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# Mucous Membrane Manifestations of Pemphigus Vulgaris

## *A 25-year Survey of 185 Patients Treated with Corticosteroids or with Combination of Corticosteroids with Methotrexate or Heparin*

NIKOLAI MASHKILLEYSON[1] and ASAF L. MASHKILLEYSON[2]

[1]*Department of Dermatology, University Central Hospital, Helsinki, Finland, and* [2]*Department of Dermatology, Medical Stomatological Institute, Moscow, USSR*

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One hundred and eighty-five patients with pemphigus vulgaris were treated and followed up over a period of 25 years, from 1962 to 1987, at the Department of Dermatology of Moscow Medical Stomatological Institute. In all these patients the diagnosis was confirmed clinically, histologically and cytologically, and in 152 patients by means of direct and indirect immunofluorescence. The patients were treated with corticosteroids or with a combination of corticosteroids with methotrexate or heparin. The initial manifestations of the disease and their development at the period before the treatment and during therapy were studied. The optimum regimens of the maintenance treatment were investigated including those in 31 patients whom the treatment could be discontinued. The treatment-related complications and 28 cases with fatal outcome are analysed. *Key words: Pemphigus vulgaris; Mucous membrane lesions; Complications of treatment; Mortality.* (Received January 15. 1988.)

N. Mashkilleyson, Department of Dermatology, Helsinki University Central Hospital, Snellmaninkatu 14, SF-00170 Helsinki 17, Finland.

The term pemphigus refers to a group of autoimmune bullous diseases characterized by acantholysis leading to intraepidermal blistering and the presence of IgG antibodies directed against the intercellular cement substance of differentiating keratinocytes. Direct immunofluorescence demonstrates these antibodies bound to the diseased epithelium. Circulating antibodies which bind to epidermal antigens (pemphigus antibodies) may be demonstrated by indirect immunofluorescence in the sera of nearly all patients with pemphigus during the course of the disease, and antibody titre generally correlates with the severity of the disease (1, 2).

Pemphigus vulgaris (PV), the commonest form, accounting for 80% of pemphigus (3), is a potentially lethal disease in which the blister occurs just above the basal cell layer. The usual medications for pemphigus treatment are corticosteroids and immunosuppressive drugs. Despite their dramatic effect in a once almost inevitably fatal disease, the mortality still remains high. Complications of therapy frequently result in severe morbidity or death (3–6). Several studies have been devoted to the epidemiologic and survival aspects of the disease with different methods and regimens of treatment (3, 7–14). In the paper 185 patients with PV, treated at the Department of Dermatology of Moscow Medical Stomatological Institute between 1962 and 1987, are reviewed.

## PATIENTS, DIAGNOSIS AND CLINICAL MANIFESTATIONS OF PEMPHIGUS

### *Patients*

During the last 25 years, from 1962 to 1987, 185 patients with PV have been treated and followed up at the Department of Dermatology of Moscow Medical Stomatological Institute. Seventy-three patients

(39.5%) were males and 112 (60.5%) were females. At the onset of the disease the ages of the patients varied between 26 and 75 (mean 56.1) years.

*Diagnosis*

The diagnosis of PV in all the patients was confirmed clinically, histologically and cytologically (Tzanck's cells in smears). Immunofluorescence methods became available in 1974, and thereafter 152 patients were examined by means of direct and indirect immunofluorescence. Circulating antibodies of IgG type bound to the intercellular cement substance of the lower part of epidermis were detectable in the active period of the disease in all of them. The highest titres of these antibodies in individual patients varied between 1:320 and 1:640, and usually correlated with the severity of PV. However, in 6 of 15 patients 70 years of age and older, circulating antibody titres remained low (1:10 – 1:20).

*Clinical manifestations*

157 (84.9%) patients had the initial lesions on the mucous membranes, and in 28 (15.1%) patients the disease started from the skin. In patients with the initial skin involvement, the eruptions were often found in the navel area, the chest, vermilion border of lower lip, and back. Most often the first signs of PV occurred on the oral mucous membrane (69.7%), laryngeal mucous membrane (10.8%), or rarely on the anterior part of nasal septum (4.3%). Just before the beginning of the treatment in 115 (62.2%) patients both the skin and mucous membranes were affected, 64 (34.6%) patients had the eruption only on the mucous membranes, and 6 (3.2%) patients had only skin lesions. The general condition of 83 (44.9%) patients was deemed to be severe, due to widespread skin and mucous membrane lesions; the condition of 95 (51.3%) patients was satisfactory, and in 7 (3.8%) patients it was good.

In 20 of 157 PV patients with the initial mucous membrane involvement the first symptom of the disease manifested as hoarseness, and all these 20 patients were diagnosed during the initial period of the disease as having acute or chronic laryngitis. The correct diagnosis was established only after the appearance of typical pemphigus lesions on the oral mucosa or on the skin.

Laryngeal lesions occurred in 82 of 179 patients with the mucous membrane eruptions (45.8%). In 22 patients the laryngeal eruptions were unilateral but more often both sides of the larynx were affected symmetrically. The epiglottis was the most usual site of the pemphigus erosions within the laryngeal area (61 patients). At laryngoscopy the free edge of epiglottis seemed thickened and the erosions merged into widespread denuded surface. Quite often the epiglottis was entirely covered with erosions. In 4 patients the erosions expanded to the anterior part of the true vocal cord. In further 78 patients the true vocal cord was free of lesions. In 15 patients the erosions also occurred on the mucous membrane of the cricoideal cartilage, enlarging in 5 of them the area of the crico-epiglottic folds. The oropharyngeal and laryngeal eruptions often caused pronounced dysphagia, sometimes so violent that patients even refused to take liquid food. After the erosions had healed under steroid treatment the newly formed epithelium was greyish-white, resembling initial lesions of leukoplakia or lichen planus. After the epithelization of the erosions in the epiglottic area, the epiglottis stayed for a time thickened and deformed.

Erosions on the nasal mucosa, mostly on the cartilaginous part of the nasal septum, occurred in 34 patients. In 11 patients the erosions expanded onto the mucous membrane of the floor of the nasal cavity. The erosions on the nasal septum were flesh-red, often covered with purulent discharge, drying into crusts. After the epithelization of erosions the nasal septum became thin, whitish and rough with the further splitting and crusting.

## TREATMENT AND ITS RESULTS

Corticosteroid therapy was, as a rule, started with a high daily dose which was varied according to the severity of the disease, from 60 to 200 mg, calculated as prednisolone. Only in 10 patients with isolated lesions on the oral mucosa was the treatment started with 40 mg a day. However, in 5 of these 10 patients the steroid dose was increased soon after because of the exacerbation of the disease. We began to taper the corticosteroid dose after complete or nearly complete disappearance of lesions, on average 20–25 days after the treatment was instituted. If a therapeutic effect was not achieved within the first 5–7 days of treatment, the daily dose of corticosteroid was increased by 50–100%.

In the combination therapy with corticosteroids and methotrexate, 25–50 mg of the latter was administered orally or parenterally once a week, or in 5-day courses of 5 mg a day

with 3-day breaks. The dose of corticosteroid varied in such a schedule from 60 to 100 mg a day, calculated as prednisolone. After a clinical remission or a considerable improvement of the disease was achieved, the dose of methotrexate was diminished by 5–10 mg a week.

Heparin treatment (15) consisted of the administration of 10000 IU intramuscularly every 12 h to a total of 15 to 40 injections. The main parameters of the blood coagulation system were screened during the entire treatment. The drug was used either before the beginning of the steroid treatment or in combination with it.

After a complete or nearly complete remission was achieved and the daily dose of corticosteroid was reduced to 30–40 mg the patients were discharged from hospital to follow-up controls which took place first once every 2–4 weeks and then once at 2–3–6 months. The results of the treatment are presented in Table I.

Eighty-six patients (46.5%) were treated only with corticosteroids (prednisolone, dexamethasone, triamcinolone). In all these patients the adequate corticosteroid dose induced a complete or nearly complete disappearance of PV lesions. However, a rapid reduction of the maintenance daily dose resulted in exacerbation in 34 patients. The management of such exacerbations required in 22 of these 34 patients the re-administration of corticosteroid doses which exceeded the initial ones.

In 16 patients the relapses of the disease were provoked by psychic stress or intercurrent diseases. However, if at the beginning of the exacerbation the dose of corticosteroid was immediately increased by 10–30 mg, it often arrested the further aggravation (13 patients).

The combination treatment of 53 patients (28.6%) with corticosteroids and methotrexate was effective in 42 of them. In 6 patients the treatment was not effective, and in 3 patients the addition of the cytostatic drug to the corticosteroid treatment could not prevent a further exacerbation of the disease. Methotrexate treatment of 2 patients was discontinued because of drug-induced side effects. In another 6 patients the side effects were slight and methotrexate was started again after a short break in the treatment. Clinical improvement was usually observed within 2–3 days of methotrexate administration. A clinical remission of PV was obtained in 31 of 42 patients after the drug had been administered 2–4 times. In 34 patients methotrexate was administered during the remission period to reduce the high maintenance dose of steroids (30–45 mg calculated as prednisolone). It succeeded in 33 of them. In a 30-year-old woman with a remission of 3 years' duration but with a pronounced Cushing's syndrome, methotrexate administration resulted in a severe aggravation of the disease within 5 days.

Table I. *The results of treatment of 185 patients with PV*

| | The results of treatment | | | | | |
|---|---|---|---|---|---|---|
| | | | | Died during the treatment | | |
| No. of patients | Treatment discontinued because of complete remission | Complete remission maintained by treatment | Occasional lesions appearing or persisting despite maintenance treatment | In the period of remission | In the period of exacerbation, receiving high doses of steroids | Severe aggravation of the disease as a result of rapid decrease of steroid dose (The management of exacerbation required corticosteroids in the doses higher than the initial) |
| 185 (100%) | 31[a] (16.8%) | 112 (60.5%) | 18 (9.7%) | 17 (9.2%) | 7 (3.8%) | 34 (22) |

[a] Four patients in this group died during the follow-up period of causes not related to pemphigus.

The hepatic and renal functions were checked in all the patients before and during methotrexate treatment. There were no significant disturbances in liver enzymes and creatinine levels screened after every 3 months of treatment. Liver biopsies checked before the treatment and after every 1.5 g of cumulative methotrexate dosage did not reveal any pathological changes.

Heparin was used in 46 patients with PV (24.9%). In 18 of them it was administered before commencing steroid treatment, and in further 28 patients it was added to the already started but not sufficiently effective corticosteroid therapy. Complete epithelization of all the erosions was registered in 4 of 18 patients in whom the treatment was started with heparin. The remission of the disease in these 4 patients lasted for 2–6 months without any treatment and was finally followed by the appearance of some isolated lesions. However, in all of them a subsequent recurrence of pemphigus was controlled by the new series of heparin injections in combination with low doses of corticosteroids (20–30 mg of prednisolone per day). The patients went into stable remission and the daily steroid dose was reduced to 5–10 mg of prednisolone. A considerable improvement with a partial healing of the erosions after heparin treatment was noted in 9 patients. In 4 patients the condition remained unchanged but new lesions did not appear. In one patient with widespread erosions on the oral and laryngeal mucous membranes, further exacerbation occurred during heparin treatment and heparin injections were stopped.

In 18 of 28 cases in which heparin was started during corticosteroid treatment (without an increase of steroid dose), complete disappearance of lesions was registered. In a further 10 patients the therapy with heparin induced a considerable improvement, with the epithelization of most of the erosions.

Seventeen of 147 patients who went into clinical remission maintained by the minimal doses of corticosteroids with or without methotrexate died during the peroid of the follow-up study of different causes not related to PV. The further 130 patients (Table II) have been treated for periods varying between 1 and 25 years. The detailed data about the duration of the maintenance therapy, the drugs used and their doses are presented in the table. Complete remission lasting for at least 6 months and for as long as 20 years was registered in 112 patients. In a further 18 patients, occasional erosions have been appearing from time to time, mostly on the oral mucosa. Such erosions have healed within 2–4 weeks without any increase in the daily dose of steroid or methotrexate.

*Cases in which treatment could be discontinued*

In 31 (16.8%) patients it was possible to discontinue the therapy after some years. Before the therapy was withdrawn the patients had been treated for at least 1 year and up to 22 years (mean 7.3 years). The remission of PV without any maintenance treatment has lasted in these patients for 2 and up to 25 years (mean 10.6 years). In all these 31 patients the treatment had been started with high steroid doses. Exacerbations of the disease during the initial treatment period occurred in 11 of them. Later, however, the maintenance doses of corticosteroids were tapered off until complete discontinuance. After the treatment had been withdrawn, recurrence of PV was registered in 4 of 31 patients: in 2 patients after 2 and 4 years, and in 2 others after 8 and 10 years. The recurrence of the disease in these patients was managed by high doses of steroids, and a clinical remission was achieved within 1–3 months. The treatment was again discontinued and all these 4 patients have remained free of lesions for a period of 6 months and up to 2 years.

In 9 of these 31 patients the course of the disease was characterized by frequent exacerbations with widespread lesions during the first years. Management of the disease in these cases required maintenance doses of 25–35 mg of prednisolone per day. After about 3–4 years the course of PV turned to more peaceful, the exacerbations became less

frequent and were characterized by the appearance of only occasional lesions which were easily controlled by a slight increase in the steroid dose. Some years later the relapses ceased, and the maintenance dose of steroids was reduced to a minimum, and finally the treatment was discontinued.

## COMPLICATIONS OF TREATMENT AND DEATHS

Various complications were recorded in PV cases as result of corticosteroid and methotrexate treatment (Table III). The Cushing's syndrome manifestations were observed in the majority of patients during the long-term corticosteroid therapy. Small tense hemorrhagic blisters with a thick roof were found on the oral mucosa in 38 steroid-treated patients, especially in the buccal and palatal areas. They usually appeared on the sites of maximal traumatization by hard food, teeth, etc. The blisters were situated under the epithelium and regressed spontaneously within some hours. The subsequent erosions which sometimes occurred on the sites of such blisters healed very quickly too. There were no Tzanck's cells in smears taken from the surface of these erosions. Such a complication of corticosteroid treatment may be a variety of the so-called bullous–vascular syndrome (16).

Among the unusual complications which arose during the treatment were renal colic in 4 patients as a result of a dysbalance of the electrolyte and water metabolism. Vincent's angina (necrotizing ulcerative gingivitis) was registered in one patient during long-term methotrexate treatment. Four other patients treated with methotrexate experienced a recurrent herpes on the oral mucosa.

Table II. *The maintenance doses of corticosteroids (calculated as prednisolone) and the duration of the maintenance treatment in 130 PV patients*[a]

| Maintenance daily dose of corticosteroid (+methotrexate/week) | No. of patients | Duration of the maintenance treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Under 3 years | 3–5 years | 6–10 years | 11–15 years | 16–20 years | 21–25 years |
| 30 mg | 2 | 1 | 1 | | | | |
| 25 mg | 2 | 1 | 1 | | | | |
| 20 mg | 2 | 1 | | 1 | | | |
| 20 mg + 5 mg methotrexate | 2 | 1 | | | 1 | | |
| 17.5 mg | 1 | 1 | | | | | |
| 15 mg | 5 | 2 | 1 | 1 | 1 | | |
| 15 mg + 5 mg methotrexate | 3 | | 1 | 1 | 1 | | |
| 12.5 mg | 7 | 2 | 2 | 2 | 1 | | |
| 12.5 mg + 5 mg methotrexate | 6 | | | 2 | 2 | 2 | |
| 10 mg | 33 | 7 | 6 | 5 | 12 | 3 | |
| 10 mg + 5 mg methotrexate | 7 | 3 | 1 | 2 | 1 | | |
| 7.5 mg | 15 | 3 | 5 | 2 | 4 | | 1 |
| 7.5 mg + 5 mg methotrexate | 6 | 1 | 1 | 3 | 1 | | |
| 5 mg | 21 | | 3 | 9 | 5 | 3 | 1 |
| 5 mg + 5 mg methotrexate | 6 | | | 5 | 1 | | |
| 5 mg every second day | 9 | | 1 | | 4 | 3 | 1 |
| 5 mg every second day + 5 mg methotrexate | 3 | | | 2 | | 1 | |
| Total | 130 | 23 | 23 | 35 | 34 | 12 | 3 |

[a] The patients who died during the period of the study are excluded.

The complications of methotrexate treatment were more often detected in patients with the developed steroid syndrome. Methotrexate's side effects (Table III) were relatively mild and tended to regress within 5–20 days under high doses of folic acid in combination with symptomatic remedies. The treatment with methotrexate was usually re-started in 2–4 weeks after the complications were eliminated.

Twenty-eight (15.1%) of 185 patients died during the 25-year follow-up period. Four patients whose treatment had been discontinued because of a complete remission died 3–22 years after the therapy was stopped, of causes not related to PV. They had been treated with corticosteroids for 7–20 years before the therapy was discontinued. They died at the age of 69–79 years: of stomach cancer (2 patients), myocardial infarction (one patient), intracerebral hemorrhage (one patient).

Three patients, 46, 49 and 58 years of age, died of PV after 8, 4 and 13 years of treatment. One of them stopped the treatment himself, 2 others themselves reduced the maintenance dose of corticosteroid. Recurrence of the disease took place in these patients in 1, 3 and 4 weeks, and within several days the lesions became widespread. Despite treatment with a high dose of corticosteroids these 3 patients died within 2–6 weeks after the treatment was re-instituted.

A severe exacerbation of PV developed also in 4 other patients who had been treated for 5, 11, 12 and 15 years and who also themselves reduced the maintenance dose of steroid. Corticosteroids were re-administered in a high dose and the treatment seemed to be

Table III. *The complications of the corticosteroid and methotrexate treatment registered during the long-term follow-up of 185 patients with PV*

| Complications | Corticosteroids (no. of patients) | Methotrexate (no. of patients) |
|---|---|---|
| "Moon" facies | 170 | |
| Hirsutism | 38 | |
| Hypertension | 46 | |
| Glucose intolerance | 18 | |
| Osteoporosis | 43 | |
| with consequent fractures | 5 | |
| Atrophy of skin on extremities | 134 | |
| Severe bruising | 117 | |
| Hemorrhagic blisters on oral mucosa | 38 | |
| Myocardial infarction | 9 | |
| Intracerebral hemorrhage | 5 | |
| Acute gastric ulcer with perforation | 3 | |
| Exacerbation of chronic gastric ulcer | 8 | 3 |
| Steroid acne | 114 | |
| Acute psychosis | 3 | |
| Insomnia | 4 | |
| Renal colic | 4 | |
| Edema of the feet | 11 | |
| Dysmenorrhea | 6 | |
| Pneumonia | 6 | 8 |
| Pyodermia | 7 | 4 |
| Moniliasis | 4 | 2 |
| Disseminated rubromycosis | 8 | |
| Exacerbation of pulmonary tuberculosis | 1 | 2 |
| Tuberculosis of larynx | 2 | 1 |
| Necrotizing gingivitis (Vincent's angina) | | 1 |
| Recurrent herpetic lesions | | 4 |

effective. However, the patients died of acute perforating gastric ulcer within 3–5 weeks after the therapy with high steroid dose was started.

Seventeen patients, 8 males and 9 females, died during the period of PV remission maintained by treatment for 4–25 years. Eleven of them were treated with corticosteroids only, and 6 other patients with the combination of corticosteroids and methotrexate. Two patients died of malignant neoplasms of stomach and rectum; 2 elderly patients died of perforation of the gastric ulcer after 11 and 25 years of treatment; 2 patients died of myocardial infarction; 4 patients, 74, 76, 78 and 79 years of age, died of acute cardiac arrest; 4 other patients died of pneumonia; 3 patients died in accidents.

## DISCUSSION

PV is a rare autoimmune bullous disease, with the skin and mucous membrane involvement. According to various sources it starts from the oral cavity in 60–66% of cases (3, 4, 10) which corresponds roughly to the data of the present study (69.7%). During the course of the disease the oral lesions develop in about 80–90% of patients (3, 4), which is close to the 96.8% in this study at the Stomatological Institute. Buccal mucosa, palate and gingivae are the predilection sites of PV lesions within the oral cavity (17, 18). Macroglossia as an unusual presentation of PV within the oral cavity has also been reported (19). The oral lesions can be very painful and because of repeated traumatization tend to persist even after successful management of the skin lesions (18, 20). Painful oropharyngeal involvement often accounts for associated dysphagia and weight loss (18). The correct diagnosis of PV in oral mucosa in the absence of the typical skin lesions may be difficult. The average delay of 6.8 months between the oral onset of PV and the establishment of the correct diagnosis has been reported (18). Mucous membrane involvement other than oral may occur in pharynx (3, 4, 10, 21), larynx (3, 4, 21), conjunctiva (3, 22), cervix uteri (23–25), rectal mucosa (26). Recently, the cases of PV with esophageal involvement were reviewed (27).

The typical manifestations of PV on the mucous membranes are erosions, since, in such a localization, the blister roof is so thin that it ruptures on minimal trauma. The erosions on the oral mucosa do not bleed spontaneously and are not covered with fibrinous shield. The lesions in the mouth are usually found at the traumatization sites: at the junction of the hard and soft palate, on the soft palate, on the edges and lower surfaces of the tongue, on the floor of the mouth, and on the gingivae. The erosions on the tongue, at the mouth corners, and in the retromolar area sometimes cause a trismus. Severe tongue damage causes a white-greyish, slightly hypertrophic and folded surface. In the bottom of such folds, painful fissures appear. Nikolsky's sign in this condition is negative, however. *Candida albicans* is often found on the lingual surface in such cases. Patients with the initial manifestations of the disease on the oral mucosa often turn to dentists, who should keep pemphigus in mind when examining patients with oral mucous membrane lesions.

The analysis of the results of PV treatment showed that mucous membrane lesions, especially those on the laryngeal mucosa, were more resistant to treatment than the skin eruptions, as has been reported by Meurer el al. (20). Thus, in 18 of 82 patients with laryngeal erosions, a relative resistance of lesions to corticosteroids, or to corticosteroids combined with methotrexate, was registered. This may probably be explained by the scarcity of submucous tissue between epithelium and cartilage, as well as by the constant traumatization of the mucous membranes, especially that of the epiglottis.

To avoid side effects it is of no use to treat the patients with persistent occasional lesions on the oral or laryngeal mucosa with high doses of corticosteroids for long periods of time. In such cases the addition of heparin seems to produce a good clinical effect. In patients

who are on maintenance therapy, with persistent resistant lesions on the vermilion border or on the skin in the nasal area, good results could be obtained by means of cryotherapy without any increase in steroid dose.

The decrease in daily dose of corticosteroids is of special importance in the effective treatment of PV. Once a clinical remission was achieved, a steroid dose exceeding 100 mg was reduced to one-third. If the dose of steroid was 80–100 mg it was decreased by 15–20%. A further decrease in the maintenance dose was attempted slowly. The best results were obtained by a regimen in which the daily corticosteroid dose was decreased for 2.5 mg (calculated as prednisolone), first once every 5 days until the daily dose of 40 mg, and thereafter once every 7–10 days. When the dose had been reduced to 30 mg daily, its further decrease was 2.5 mg every 20–30 days. After a stable clinical remission was achieved the daily dose was decreased by 2.5–1.25 mg once in 2–3 months. Such a slow gradual regimen made it possible to titrate out the minimal maintenance dose of corticosteroid.

The question arises whether pemphigus is at all curable, particularly in patients whose treatment has been withdrawn. Twenty-seven of our 31 patients had no recurrence of the disease during many years after the treatment had been discontinued. Nikolsky's sign in these patients was negative, as also was direct and indirect immunofluorescence. This suggests that pemphigus can be cured. This depends, however, as does the success of pemphigus treatment on the whole, on the severity of the disease, on the patient's tolerance of the treatment, and on the rapidity of corticosteroid metabolism, circumstances of treatment initiation, methods of treatment, etc. The proportion of patients who were in prolonged clinical remission without any therapy (16.8%) is in line with that reported by Rosenberg et al. (3) and Krain (4) but is lower than that quoted by Ryan (10), Lever & Schaumburg-Lever (11) and Provost (28).

We could not establish any correlation between the duration of the preceding therapy and the possibility of discontinuing the treatment. However, the long-term follow-up study of PV patients shows that in cases of good tolerance of steroids, the severity of recurrences diminishes with time. This agrees with the conclusion (3) that the prognosis for survival in patients with pemphigus improves with increased duration of the disease, especially after 3 years. In that study, as well as in another one (10), the mortality was significantly greater during the first years of the disease, especially the very first year.

Only 7 of our 185 patients (3.8%) died during the follow-up period of causes closely related to the disease or its treatment. Thus, the disease-related mortality in the present study is significantly lower than those reported by Rosenberg et al. (3), Ryan (10) and Roenigk & Deodhar (29), and is fairly close to the percentages quoted by Krain (4), Lever (9), Lever & Schaumburg-Lever (11).

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