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Effect of High-dose Dexamethasone in Carcinomatous Metastatic Spinal Cord Compression Treated with Radiotherapy: a Randomised Trial

Per Soelberg Sørensen, Susanne Helweg-Larsen, Henning Mouridsen and Heine Høi Hansen

We performed a randomised single blind trial of high-dose dexamethasone as an adjunct to radiotherapy in patients with metastatic spinal cord compression from solid tumours. After stratification for primary tumour and gait function, 57 patients were allocated randomly to treatment with either high-dose dexamethasone or no steroidal treatment. Dexamethasone was administered as a bolus of 96 mg intravenously, followed by 96 mg orally for 3 days and then tapered in 10 days. A successful treatment result defined as gait function after treatment was obtained in 81% of the patients treated with dexamethasone compared to 63% of the patients receiving no dexamethasone therapy. Six months after treatment, 59% of the patients in the dexamethasone group were still ambulatory compared to 33% in the no dexamethasone group. Life table analysis of patients surviving with gait function showed a significantly better course in patients treated with dexamethasone ($P < 0.05$). Median survival was identical in the two treatment groups. Similar results were found in subgroup analysis of 34 patients with breast cancer as the primary malignancy. Significant side-effects were reported in 3 (11%) of the patients receiving glucocorticoids, 2 of whom discontinued the treatment. We conclude that high-dose glucocorticoid therapy should be given as adjunct treatment in patients with metastatic epidural spinal cord compression.
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INTRODUCTION

COMPRESSION OF the spinal cord or cauda equina by epidural metastasis is often a devastating complication to systemic cancer. The definitive treatment is either radiation therapy, surgical decompression or a combination of the two. It is still debatable whether surgical decompression offers any advantages compared to treatment with radiotherapy alone [1–4]. A large retrospective analysis suggested a superior effect of the combination of laminectomy and radiotherapy compared to radiotherapy alone in patients who had lost gait function due to spinal cord

compression [5]. Only one prospective, randomised study with a small number of patients has compared surgery plus radiotherapy with radiotherapy alone. No differences between the two treatment modalities were found, but the statistical power of the trial was too weak to allow any definite conclusions [6]. All studies of treatment of spinal cord compression agree on the importance of early treatment. In ambulatory patients, gait function can be preserved in 75–85% of the patient, whereas gait function can only be restored in 10–20% of patients who are non-ambulatory at the start of treatment [1–5].

Initial treatment with glucocorticoids has often been recommended [3, 7–9], but their role in the therapy of epidural spinal cord compression is less well-established than their role in metastatic brain tumours. Animal experiments with epidural carcinomas in rats have demonstrated that steroids are effective in restoring neurological function [10]. In humans, the evidence of efficacy is less well documented because definitive treatment of spinal cord compression is usually instituted immediately after diagnosis, and hence prevents the observation of the effect of glucocorticoids. A few anecdotal reports indicate neurological improvement within 24–48 h after systemic glucocorticoid administration to patients with epidural metastasis [11–13]. There are, however, no systematic series studying the efficacy of steroids as adjunct therapy to radiotherapy or surgery, and their contribution to overall neurological outcome in metastatic spinal cord compression is unknown.

Previously, the two Departments of Oncology at the Finsen Institute had different routines as to the use of glucocorticoids for acute treatment of epidural spinal cord compression. One department routinely gave prednisone in doses equivalent to those used for treatment of brain metastasis; the other did not use steroids prior to radiotherapy. In order to achieve a consensus regarding acute glucocorticoid administration as an adjunct to radiotherapy, we conducted a randomised study of high-dose dexamethasone versus no steroid treatment in patients with metastatic spinal cord compression from solid tumours.

PATIENTS AND METHODS

In this study we included consecutive patients with compression of the spinal cord or cauda equina by epidural metastasis from a carcinoma. Patients with lymphoma were not included. All patients were admitted to one of the Departments of Oncology at Rigshospitalet (formerly the Finsen Institute) between May 1987 and April 1989. The diagnosis of spinal cord compression was confirmed by myelography and, in some of the patients, by supplementary magnetic resonance imaging (MRI), with definition of the cranial and caudal margins of the epidural block. All patients were referred for radiation therapy. Patients who underwent surgery were not included. Surgery was considered in patients without previously established diagnosis of cancer, and in a few patients with unstable vertebral lesions. In all other patients, radiotherapy was offered as the department's standard treatment.

We excluded patients who had been treated previously for epidural metastasis, patients with meningeal carcinomatosis and patients with infectious disease or peptic ulcers in whom treatment with high-dose dexamethasone was considered inappropriate.

The study design was a single blind, randomised trial comparing high-dose dexamethasone therapy with no dexamethasone treatment. Eligible patients were stratified before randomisation according to their primary tumour (breast cancer or other cancer), and according to gait function at the time of diagnosis (gait function preserved or gait function lost). After randomisation, the patients were informed orally of whether they had been allocated to treatment with dexamethasone or not, and all gave consent to participate. The study was approved by the Ethical Review Committee for Copenhagen (record No. 200.1083/86). All patients were examined by the same neurologist who was not informed whether or not the patients had received dexamethasone treatment.

Immediately after myelography or MRI, patients randomised to dexamethasone treatment received an intravenous bolus of 96 mg. The patients were then maintained on a dose of 96 mg dexamethasone for 3 days (given orally when possible in four divided doses), and the treatment was then tapered in 10 days (Fig. 1). Prophylactic medication against gastro-duodenal ulceration was not given routinely—only in patients with a history of peptic ulcers and in patients complaining of dyspepsia.

Radiation therapy was delivered with 6 MV photon beams, administered in two parallel opposing anterior and posterior fields, encompassing one normal vertebra, cranial and caudal to the epidural block. A radiation dose of 28 Gy was given in fractions of 4 Gy on each of 7 consecutive days. The first dose of irradiation was given 1–20 h after myelography, usually within a few hours.

Clinical examinations were performed by the same neurologist before treatment, at the end of radiotherapy, 3 weeks and 3 months after treatment, and then at intervals of 3 months for 2 years or until death. We assessed treatment results according to gait function. A successful treatment result was defined as walking ability retained in ambulatory patients and walking ability regained in non-ambulatory patients. Intention-to-treat analysis was used for evaluation of efficacy. Pain relief was not an end-point because the intensity of pain was not recorded systematically. All patients who were randomised and fulfilled the inclusion and exclusion criteria were included in the comparison of the two treatment groups according to the randomisation, irrespectively of whether or not the dexamethasone therapy had been administered in agreement with the schedule.

Statistical evaluation of differences between treatment groups was performed on a Kaplan–Meier plot using Gehan's Wilcoxon test for comparing the survivorship function in the two groups. Subgroup analyses were made by contingency table analysis (χ^2 or Fisher's exact test). The level of significance was set at $P = 0.05$.

RESULTS

59 patients were randomised, although 2 patients were excluded after randomisation. Both patients belonged to the dexamethasone-treated group: 1 patient had meningeal carcinomatosis and 1 patient had a lymphoma as the primary malignancy. Hence, the study population comprised 57 patients, 18 men and 39 women with a median age of 62 years (range 25–82). The interval between diagnosis of cancer and development of spinal cord compression varied from 0 months to 17 years.

27 patients were randomised to treatment with dexamethasone and 30 patients to no treatment with dexamethasone. Table 1 lists sex and age, primary tumour, site of compression and motor

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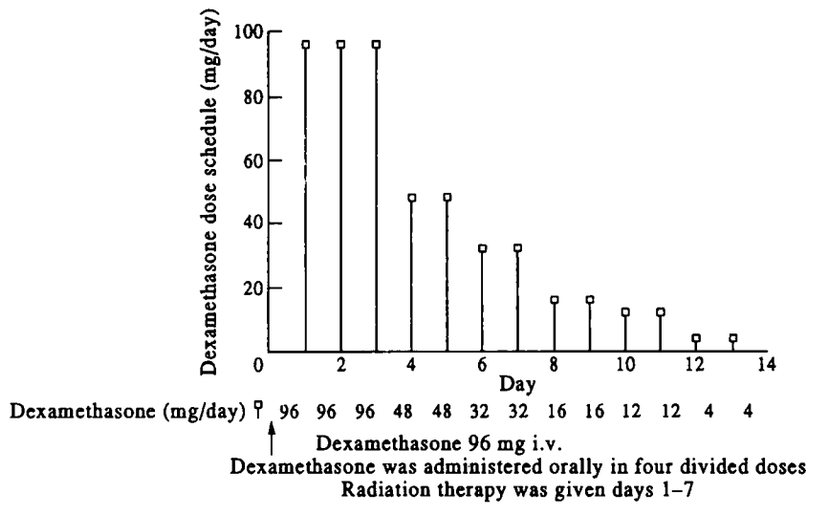

Fig. 1. Dexamethasone dose schedule for treatment of metastatic spinal cord compression. The arrow on day 0 denotes the initial intravenous bolus of 96 mg dexamethasone given 1–20 h before start of radiotherapy on day 1.

Table 1. Sex, age, location of primary tumour, site of epidural compression and pretreatment motor function by treatment group in 57 patients with spinal cord compression

	Dexamethasone treatment (27 patients)	No dexamethasone treatment (30 patients)	Statistical group comparison
Sex			
Males	6	12	N.S.
Females	21	18	
Age			
Median (years)	60	64	N.S.
Range (years)	25–81	41–82	
Primary tumour site			
Breast	18	16	N.S.
Gastrointestinal	3	3	
Prostate	1	4	
Lung	2	1	
Sarcoma	1	3	
Melanoma	1	1	
Kidney	1	0	
Mesothelioma	0	1	
Thyroid	0	1	
Site of compression			
Cervical	2	1	N.S.
Thoracic	17	16	
Lumbar	8	13	
Pretreatment motor function			
Ambulatory	17	19	N.S.
Paretic without gait	7	8	
Paraplegic	3	3	

N.S., no statistically significant difference.

function at the time of diagnosis in the two treatment groups. No statistically significant differences were found, although the number of patients with primary tumour located at other sites than the breast was higher in the group without dexamethasone therapy. Complete block on myelography was found in 30 patients: 14 patients in the dexamethasone group and 16 patients in the no dexamethasone group, while 27 patients had partial blockage of the subarachnoid space: 13 patients treated with dexamethasone and 14 patients receiving no dexamethasone.

Successful treatment, defined as preservation of gait in ambulatory patients or restoration of gait within 3 months in non-ambulatory patients, was obtained in 22 out of 27 patients (81%)

Table 2. Result of treatment of metastatic spinal cord compression by treatment group in 57 patients

	Dexamethasone therapy (27 patients)	No dexamethasone therapy (30 patients)
Successful treatment	22 patients (81%)	19 patients (63%)
Pretreatment ambulatory: remained ambulatory	17 patients	17 patients
Pretreatment paretic: regained gait function	4 patients	1 patient
Pretreatment paraplegic: regained gait function	1 patient	1 patient
Treatment failure	5 patients (19%)	11 patients (37%)
Pretreatment ambulatory: lost gait function	0 patients	2 patients
Pretreatment paretic: remained non-ambulatory	3 patients	7 patients
Pretreatment paraplegic: remained non-ambulatory	2 patient	2 patients

treated with dexamethasone compared to 19 out of 30 patients (63%) without dexamethasone treatment. All ambulatory patients treated with dexamethasone remained ambulatory, whereas 2 ambulatory patients in the group receiving no dexamethasone therapy lost gait function. In the dexamethasone group, 4 paretic patients (3 with breast cancer and 1 with sarcoma) and 1 paraplegic patient with cancer of the prostate regained gait function; in the no-dexamethasone group, 1 paretic patient with breast cancer and 1 paraplegic patient with cancer of the prostate regained gait function (Table 2).

Figure 2 shows a Kaplan–Meier plot of the percentage of patients who survived with gait function during 1 year (P = 0.046; Gehan's Wilcoxon test). At follow-up 6 months after treatment 16 patients (59%) who had been treated with dexamethasone were still ambulatory compared to 10 patients (33%) in the group who had not received dexamethasone therapy (χ^2 = 3.850; P = 0.05). One year after treatment for spinal cord compression, 8 patients (30%) in the dexamethasone group were alive and ambulatory compared to 6 patients (20%) in the no dexamethasone therapy group (χ^2 = 0.711; P = 0.40). The median survival was 6 months in both groups, and 3 patients in both groups were still alive at the end of the study (survival > 2 years after spinal cord compression).

Subgroup analyses were made in breast cancer patients because this group of patients was homogeneous and constituted more than half of the material. Patients with breast cancer had a more favorable prognosis (success rate 82%) than patients with other primary tumours (success rate 57%) ($P < 0.05$; Fisher's exact test). A successful treatment result was achieved in a higher percentage of the patients receiving dexamethasone (94%) than in patients without steroid therapy (69%) (Table 3), although the difference was not statistically significant ($0.05 < P < 0.10$; Fisher's exact test).

Analysis of the treatment result in relation to the site of compression in the spinal canal was performed in patients with breast cancer, of whom 1 had cervical, 21 had thoracic and 11 had lumbar epidural metastasis. All patients with lumbar epidural metastasis had gait function before and after treatment, and were hence successfully treated. In the group of 21 patients with thoracic spinal cord compression, 12 out of 13 patients (92%) on dexamethasone had gait function after treatment compared to 4 out of 8 patients (50%) without dexamethasone treatment (P = 0.05; Fisher's exact test).

1 patient who did not receive dexamethasone therapy underwent surgical decompression on the third day of radiation therapy because of progression of motor deficits to paraplegia. Significant side-effects of high-dose dexamethasone were reported in 3 patients. 1 patient became hypomanic, 1 had a manifest psychosis with confusion and blurred consciousness, and 1 experienced a perforated gastric ulcer requiring surgery. Dexamethasone therapy was discontinued in 3 patients. 2 patients stopped steroid treatment because of adverse experiences, psychosis and perforated peptic ulcers, respectively. In 1 patient treatment was stopped because of deterioration of the patient's condition, probably owing to systemic infection.

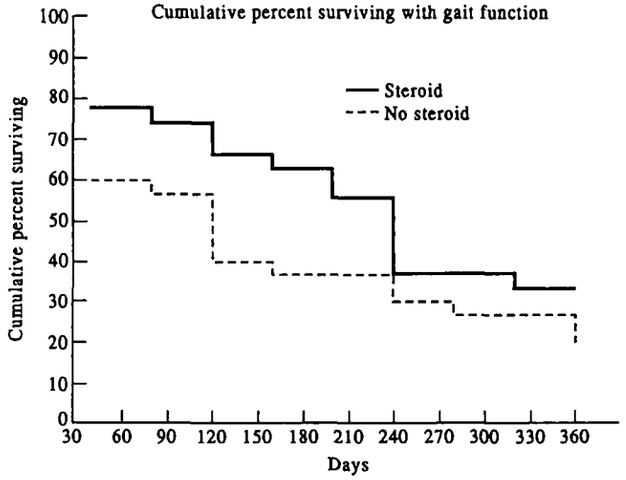

Fig. 2. Life table analysis of patients surviving with gait function in the dexamethasone group and no dexamethasone group (P = 0.046).

Table 3. Results of treatment of metastatic spinal cord compression by treatment group in 34 patients with breast cancer

	Dexamethasone therapy (18 patients)	No dexamethasone therapy (16 patients)
Successful treatment	17 patients (94%)	11 patients (69%)
Remained ambulatory	15 patients	10 patients
Regained gait function	2 patients	1 patient
Treatment failure	1 patient (6%)	5 patients (31%)
Remained non-ambulatory	1 patient	4 patients
Lost gait function	0 patient	1 patient

DISCUSSION

The present study supports the suggestion of a beneficial effect of high-dose glucocorticoid as adjunct therapy in patients treated with radiotherapy for metastatic spinal cord compression. Based on the percentage of patients who had gait function after treatment, a clear trend towards a more favourable outcome was seen in the group of patients treated with dexamethasone. This trend became a statistically significant difference at follow-up 6 months after treatment. The two treatment groups were comparable with respect to sex and age of the patients, the level of spinal cord compression, and, most importantly, the pretreatment motor function, which is the major determinant for gait function after treatment, irrespective of the treatment modality [5]. However, the group that did not receive dexamethasone therapy comprised more patients with primary tumours originating from sites other than the breast: 14 patients compared to 9 in the dexamethasone-treated group. Although the difference was not statistically significant, it could have influenced the treatment result because patients with breast cancer and spinal cord compression have a more favourable prognosis [5, 8]. However, in the group without dexamethasone treatment, 4 of the 14 patients with primary malignancy other than breast cancer had cancer of the prostate, which carries a similar prognosis [5]. Subgroup analysis of breast cancer patients with treatment groups comparable in any respect showed the same trend towards a more favourable prognosis in patients treated with dexamethasone. This applied, in particular, to patients with thoracic spinal cord compression which carries a more unfavourable prognosis for gait function compared to lumbar epidural metastasis [8].

The course of the cancer disease was not influenced by dexamethasone therapy since no difference in survival between the two treatment groups was observed.

Previous anecdotal reports have described benefits from lower doses of steroids in patients with metastatic spinal cord compression. Cantu [11] reported 2 patients with disseminated cancer, 1 from endometrial and 1 from ovarian carcinoma. Both had severe paraparesis from epidural metastasis, and improved significantly within 48 h after one injection of methylprednisolone 40 mg intravenously and 40 mg intramuscularly.

Clarke and Saunders [12] administered prednisolone 60–80 mg/day to two children of 15 and 16 years with severe weakness of the legs, erroneously diagnosed to be caused by Guillian–Barré syndrome. Both patients improved rapidly, but the symptoms recurred 7–11 weeks after cessation of steroid therapy. Myelography revealed an epidural spinal block. Surgical decompression was performed and disclosed intraspinal tumour growth. Histological examination of the removed tumour tissue showed reticulum cell sarcoma.

Posner *et al.* [13] treated 4 patients with metastatic spinal cord compression with dexamethasone 12–24 mg daily. In 2 patients with lymphoid tumours (lymphoma and thymoma), profound neurological improvement was reported associated with shrinkage or disappearance of the epidural block on repeated myelography. The 2 other patients, 1 with metastatic seminoma and 1 with Ewing's sarcoma, received concomitant chemotherapy, and in 1 case radiotherapy, making assessment of the effect of steroid more difficult.

In an experimental model of spinal cord compression, produced by injection of Walker 256 carcinoma cells anterior to the vertebral bodies in rats [14], Ushio *et al.* found that dexamethasone was effective in restoring neurological function. The improvement was significant within 48 h, but was transient lasting only up to 6 days. Dexamethasone was only effective if used before the animals became paraplegic. When dexamethasone was combined with radiotherapy the initial improvement was protracted [10].

Inspired by these results, Greenberg *et al.* [3] designed a protocol treating patients with metastatic spinal cord compression with an equivalent dose of dexamethasone (96 mg/day) as adjunct treatment to radiotherapy. After an intravenous bolus of 96 mg, the patients were treated with 96 mg of dexamethasone daily for 3 days followed by a 2-week tapering schedule very similar to that used in the present study. At the completion of therapy they were unable to demonstrate a better neurological outcome compared with a retrospective series of patients treated with conventional dexamethasone doses. However, the authors reported substantial pain relief in the majority of the patients often within hours after the first dose was given.

With only a few encouraging reports published, the clinical effects of steroids in epidural metastasis is much less well-documented than it is in brain metastasis. The main reason is that the diagnosis of spinal cord compression demands immediate treatment with either surgery or radiotherapy, which makes it impossible to evaluate the effect of steroids on neurological function. Hitherto, no randomised studies of steroids as adjunct to surgery or radiotherapy have been performed. Another important factor could be the different pathophysiology of oedema formation in brain metastasis and in epidural metastasis. In brain metastasis, the tumour oedema is produced by extravasation of plasma constituents leaking from tumour vessels without the blood–brain barrier into the brain parenchyma. Steroids are highly effective in resolution of peritumoral oedema in brain metastasis [15]. Epidural metastases lie outside the central nervous system, and the oedema, which appears to be of the vasogenic type [14, 16], may be produced by ischaemia caused by mechanical compression of the spinal cord, or by epidural venous compression [9]. Steroids might be less effective in the treatment of this type of oedema.

The mechanism by which steroids ameliorate neurological deficits in metastatic spinal cord compression is not fully elucidated. In their rat model, Ushio *et al.* demonstrated that the abnormally high spinal cord water content at the site of compression was decreased by dexamethasone [14]. The rapid resolution of clinical symptoms, and the transient benefit suggest that the mechanism of action of dexamethasone was a reduction in spinal cord oedema rather than shrinkage of the epidural metastasis [10]. In the same rat model cyclophosphamide and radiation therapy had a delay in effect of several days [10]. In contrast, Posner *et al.* [13] argued that a steroid may have an oncolytic effect because treatment with dexamethasone induced shrinkage or disappearance of epidural block on myelography. Interestingly, the majority of reports of long-lasting beneficial effect from steroids as the sole treatment for spinal cord compression have been in patients with lymphoma [12, 13], and in these patients the mechanism may have been steroid-induced tumour regression caused by the well-known lymphocytotoxic activity of glucocorticoid. The present study does not contribute to the clarification of the relative importance of anti-oedema effects and oncolytic effects of steroids in epidural metastasis because only patients with metastatic spinal cord compression from carcinomas were included, and all patients were given radiation therapy immediately after the diagnosis was made and dexamethasone administered.

The optimal dose of glucocorticoid for intraspinal metastasis in humans has not yet been established. We chose a high-dose

schedule based upon the results in animal experiments [10] and the recommendations of Gilbert *et al.* [2] and Greenberg *et al.* [3], who demonstrated a substantial effect on pain with this dose. Apart from the initial intravenous bolus, dexamethasone was given orally whenever possible because this route of administration is the most convenient to the patient, and no difference in efficacy between intravenous and oral administration has ever been documented in prolonged treatment with glucocorticoids. A lower dose may, however, prove equally effective. Vecht *et al.* [17] compared two doses of dexamethasone (10 or 100 mg) as initial intravenous bolus in 37 patients with metastatic spinal cord compression. The initial bolus was followed by a conventional dose of 16 mg dexamethasone orally daily. There were no differences between the conventional and high-dose bolus group on pain or ambulation.

High-dose steroid treatment is not without hazards. Hyperglycaemia, infections, gastritis, gastrointestinal ulceration or bleeding, proximal myopathy, peripheral oedema, weight gain and psychosis are commonly reported, and are often serious side-effects of glucocorticoid treatment [18]. The frequency of corticosteroid toxicity in patients with intracranial or intraspinal malignancy has been reported to be as high as 51% [19]. However, the side-effects are closely related to the duration of administration. When steroids are used for a period longer than 3 weeks, the occurrence of severe complications increases considerably [19, 20]. In one retrospective study, patients receiving dexamethasone for longer than 3 weeks had a toxicity incidence of 76% compared to 5% for treatment durations of less than 3 weeks [19]. In line with others [3, 7], we observed rather few serious side-effects from the use of a short course of high-dose dexamethasone in patients with metastatic spinal cord compression. The frequency of side-effects might be reduced by prophylactic treatment against gastrointestinal ulceration in all patients.

In conclusion, the present study suggests that high-dose glucocorticoids are a valuable supplement to radiotherapy in patients with spinal cord compression from epidural metastasis. From these results, as well as from other reports of glucocorticoid therapy for spinal cord compression, it seems that the treatment is beneficial: it induces rapid relief of pain and may lead to better neurological outcome, and can be given with acceptable side-effects in most patients. The optimal dose of glucocorticoids for treatment of epidural metastasis is not known, but encouraged by the present observations, we suggest that high-dose glucocorticoids should be given to all patients with epidural spinal cord compression.

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