Intrathecal betamethasone for cancer pain in the lower half of the body: a study of its analgesic efficacy and safety

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Background. Sufficient analgesia for cancer pain is sometimes difficult to achieve with conventional treatments. We aimed at investigating the analgesic efficacy and safety of intrathecal betamethasone in patients with uncontrollable cancer pain.

Methods. Betamethasone 1 mg mixed with saline was injected into the lumbar intrathecal space once a week in 10 patients with persistent cancer pain in the lower half of the body. During the 4-week study period, the analgesic efficacy and adverse effects related to intrathecal betamethasone were observed.

Results. Long-lasting analgesia (mean numerical pain score ≤5) for 7 days, after immediate analgesia within 10 min, was obtained without the need to increase the morphine dose in 5 of 10 patients. In almost all of the patients, not only pain, but also uncomfortable symptoms were improved. Adverse effects related to neurotoxicity of intrathecal betamethasone, such as sensory and motor dysfunctions, were not observed in any patients.

Conclusion. When conventional cancer pain treatments are not successful, intrathecal betamethasone may be useful, as it probably induces long-lasting analgesia without adverse effects and improves activities of daily living, especially in patients with vertebral bone metastases.


Keywords: analgesics anti-inflammatory, steroid; analgesic techniques, subarachnoid; cancer; pain; toxicity, neurotoxicity

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Despite advances in pain management, cancer pain is still often intractable. In terminal cancer patients, glucocorticoids are given systemically to alleviate pain, anorexia, and malaise but are rarely used topically. It is thought that the effects of glucocorticoids are mediated by their anti-inflammatory or immunosuppressive actions. Recently, evidence for the involvement of various neurotransmitters and pain modulators in pain perception has been reported, and treatments that target this aspect of the pathogenesis of pain are being developed.

The intrathecal use of glucocorticoid may be effective for the treatment of inflammatory or neuro-injury associated pain in the spinal cord and roots, as it has an inhibitory action on prostaglandins and other algogenic substances. However, adverse effects related to neurotoxicity of intrathecal glucocorticoid have been reported. We previously reported that intrathecal betamethasone produced long-lasting analgesia without any adverse effects in advanced pelvic and perineal cancer patients.

Intrathecal injection of glucocorticoid may alleviate intractable pain caused by inflammation and sensitization without the development of neurotoxicity in the spinal cord and nerve roots, when the injection consists of a small dose of glucocorticoid that includes relatively safe preservatives.

Methods

This study was approved by the Research Ethics Committee of Kansai Medical University. After obtaining the patient’s medical history and present illness, the vital signs were taken and a neurological examination was performed. Simple X-ray, CT, and MRI data were evaluated. Inclusion criteria consisted of the presence of advanced cancer, cancer pain located in the lower half of the body, and uncontrollable pain despite conventional analgesic therapies.

Ten patients who met the inclusion criteria were enrolled, and written informed consent was obtained from
all of them. During the 4-week study period, intrathecal betamethasone was scheduled to be given once a week. The dose of slow-release oral morphine was to remain unchanged during the treatment, but rescue doses of oral morphine and NSAIDs, which were received 0–3 times a day before the treatment, could be given based on the patients’ needs.

In the lateral decubitus position, a 25-gauge pencil-point spinal needle was inserted through the interlaminar space in the lumbar vertebrae to avoid the metastatic region. Betamethasone solution (Rinderon Injection, Shionogi Pharmaceuticals, Osaka, Japan), including 2 mg of betamethasone, 0.5 mg of sodium sulphite, and 15 mg of D-sorbitol in a volume of 0.5 ml, mixed with saline was injected into the lumbar subarachnoid space. The betamethasone dose was 1 mg (0.25 ml), and the total volume of the solution was 2 ml.

Immediately after intrathecal injection of betamethasone, the acute analgesic effect was examined at 5, 10, 20, and 30 min using the visual analogue scale (VAS). Analgesia was defined as a 50% or greater reduction in pain compared with the VAS score (100 mm) just before the treatment. The development of abnormal neurological signs and symptoms was observed for 1 h. During the 4-week study period, the patients themselves assessed their pain intensity; the daily pain assessment was done before going to sleep at night using the numerical pain score (PS; 0=no pain and 10=the worst pain in the 10 days before treatment). We used a PS as a pain relief scale after the treatment, considering the variability and multiple dimensions of cancer pain during the course of the disease. Potential adverse effects related to the neurotoxicity of betamethasone and the intrathecal injection procedure, such as headache, back pain, low back pain, numbness in the limbs, sensory weakness, motor weakness, gait disturbance, and recto-bladder dysfunction, were assessed weekly.

### Results

The site of pain, cancer origin, bone metastasis, morphine dose, and the number of intrathecal betamethasone injections are shown in Table 1. Despite having been given anti-cancer therapies and systemic analgesic pharmacotherapies, the patients had severe and persistent pain in the low back, pelvis, perineum, or lower limb region. Before treatment, half of the patients were given small doses of morphine, because of their conditions or adverse effects such as nausea or somnolence.

Betamethasone was injected in the intrathecal space one to four times during the 4-week study period, depending on the patient’s physical and mental condition. In four patients with bone metastasis in the lumbar vertebrae, the intrathecal approach was chosen to avoid the metastatic region. Injection failure, paresthesia, bleeding, and other technical difficulties were not seen in any of the patients.

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Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Gender</th>
<th>Site of pain</th>
<th>Origin of cancer</th>
<th>Bone metastasis</th>
<th>Oral morphine dose (mg day(^{-1}))</th>
<th>Number of intrathecal betamethasone injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Low back and lower limb</td>
<td>Lung</td>
<td>L3</td>
<td>None</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>Pelvis and bilateral lower limb</td>
<td>Liver</td>
<td>None</td>
<td>None</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>Pelvis and lower limb</td>
<td>Rectum</td>
<td>L2</td>
<td>3</td>
<td>120</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>M</td>
<td>Pelvis and lower limb</td>
<td>Rectum</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>M</td>
<td>Pelvis and lower limb</td>
<td>Uterus</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>F</td>
<td>Perineum and low back</td>
<td>Sigmoid colon</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>Low back and low abdomen</td>
<td>Sacrum</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>Pelvis and lower limb</td>
<td>Gallbladder</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>M</td>
<td>Low back and lower abdomen</td>
<td>Prostate</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>M</td>
<td>Low back and low abdomen</td>
<td>None</td>
<td>L2</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>
During the study period, three patients dropped out; of these three patients, two were transferred to another hospital, and one patient died.

Seven of 10 patients showed immediate analgesia (more than a 50% reduction in pain compared with the pre-treatment VAS) within 30 min after the first intrathecal injection of betamethasone (Table 2); five patients showed immediate and sufficient analgesia within 10 min. Abnormal symptoms and signs related to sensory and motor nerve dysfunction were not seen. Hypotension, bradycardia, headache, and recto-bladder dysfunction were not observed in the hour after betamethasone injection.

Long-lasting analgesia was maintained after immediate analgesia in many of the patients. During the first week of treatment, five patients (No. 1, 4, 5, 6, 8) had good analgesia (mean PS ≤ 5) for 7 days without the need to increase their analgesics (Table 2). Good and long-lasting pain relief for 4 weeks was obtained in five of seven patients who completed the study. The rescue morphine dose had to be increased in three of the five patients without increasing the other analgesics, whereas two patients (No. 5, 6) had excellent analgesia without any need to increase their morphine or other analgesics in the 4-week study period. In patients with satisfactory pain relief, uncomfortable symptoms improved, and activities of daily living gradually recovered. Some patients could walk better; however, if vertebral bone stability could not be maintained, the patients had pain when walking and standing. Adverse effects related to neurotoxicity of intrathecal betamethasone, such as sensory and motor dysfunctions, did not occur in any of the patients (Table 3).

### Table 2: Analgesic effects during the first week of treatment. Acute analgesia was defined as a 50% or greater reduction in pain intensity compared with the pre-treatment VAS score (100 mm) after the first intrathecal injection of betamethasone. Daily pain intensity was assessed by the patients themselves using the numerical pain score (PS).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Acute analgesia in 30 min</th>
<th>Analgesia (everyday PS ≤ 5) for 3 days</th>
<th>Analgesia (mean PS ≤ 5) for 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7/10</td>
<td>6/10</td>
<td>5/10</td>
</tr>
</tbody>
</table>

### Table 3: Adverse effects during treatment. Symptoms related to neurotoxicity of intrathecal betamethasone and other adverse effects were not found in any of the patients during the 4-week study period. Motor nerve functions such as motor weakness and gait disturbance improved in some patients.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Before treatment (n=10)</th>
<th>During the first 2 weeks of treatment (n=10)</th>
<th>During the last 2 weeks of treatment (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Newely developed</td>
<td>Unchanged</td>
<td>Improved</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Low back pain</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Numnness</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Sensory weakness</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Motor weakness</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Recto-bladder dysfunction</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other neural disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Discussion

We have previously reported on the achievement of long-lasting analgesia using intrathecal betamethasone with saline in three cancer patients. In the current study, the safety and analgesic efficacy of intrathecal betamethasone were investigated in 10 cancer patients who had not obtained sufficient analgesia despite conventional treatments. With intrathecal betamethasone treatment, none of the patients developed adverse effects such as neurological dysfunction, and about a half of the patients achieved sufficient analgesia against intractable pain. In the current study, we did not use a controlled design, as intrathecal injections of clonidine, midazolam, or opioids, which would be used in the control group, are often associated with uncomfortable adverse effects. Thus, it would be difficult to perform a controlled study of intrathecal analgesia in terminally ill patients.

### Safety of intrathecal glucocorticoid

There are several arguments concerning the safety of intrathecal injection of steroids. Complications such as arachnoiditis and meningitis have been reported. Nelson and Landau argued that the intrathecal administration of glucocorticoids is unsafe and indicated that intrathecal glucocorticoids could lead to the development of neurotoxicity in the spinal cord and meninges. However, the safety of intrathecal glucocorticoids has been advocated in some clinical and experimental studies. In the clinical study by Kotani and colleagues, there were no complications in 89 patients with postherpetic neuralgia who received four doses of intrathecal methylprednisolone acetate (60 mg) containing propylene glycol. Langmayr and colleagues indicated that, after lumbar disc surgery, intrathecal betamethasone provided significant pain reduction without any disadvantageous effects. Latham and colleagues showed in sheep that repeated intrathecal administration of 5.7 mg (1 ml) betamethasone containing benzalkonium chloride did not result in pathological changes. However, large doses of betamethasone, such as 11.4 mg (2 ml) and more,
were associated with dose-dependent neurotoxicity. Furthermore, it has been found that intrathecal triamcinolone diacetate containing polyethylene glycol did not induce spinal neurotoxicity in rat model.\textsuperscript{15} It is believed that the chemicals responsible for neurotoxicity when glucocorticoids are administered intrathecally are not the glucocorticoids themselves, but the additives such as antioxidants, preservatives, and excipients that are present in the injected solution.\textsuperscript{16}

We chose betamethasone as the glucocorticoid for intrathecal injection because of its water solubility, the presence of small dose additives in the solution, its safety in animal studies, and the fact that the intrathecal use of betamethasone is recommended for meningeal leukaemia, cerebrospinal meningitis, malignant lymphoma, etc. by the manufacturer of betamethasone. To avoid possible neural damage, we used a small dose (1 mg) and volume (0.25 ml) of betamethasone solution. The 0.5 ml volume of betamethasone solution used contains 2 mg of betamethasone, 0.5 mg of sodium sulphite, and 15 mg of D-sorbitol. The sulphites (Na\textsubscript{2}SO\textsubscript{3}, NaHSO\textsubscript{3}) act as antioxidants by combining with free oxygen at physiological pH.\textsuperscript{17} They are not neurotoxic in solution at physiological pH, but can be neurotoxic in low pH conditions through the production of SO\textsubscript{2}.\textsuperscript{18} The combination of betamethasone at pH 7.5–8.5 and saline at pH 4.5–8.0 used in the present study is not likely to provoke neurotoxicity as it has almost a physiological pH. Additionally, it has been reported that intrathecal bisulphite can reduce the neurotoxic damage induced by the intrathecal injection of local anaesthetic (chloroprocaine).\textsuperscript{19}

In the current study, clinical neurotoxicity was not seen after intrathecal betamethasone injection. On the contrary, neurological symptoms such as motor weakness and gait disturbance improved, and activities of daily living gradually recovered in many patients. Nevertheless, the sample size of this study (10 patients) is too small to conclusively demonstrate the safety of intrathecal betamethasone; for this, a larger study is needed.

**Analgesic effects of intrathecal glucocorticoid**

Glucocorticoids have multipurpose use, offering symptomatic relief in the management of patients with cancer pain. Principally, the analgesic effect of glucocorticoids is assumed to occur in inflammatory conditions. Recently, the analgesic effects of intrathecal steroids have been observed in both human and animal studies.\textsuperscript{13,14,20} In patients with postherpetic neuralgia, the intrathecal injection of methylprednisolone with lidocaine induced excellent and long-lasting analgesia for burning pain, lancinating pain, and allodynia.

It is thought that the long-lasting analgesia that results from the intrathecal injection of betamethasone is achieved through a decrease in the inflammatory reactions in the injured nerves and a reduction in algogenic substances such as prostaglandins, glutamate, and substance P in the spinal cord. The suppression of spinal glial activation and the inhibition of inflammatory cells and cytokines may accelerate analgesic effects.\textsuperscript{21,22} Almost all of the 10 patients studied showed an immediate analgesic effect within 30 min, which was followed by long-lasting analgesia; this was similar to the first observation in the previous three patients we reported. The effects of steroids are not expected to be immediate, as the changes in gene expression and synthesis of proteins take several hours.\textsuperscript{23} In the traditional theory of steroid action, steroids bind to intracellular receptors and modulate nuclear transcription. Anti-inflammatory effects of glucocorticoids are induced by the inhibition of phospholipase A2 resulting from lipidolysis production through the fundamental steroid pharmacology. However, this mechanism for the analgesic effect of intrathecal glucocorticoid does not explain the immediate analgesia that was seen. This rapid effect may be transmitted by specific membrane-bound receptors.\textsuperscript{24,25} Although a relationship between immediate and long-lasting analgesia is unknown, all of the patients with long-lasting analgesia had immediate analgesia after the first intrathecal betamethasone treatment. Given our findings, the mechanism of the analgesic effects of intrathecal glucocorticoid should be studied in greater depth in the future.

**Treatments of cancer pain and intrathecal glucocorticoid**

Opioids are widely used in the management of cancer pain, but sufficient pain relief without side-effects is sometimes difficult to obtain. Although intrathecal or epidural opioid injections may be a good option for cancer pain treatment, the patients develop side effects similar to oral opioids, and a catheter must be implanted for continuous opioid injection.\textsuperscript{26} The intrathecal injection of neurolytic agents is a useful anaesthetic technique for treating some cancer pain, but there are practical difficulties with the procedure, and also as risks of neural complications.\textsuperscript{27}

Oral glucocorticoids are used palliatively for cancer pain treatment, especially in patients with bone metastases.\textsuperscript{28} In the current study, small-dose betamethasone was used intrathecally once a week and sufficient pain relief was achieved in about a half of the patients, and no clinical complications were seen. Therefore, certain types of uncontrollable cancer pain can be better treated with intrathecal betamethasone, especially in patients with vertebral metastases whose pain is frequently difficult to control.

In contrast to epidural procedures, the intrathecal technique is easy and safe to perform in the lumbar region. Therefore, the intrathecal injection of betamethasone has a technical advantage over other anaesthetic procedures for the management of cancer pain.
Conclusions

When conventional treatments for cancer pain are not successful, intrathecal injection of small-dose betamethasone may be a useful approach, especially in patients with vertebral bone metastases. Intrathecal betamethasone may induce long-lasting analgesia without adverse effects. As a result, intrathecal betamethasone may be able to improve activities of daily living and quality of life in patients with cancer pain.

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