A novel dynamic model for experimental spinal cord compression

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Object. The goal of this study was to develop a novel dynamic model for experimental spinal cord compression that closely approximates neoplastic epidural compression of the spinal cord in humans.

Methods. In 30 New Zealand white rabbits, the thoracic spine was exposed via a posterior approach. On each side of one vertebral lamina a small hole was drilled caudal to the articular process. A silicone band was passed through these holes, forming a loop. The spinal dura mater was exposed via an interlaminar approach. The loop was brought into contact with the dura mater and fixed in its position encircling 270° of the circumference of the spinal cord. Thereafter, the loop was gradually tightened at set times by pulling at the ends of the band and fixing them again in their new position. The spinal cord was thus increasingly compressed in a circular and dynamic manner.

Neurological deficits of various degrees were created in all animals in the compression group, and the compressive effect of the loop was reliably demonstrated on MR imaging. After decompression of the spinal cord, the neurological deficits were reversible in the majority of animals, and MR imaging revealed either no signal changes or only circumscribed ones within the cord. In contrast, MR images obtained in animals that did not recover revealed the occurrence of extensive chronic myelopathy.

Conclusions. This novel model features reproducibility of paresis and neurological recovery. It is a dynamic model simulating circular tumor growth and is characterized by its easy, straightforward, and cost-saving applicability.

KEY WORDS • spinal cord compression • epidural metastasis • spinal tumor • rabbit

The spine is the most common site for skeletal metastases. Despite increasing clinical awareness of this fact, loss of ambulation continues to occur in more than half of the affected patients, and because of improved survival of cancer patients, the incidence of metastatic spinal cord compression is expected to rise. This is of substantial importance for the individual patient and not only with respect to its impact on their private and social life in the event of persistent paresis. It is also of utmost importance to life expectancy; researchers in several clinical studies have demonstrated that an intact postoperative walking ability is an important factor for survival, and that patients with paraplegia have a significantly worse prognosis. Consequently, the most important benefit that may result from treatment of symptomatic spinal metastases is the restoration of gait function.

Nevertheless, even though results have improved during the last decade within the framework of a multidisciplinary treatment concept, there is still a considerable number of patients who do not benefit from therapy. To some extent these unfavorable results are caused by the fact that several fundamental questions about the pathophysiological features of subacute epidural compression of the spinal cord that may bear on the optimal therapy of this entity remain unanswered. In part, such deficiencies are due to the unavailability of a simple, reproducible animal model that would permit large-scale studies.

In this context, the purpose of this paper was to present a novel dynamic model for experimental spinal cord compression that closely approximates neoplastic epidural compression of the spinal cord in humans.

Materials and Methods

Experimental Animals

Thirty New Zealand white rabbits weighing a mean of 3 kg were used. Neurological examinations were performed daily and the animals were graded according to the following modified scale: Grade V, no motor deficits (rabbits able to run); Grade IV, mild weakness (rabbits able to walk but not to run); Grade III, moderate weakness (rabbits able to stand but not to walk); Grade II, marked weakness (movements of the limbs visible but rabbits not able to stand); Grade I, severe weakness (only slight movements of the limbs visible); and Grade 0, paraplegia. At the end of the study, functional outcome was classified as favorable or unfavorable.

Outcome was considered to be favorable in cases of primarily moderate, marked, or severe weakness if the animals, after decompression of the spinal cord, had recovered their walking ability (that is, if they had improved at least up to Grade IV). In cases of initial mild weakness, an improvement or preservation of this Grade IV outcome was also regarded as favorable. On the other hand, lack of improvement or further neurological deterioration without restora-
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tion of gait function, meaning a grade of III or worse, was considered to be an unfavorable result. During the entire study the animals were maintained in cages under normal conditions in the central research facility under the care and supervision of a veterinarian, according to the Institutional Animal Care and Use Guidelines.

Surgical Procedure

After induction of general anesthesia, a longitudinal incision was made on the animal’s back with the aid of an operating microscope, exposing the spine at the midthoracic level. On each side of one vertebral lamina, a small hole was drilled caudal to the articular processes. A silicone band was inserted top down through one hole, crossed over the midline, and passed through the second hole bottom up, resulting in formation of a loop. Performing an interlaminar approach, the spinal dura mater was exposed. By gently pulling at the ends of the band, the loop was brought into contact with the dura mater without exerting compression on the spinal cord. The ends of the silicone band then were passed through rubber tubes, and a hemoclip was attached to the band at the top of the tubes on each side (Fig. 1). Thus the loop was secured in its position encircling 270° of the circumference of the spinal cord. Postoperatively the rabbits were checked for absence of motor paresis, and then 22 animals were allocated to the compression group; eight animals served as controls.

After reexposure of the loop in the animals in the compression group, it was gradually tightened by gently pulling at the ends of the bands until a new hemoclip could be placed directly beneath the first clip, thus fixing the loop in its new position. This resulted in a slight compressive effect on the spinal cord similar to a tourniquet, because the cord now was compressed dorsally and laterally by the loop and anteriorly by the VB (Fig. 2). If the animal did not exhibit a neurological deficit after an observation period of 1 week, this surgical procedure was repeated, and again the loop was tightened by pulling at the ends and applying a new clip directly beneath the last one, leading to an increase of the compressive effect. If the animal continued to be neurologically intact, this process was repeated until the first motor paresis developed. In this way, a gradual, dynamic increase of circular compression of the spinal cord resulted.

Once neurological deficits had evolved, no further intensification of the compression was performed, and the following day, after obtaining MR images, decompression of the spinal cord was easily achieved by cutting one end of the band and removing the entire device. A repeated MR image was obtained 7 to 14 days after spinal decompression. To demonstrate that paresis was not due to the surgical procedure itself but was caused by the compression loop, the animals in the control group underwent repeated exposures of the loop, but without its being tightened. Additionally, these animals underwent MR imaging to demonstrate that the compression loop was in situ but not exerting a compressive effect on the spinal cord.

Protocol for MR Imaging

With the animals in a lateral position, MR imaging was performed with a 1.5-tesla field strength magnet (Gyrospec Intera T15; Siemens, Erlangen, Germany) by using a commercially available miniature coil (TMJ-coil). The following sequences were applied: for T1-weighted imaging, TR 400 msec and TE 11 msec; and for T2-weighted imaging, TR 3500 msec and TE 120 msec. For all T1- and T2-weighted images the field of view was 160/1.8 and the slice thickness was 2 mm. For analysis of the images, first the width of the spinal canal and the diameter of the spinal cord were measured in one animal in a noncompressed segment on a T2-weighted sagittal MR image. After that, the degree of narrowing of the spinal canal caused by the compression loop was determined. This was expressed as the percentage of constriction of the canal and was correlated both with the most severe degree of paresis before spinal decompression and functional outcome after decompression.

The images obtained after decompression were analyzed for signal changes within the spinal cord and were graded according to the following scale: 0, no change; 1, signal changes exclusively confined to the site of previous compression; and 2, signal changes extending the area of previous compression caudally and/or cephalad. After that the different grades of signal alterations were corre-

FIG. 1. Photograph showing fixation of the compression loop with rubber tubes and hemoclips. The loop has contact with the spinal dura but without exerting compression.

FIG. 2. Drawing of experimental setup. The loop encircles 270° of the circumference of the spinal cord. Gently pulling at the ends of the bands until a new hemoclip can be placed directly beneath the first clip results in a compressive effect on the spinal cord, which is compressed posteriorly and laterally by the loop and anteriorly by the VB.
Results

Neurological Findings

The entire experimental schedule was completed in all 30 animals. Each rabbit was neurologically normal after initial placement of the compression loop. Paraparesis could be provoked in every animal in the compression group and was observable between several hours after cessation of anesthesia and 3 days postsurgery. To achieve paraparesis, two to seven subsequent surgical procedures with concomitant tightening of the loop were necessary. As mentioned, no further intensification of compression was performed once the neurological deficits had evolved. Notwithstanding, a spontaneous increase in the degree of paresis was observed in eight animals. All animals with severe weakness (Grade I) showed overflow incontinence, whereas in all other animals sphincter function remained intact. The most severe degrees of paresis before spinal decompression are outlined in Table 1, and include eight animals with a grade of V. These are the rabbits in the control group, in which the loop was exposed seven to 10 times but without being tightened. These animals were neurologically intact throughout the whole study. Table 1 also illustrates the effect of decompression on functional outcome, which was favorable in 17 animals and unfavorable in five. All rabbits that initially had only mild paresis remained ambulatory after decompression, and in nine (64%) of 14 previously nonambulatory animals the ability to walk was regained. Seven of these animals initially had severe paraparesis (Grades I and II). In five other rabbits that had paresis classified as Grade I or II, restoration of gait function was not observed.

Results of MR Imaging

 Whereas the diameter of the spinal cord in a noncompressed segment was 2.5 mm in each animal, the normal width of the spinal canal showed some variation, ranging from 4 to 4.5 mm. The MR images obtained in control animals revealed that the compression loop was in place but was not exerting pressure on the spinal cord (Fig. 3). In contrast, the images obtained in the compression group demonstrated a narrowing of the spinal canal of 11 to 66% due to the compressive effect of the loop, which was best visualized on sagittal T2-weighted images. The number of times that the animals underwent loop tightening and the respective extent of spinal constriction, however, were not correlated with either the degree of paresis before decompression (r = 0.270; p = 0.295) or with functional outcome after decompression (r = 0.198; p = 0.309). Figure 4 consists of representative MR images obtained in three animals with different degrees of spinal cord compression.

The signal alterations within the spinal cord seen on the MR images obtained after decompression were not correlated with the degree of narrowing of the spinal canal (r = −0.082; p = 0.771) but were positively correlated with functional outcome. Only those animals with favorable outcomes had signal changes of Grade 0 or 1, whereas none of the animals with Grade 1 alterations showed complete recovery, retaining mild residual deficits and being classified as Grade IV according to the modified paresis scale. In contrast, all animals with unfavorable outcome invariably showed signal changes of Grade II. These different findings for both outcome groups were significant (p < 0.0001). In Fig. 5, representative MR images obtained in three animals with different signal changes after spinal decompression are presented.

Discussion

Animal Model

Different animal models have been used to produce subacute compression of the spinal cord. One method is the implantation of tumor cell suspensions into the dorsal epidural space, which results in tumor growth and subsequent spinal cord compression. \[^{10,11,13,23}\] In applying this model, however, it appears disadvantageous that it involves an intricate cytobiological effort. Also, compression does not seem to be reproducible in every animal in an equal measure, because the compressive effect on the spinal cord largely relies on growth rates of the tumor cells (that is, factors that are hard to control in this experimental set up). The same disadvantage applies to a model in which an expand-

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**TABLE 1**

Degrees of paresis before spinal decompression and effect of operation on functional outcome in 30 New Zealand white rabbits

<table>
<thead>
<tr>
<th>Status</th>
<th>Grade (no. of rabbits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>before decompression</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>after decompression</td>
<td>0 1 2 3 4 5</td>
</tr>
</tbody>
</table>

* Control group.

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**FIG. 3.** Postoperative sagittal T1-weighted (A) and T2-weighted (B) and axial T2-weighted (C) MR images obtained in an animal from the control group. The compression loop (arrows) is in place without exerting pressure on the spinal cord. The dorsal artifacts (asterisks) are caused by the rubber tubes fixing the loop.
ing epidural mass (methyl cellulose–polyacrylonitrile compound) is used.2 Another model, in which inflatable balloons are placed into the epidural space,4,7,16 likewise features a few drawbacks. First of all, by itself placement and inflation of a balloon will require a considerable intraspinal volume. To some extent this always entails an acute compression of the spinal cord, which may result in acute paraplegia. Beyond the eventual inevitable relative deflation, the potential risk of sideways shifting of the balloon may cause the desired compression of the cord to be at least partially attenuated. Thus, the expectation of reliable reproducibility of a specific amount of compression does not seem to be warranted. This, however, can be achieved with a method in which Teflon devices are implanted anteriorly and posteriorly.1,5 In terms of its compressive effect on the spinal cord, though, this model is static. In contrast, in humans the effect of spinal metastases on the cord is dynamic; further growth of the tumor will increase the medullary compression. The aforementioned models, however, do not allow for this dynamic (as with the Teflon device) or do so only on a limited scale (for example, cell suspensions, expanding epidural mass, balloons).

In this regard, the novel model presented here is suited to imitate this dynamic reliably, in that stepwise tightening of the compression loop results in a gradual intensification of the compressive effect on the spinal cord. Because the loop is tightened each time in an equal manner by pulling at its end until a new clip can be placed directly beneath the other one, this method permits a uniform and reproducible compression of the spinal cord in each animal. Additionally, the commonly circular growth of metastases is simulated, insofar as the compression loop encircles 270° of the circumference of the spinal cord, so that the cord is compressed posteriorly and laterally by the loop and anteriorly by the VB. A decrease in the compressive effect caused by slipping of the band is averted by fixing it with rubber tubes and hemoclips. An acute compression of the spinal cord is definitely prevented because in the initial procedure the loop is tightened only until it is brought into contact with the dura mater, but without exerting any compression. Finally, this novel model is characterized by its easy, straightforward, and cost-saving applicability.

The application of compression screws is a well-established model for chronic spinal cord compression.9,20,21 One or more screws placed through VBs of the cervical spine are used and are gradually turned, resulting in an increasing constriction of the spinal canal. In this way a dynamic of the compressive effect is achieved as well. Applying this model, it is advantageous in that compression of the spinal cord is definitely reproducible. Besides, the extent of mobility of the animals is not affected by the implants, allowing for observations over a long period of time, normally months. In principle this is also possible with our novel model, because the animals are not bothered by the compression loop either. Additionally, our model has the advantage that compression of the cord can be produced at any site in the spine, whereas the implantation of compression screws is reserved for the cervical section.

Other models for subacute and/or chronic spinal cord compression will be mentioned here in brief. One model has been described that uses the implantation of bone morphogenetic protein on the ligamentum flavum, resulting in spinal cord lesions.19 In another model of cervical myelopathy, press injections of saline into the space between C-5 and C-6 are made, inducing formation of osteophytes 4 months after the injection.25 Finally, the tiptoe-walking Yoshimura mouse is used as a model of chronic spinal cord compression caused by a genetically induced ossification of intraspinal ligaments.24 With regard to these models it is questionable, however, whether a reproducible compressive effect on the spinal cord may be produced with certainty in each animal.

**Neurological Findings**

In this experimental study, the effects of decompression on functional outcome are concordant with the results of numerous clinical (both surgical and radiooncological)
series, demonstrating that pretreatment ambulatory function is one of the main determinants for posttreatment gait function. These series show, on the one hand, that patients who are ambulatory before initiation of therapy mostly keep their walking ability. Reported rates of favorable results range between 75 and 100%, findings that are in accordance with the results of our experimental study; all animals initially exhibiting mild Grade IV paresis remained ambulatory after decompression. On the other hand, it is obvious that the more severe the initial palsy the less probable the recovery. Reported recovery of gait function in patients suffering from spinal metastasis who were not able to walk before treatment ranges from 16.5 to 83%. Similar results were reproduced using our animal model; two thirds of previously nonambulatory rabbits regained their gait function, whereas one third did not. These congruent findings demonstrate that our novel model closely approximates the neurological results found in neoplastic epidural compression of the spinal cord in humans.

Role of MR Imaging

The compressive effect of the loop on the spinal cord is unequivocally presented using MR imaging. Whereas the images obtained in the control group demonstrated the compression loop in situ with no pressure being exerted on the cord, the images obtained in the animals in the compression group revealed that different degrees of narrowing of the spinal canal may be produced in this experimental setup. These findings and the fact that the constriction of the spinal canal is fashioned in a dynamic manner again underline the potential of this novel animal model to imitate metastatic epidural tumor growth that would result in varying extents of spinal cord compression.

At the same time it is noteworthy that the extent of spinal cord compression (reflecting the number of surgical procedures necessary to provoke paraparesis) was not correlated either with the degree of paresis before decompression nor with functional outcome. Simultaneously, it was not correlated with the occurrence of signal alterations within the spinal cord after decompression either. This, however, means that the extent of spinal cord compression in itself, as demonstrated on MR imaging, apparently has no prognostic significance.

This seems to be of particular interest because it became obvious, on the other hand, that functional outcome depended exclusively on the signal changes observed within the spinal cord after removal of the loop. After decompression of the spinal cord, the neurological deficits were reversible in the majority of animals, even in those with marked or severe paresis, and the corresponding MR images showed either no signal changes or alterations of Grade 1. In animals that did not recover, however, subsequent MR imaging revealed occurrence of Grade 2 changes in terms of a severe myelopathy. These changes were interpreted as the expression of an ongoing pathophysiological process leading to secondary damage of the spinal cord, thus hindering recovery of neurological function, which was analogous to the perceptions in acute spinal cord injuries. The clarification of the pathophysiological aspects of these phenomena, which apparently occur in subacute epidural compression of the spinal cord as well, might have a bearing on the optimal therapy of this entity. In this regard, our novel animal model might provide a reliable experimental basis for further research.

Conclusions

This novel model features reproducibility of paresis and
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neurological recovery. It is a dynamic model of subacute epidural compression simulating circular tumor growth, but is also convenient for the study of many disease states. It is characterized by its easy, straightforward, and cost-saving applicability. Beyond that, because the rate and degree of compression can be chosen arbitrarily, it can be used for acute, subacute, and chronic spinal cord compression in equal measure.

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References


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