widely and penetrate the tissue around the vertebral column that has been injured by the cancer mass, leading to direct effects on cancer pathology.

The rapid induction of pain relief, followed by long-lasting analgesia, achieved by ITB is surprising, given the traditional theory of steroid action; steroids modulate nuclear transcription after binding to intracellular receptors, and the synthesis of proteins, such as lipocortin, takes several hours.[21]

The immediate effects caused by glucocorticoids are thought to be mediated via a non-genomic mechanism of action, such as an effect on specific membrane-bound receptors[22] or intracellular signal transmission, rather than a nuclear mechanism of action.[23,24] Glucocorticoids have also been shown to induce apoptosis of cancer cells

via activation of caspase in the mitochondrial pathway,[25,26] and the development of cancer immunotherapies related to glucocorticoids and their receptors is progressing.[27,28]

The relation between the immediate and long-lasting pain relief induced by ITB shown in the present study is unclear; however, we speculate that the analgesic effects of ITB may be mediated by both its anti-inflammatory action and induction of apoptosis of metastatic cancer cells. In support of this hypothesis, tumor size decreased after ITB administration in some patients in whom the anticancer therapy was ineffective (unpublished data).

4.5 | Advantages of betamethasone injection solution

We chose Rinderon® injection as the betamethasone solution for intrathecal administration, because it is water-soluble and contains few additives, and the safety of low-dose betamethasone has been shown in both clinical and experimental studies.[29,30] Moreover, the intrathecal use of betamethasone has been recommended, by the manufacturer of the agent (Shionogi & Co., Ltd), for meningeal leukemia and cerebrospinal meningitis.[7]

The Rinderon® injection preparation used in the present study contains 2 mg of betamethasone and 0.5 mg of sodium sulfite/bisulfite (Na_2SO_3, $NaHSO_3$), which act as antioxidants,[31] in a volume of 0.5 mL. The solution has a specific gravity of 1.018 and a pH of 7-8.

Neurotoxicity of glucocorticoids was not detected in an animal model. Some additives contained in the preparations have been suggested to be associated with complications such as arachnoiditis.[32] Intrathecal bisulfite can reduce neurotoxic damage when injected with a local anesthetic (chloroprocaine).[33]

4.6 | Safety of ITB

The AEs regarding intrathecal injection of glucocorticoids include neurotoxicity to the spinal cord and the meninges.[34] However, reports confirming the evidence for safety of intrathecal glucocorticoids include a clinical study of intrathecal methylprednisolone for post-herpetic neuralgia[35] and an experimental study of intrathecal triamcinolone.[36] Moreover, intrathecal glucocorticoids have been used in combination with anticancer drugs to treat spinal dissemination of leukemia in children.[37,38]

Regarding ITB, its safety has been assessed in a clinical study of postoperative analgesia[29] and in an experimental study using a sheep model.[30] In the experimental study, 5.7 mg of betamethasone produced no pathological changes; dose-dependent neurotoxicity was found only at doses of >11.4 mg. Considering the possibility of dose-dependent neurotoxicity, we used betamethasone at 2 or 3 mg in the present study, after confirming the safety of betamethasone at 1 mg in the preliminary study. No AEs related to ITB were observed, and interestingly, neurological symptoms such as motor weakness and behavioral disability improved in many patients.

4.7 | Limitations

The present study was not a prospective randomized controlled study, generally considered the gold standard for clinical trials.[39] However, a randomized controlled design would have been inappropriate and premature for our study, in light of the large variation in cancer type, disease stage, physical status, previous treatment methods, and site of pain among the patients. Control data of pain intensity for 7 days before ITB administration were not collected because of ethical reasons; patients enrolled in the present study were suffering from severe uncontrollable pain, and were willing to receive treatment immediately. To minimize potential researcher bias, pain was assessed by the patient themselves. Safety was assessed through weekly medical examination by a physician and patients' own assessment recorded in a diary. Our priority was to avoid worsening serious illness and to maintain patient safety; therefore, ITB administration was occasionally canceled when the patient's condition was poor. The selection of NRS score ≤5 as the cutoff was based on our patients' perception of satisfactory pain relief, which is subjective and may not be applicable to other patient populations.

5 | CONCLUSION

Intrathecal injection of betamethasone once a week may be an optimal option for producing long-lasting analgesia and improving activities of daily living in patients with intractable cancer pain, especially that caused by vertebral and nerve plexus metastases. ITB-induced analgesia may be closely related to induction of apoptosis of cancer cells, resulting in a therapeutic attack on the cancer pathology; further detailed studies are necessary to confirm these findings.

ACKNOWLEDGEMENTS

We are deeply grateful to the members of our pain clinic. We thank S. Matsumoto, S. Sakamoto, E. Yamazaki, M. Shirakawa, M. Nakao, M. Yamada, N. Nishizawa, N. Sato, T. Kanouda, K. Kozima, and Y. Uchiyama for their contribution as the clinical practitioners and investigators of the study.

CONFLICT OF INTEREST

No conflicts of interest for any of the authors.

ORCID

Hitoshi Taguchi https://orcid.org/0000-0003-0194-2633

REFERENCES

1. Portenoy RK, Lesage P. Management of cancer pain. *Lancet*. 1999;353:1695-1700.
2. Abrahm J, Ross E, Klickovich RJ. Cancer-related bone pain. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. *Bonica's Management of*

Pain (4th ed.). Philadelphia, PA: Lippincott Williams & Wilkins; 2010; 629-635.
3. Smith TJ, Saiki CB. Cancer pain management. *Mayo Clin Proc*. 2015;90:1428-1439.
4. Ferrer-Brechner T. Anesthetic techniques for the management of cancer pain. *Cancer*. 1989;63:2343-2347.
5. Schell HW. Adrenal corticosteroid therapy in far advanced cancer. *Geriatrics*. 1972;27:131-141.
6. Taguchi H, Shingu K, Okuda H, Matsumoto H. Analgesia for pelvic and perineal cancer pain by intrathecal steroid injection. *Acta Anaesthesiol Scand*. 2002;46:190-193.
7. Rinderon® Injection 2mg/4 mg (0.4%). *Package Insert (ver 13)*. Osaka: Shionogi & Co., Ltd; 2015 [in Japanese].
8. Taguchi H, Oishi K, Sakamoto S, Shingu K. Intrathecal betamethasone for cancer pain in the lower half of the body: a study of its analgesic efficacy and safety. *Br J Anaesth*. 2007;98:385-389.
9. Sodji Q, Kaminski J, Willey C, Kim N, Mourad W, Vender J, Dasher B. Management of metastatic spinal cord compression. *South Med J*. 2017;110:586-593.
10. Lin CP, Kang KH, Tu HJ, Wu MY, Lin TH, Liou HC, Sun WZ, Fu WM. CXCL12, CXCR11 signaling contributes to the pathogenesis of opioid tolerance: a translational study. *Anesth Analg*. 2017;124:972-979.
11. Walker SM, Goudas LC, Cousins MJ, Carr DB. Combination spinal analgesic chemotherapy: a systematic review. *Anesth Analg*. 2002; 95:674-715.
12. Mercadante S. Problems of long-term spinal opioid treatment in advanced cancer patients. *Pain*. 1999;79:1-13.
13. Ashburn MA, Lipman AG. Management of pain in the cancer patient. *Anesth Analg*. 1993;76:402-416.
14. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. *Oncologist*. 2004;9:571-591.
15. Haywood A, Good P, Khan S, Leupp A, Jenkins-Marsh S, Rickett K, Hardy JR. Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst Rev*. 2015;4:CD010756.
16. Twycross R. The risks and benefits of corticosteroids in advanced cancer. *Drug Saf*. 1994;11:163-178.
17. Vecht CJ. Clinical management of brain metastasis. *J Neurol*. 1998;245:127-131.
18. Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines and pain enhancement. *Neurosignals*. 2005;14:166-174.
19. Hains BC, Waxman SG. Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. *J Neurosci*. 2006;26:4308-4317.
20. Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. *Nat Rev Immunol*. 2014;14:217-231.
21. Cunningham FM, Lees P. Advances in anti-inflammatory therapy. *Br Vet J*. 1994;150:115-134.
22. Rudolph LM, Cornil CA, Mittelman-Smith MA, Rainville JR, Remage-Healey L, Sinchak K, Micevych PE. Actions of steroids: new neurotransmitters. *J Neurosci*. 2016;36:11449-11458.
23. Wehling M. Specific, nongenomic actions of steroid hormones. *Annu Rev Physiol*. 1997;59:365-393.
24. Losel RM, Falkenstein E, Feuring M, Schultz A, Tillmann HC, Rossol-Haseroth K, Wehling M. Nongenomic steroid action: controversies, questions, and answers. *Physiol Rev*. 2003;83:965-1016.
25. Sionov RV, Spokoini R, Kfir-Erenfeld S, Cohen O, Yefenof E. Mechanisms regulating the susceptibility of hematopoietic malignancies to glucocorticoid-induced apoptosis. *Adv Cancer Res*. 2008;101:127-148.
26. Schlossmacher G, Stevens A, White A. Glucocorticoid receptor–mediated apoptosis: mechanisms of resistance in cancer cells. *J Endocrinol*. 2011;211:17-25.
27. Pufall MA. Glucocorticoids and cancer. *Adv Exp Med Biol*. 2015;872:315-333.
28. Burugu S, Dancsok AR, Nielsen TO. Emerging targets in cancer immunotherapy. *Semin Cancer Biol*. 2017;52:39-52.
29. Langmayr JJ, Obwegeser AA, Schwarz AB, Laimer I, Ulmer H, Ortler M. Intrathecal steroids to reduce pain after lumbar disc surgery: a double-blind, placebo-controlled prospective study. *Pain*. 1995;62:357-361.
30. Latham JM, Fraser RD, Moore RJ, Blumbergs PC, Bogduk N. The pathologic effects of intrathecal betamethasone. *Spine*. 1997;22:1558-1562.
31. Feroci G, Fini A. Study of the antioxidant effect of several selenium and sulphur compounds. *J Trace Elem Med Biol*. 1998;12:96-100.
32. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). *Anesth Analg*. 1999;88:797-809.
33. Taniguchi M, Bollen A, Drasner K. Sodium bisulfite: scapegoat for chloroprocaine neurotoxicity? *Anesthesiology*. 2004;100:85-91.
34. Nelson DA, Landau WM. Intrathecal steroids. history, efficacy, accidentality, and controversy with review of United States Food and Drug Administration reports. *J Neurol Neurosurg Psychiatry*. 2001; 70:433-443.
35. Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, Asai M, Matsuki A. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med*. 2000;343:1514-1519.
36. Abram SE, Marsala M, Yaksh TL. Analgesic and neurotoxic effects of intrathecal corticosteroids in rats. *Anesthesiology*. 1994;81:1198-1205.
37. Sullivan MP, Chen T, Dyment PG, Hvizdala E, Steuber CP. Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology group study. *Blood*. 1982;60:948-958.
38. Lin WY, Liu HC, Yeh TC, Wang LY, Liang DC. Triple intrathecal therapy without cranial irradiation for central nervous system preventive therapy in childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2008;50:523-527.
39. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340: c332–c332.

How to cite this article: Taguchi H, Oishi K, Shingu K, Matsumoto H, Masuzawa M. Intrathecal betamethasone for cancer pain: A study of its analgesic efficacy and safety. *Acta Anaesthesiol Scand*. 2019;63:659–667. https://doi.org/10.1111/aas.13305