Do corticosteroids affect lumbar spinal fusion? A rabbit model using high-dose methylprednisolone

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Abstract

Background  The effect of corticosteroids on spinal fusion healing has not yet been determined. To evaluate the effect of corticosteroids on lumbar spinal fusion we designed a randomized, placebo-controlled animal study using high-dose methylprednisolone sodium succinate, which is widely used in patients with spinal cord injury who are undergoing spinal fusion.

Methods Two groups of 18 rabbits underwent a posterolateral fusion at L5–L6 with autologous bone graft. After surgery, the animals were assigned to receive: (a) methylprednisolone sodium succinate 30 mg/kg over 15 min, followed by an intravenous infusion of 5.4 mg/kg/h for 23 h, or (b) normal saline in the same volume. Animals were killed 8 weeks after surgery; the presence of fusion was analyzed by use of two different methods: a manual palpation test and an antero-posterior radiograph.

Results Both groups of animals were comparable in weight. Fusion was achieved in 5/18 rabbits (27.8%) in the methylprednisolone group and in 9/18 animals (50%) in the control group ($p = 0.17$).

Conclusion In a lumbar posterolateral fusion rabbit model, high-dose methylprednisolone sodium succinate reduced the success of lumbar fusion; however, our data did not reach statistical significance.

Introduction

Posterolateral spinal fusion (PLF) is frequently performed to treat degenerative disorders, tumors, infections, trauma, and deformities of the spine. Lack of fusion success reported for PLF in the lumbar spine varies from 0 to 60% [1–6]; factors that affect fusion healing include the disease for which the fusion was indicated, type of graft used, number of levels fused, fusion technique, presence of instrumentation, smoking habits, and the drugs the patients receive [1, 2, 4, 7, 8].

Although a few animal model studies have shown that corticosteroids can inhibit bone healing in long bone fracture and osteotomy models [9–12], the effect of corticosteroids on spinal fusion healing has not yet been determined. Only one animal study has evaluated the effect of corticosteroids on spinal fusion healing; this showed complete lack of lumbar fusion consolidation in rabbits receiving a high dose of dexamethasone [13]. That study utilized unusual steroid administration for patients undergoing spinal fusion, which makes their results difficult to transfer to human beings. High-dose methylprednisolone sodium succinate (MP) administration as described in the Second National Acute Spinal Cord Injury Study (NASCIS-2) is used in many centers, even though many studies have raised concerns about the lack of evidence of neurologic improvement and the increased incidence of complications associated with its use [14–21].

In order to determine the effect of corticosteroids on the success of spinal fusion, we evaluated the consequences of high-dose MP administration (as in the NASCIS-2 protocol) in a validated rabbit model [22]. The rationale of using this model is that most patients with traumatic SCI receiving high-dose MP also undergo spinal fusion.
Materials and methods

Institutional review board approval for animal research was obtained before initiation of this study.

Thirty-six New Zealand male rabbits (weighing between 2,650 and 4,000 g) underwent bilateral, intertransverse process, single level fusion at L5–L6, by using autologous bone graft obtained from both iliac crests, as described by Boden et al. [22]. Animals were sedated with 0.2 mg/kg acepromazine hydrochloride and 15 mg/kg i.m. ketamine hydrochloride solution. General anesthesia was administered with an intravenous solution consisting of 20 mg/kg ketamine hydrochloride plus 5 mg/kg xylazine.

Bilateral posterolateral (intertransverse) spinal fusion was performed between L5 and L6. A standard posterior midline incision was performed through the subcutaneous tissues. By bilateral, independent, intermuscular approaches the transverse processes of L5 and L6 were exposed and decorticated with a high-speed circular burr. Autologous cortico-cancellous iliac crest bone graft was obtained through the same skin incision, but via a different fascial approach. Bone graft was applied between the decorticated intertransverse processes. The fascia and the skin were both closed with absorbable 1-0 sutures. After surgery, animals were assigned to receive:

1. MP 30 mg/kg over 15 min, followed by intravenous infusion of 5.4 mg/kg/h over 23 h; or
2. normal saline in the same volume.

Each group consisted of 18 rabbits. The animals were coded and administration of the drug was performed by personnel other than the surgeons and evaluators. The investigators were unaware of the group the animals belonged to. Post-operative analgesia was achieved with subcutaneous Tramadol hydrochloride 4 mg/kg (Tramal®, Grüenthal) every 12 h for 5 days and then every 24 h for three additional days. Postoperative prophylactic subcutaneous enrofluoxacin (5 mg/kg) was used before starting surgery and every 24 h for 5 days.

Animals were killed with an overdose of anesthetic 8 weeks after surgery. The whole lumbar spine was dissected and soft tissues were removed to enable complete visualization of L5–L6. The presence of fusion was analyzed by use of two different methods. A manual palpation test, as described by Boden [22], was applied by two independent observers unaware of animal group; if the fused level moved as a block, it was regarded as solid. An anteroposterior X-ray obtained from each specimen after removal from the animal was evaluated by two independent observers unaware of animal group and of result from the manual palpation test; fusion was regarded as consolidated if there was a continuous bony mass, crossing both transverse processes, without radiolucent lines on the radiograph (Fig. 1). For a specimen to be regarded as bearing solid fusion, absence of movement on palpation test plus bone bridging on radiographs had to be demonstrated. The examiners were not aware during the whole evaluation stage whether MP or saline solution had been administered.

Sample size was estimated on the basis of data from a previous study by Sawin et al. [13]. It was assumed that the success of fusion for the MP group would be 50% lower than for the control group. With a significance level of 5% and a power of 80%, the smallest appropriate sample size was 17 animals for each group. Statistical analysis of the data obtained was carried out using the chi-squared test and the Student t-test. A p value <0.05 was regarded as indicative of a statistically significant difference.

Results

Considering absence of mobility in flexion and extension plus bone bridging among transverse processes on radiographs, fusion healing was observed in 5 of 18 rabbits...
(27.8%) in the MP group and in 9 of 18 animals (50%) in the control group ($p = 0.17$).

The weight of the animals was similar in both groups; the mean weight of the animals was 3,220 g (2,780–3,680) in the MP group and 3,152 g (2,650–4,000) in the control group, $p = 0.47$. The iliac crest bone graft volume was also similar in both groups, with a mean volume of 3.16 cc in the MP group and 3.05 cc in the control group ($p = 0.37$).

**Discussion**

A potential complication related to the use of corticosteroids is that they can affect bone healing. This effect has been described in animal studies which have shown that corticosteroids can inhibit bone healing in long bone fracture and osteotomy models [9–12]. Several theories are used to explain this effect of corticosteroids on bone formation: they can cause osteoblast apoptosis, osteocyte apoptosis, and inhibition of osteoblastogenesis [23, 24], and they can also suppress the inflammatory phase of the healing cascade [25, 26]. A delay in endochondral ossification in animals treated with cortisone has also been reported, although membranous ossification is not affected [27, 28]; this latter effect may be explained by the presence of glucocorticoid receptors GRx in osteoblasts, chondrocytes, and osteocytes, which might be involved in endochondral ossification [29].

Intertransverse fusion healing is achieved through endochondral ossification, and corticosteroids might also affect lumbar posterolateral spinal consolidation; this effect, however, cannot be extrapolated from the effect observed in experimental studies of long bone fractures. Only one experimental study has previously evaluated the effect of a corticosteroid (dexamethasone) on the success of lumbar fusion; that animal study showed a complete inhibition of intertransverse fusion healing (0% fusion success), compared with 58% fusion success in controls [13]. However, it is difficult to transfer those results to humans, because continuous administration of such a high dose of dexamethasone (0.1 mg/kg/day) is very unusual in patients undergoing a spinal fusion; in addition, complete lack of fusion associated with use of corticosteroids is not concordant with clinical observations. To determine the effect of a commonly used steroid administration in the context of spinal fusion, we decided to replicate the dosage used in the NASCIS-2 protocol, because most patients with traumatic SCI receiving high-dose MP also undergo a spinal fusion. Although we administered MP after surgery, whereas patients receive it as soon as possible after the SCI (mainly preoperatively), the effect of this high dose of MP should last for several days [30]. In addition, patients undergoing spinal fusion in accordance with the NASCIS-2 protocol should be under the effect of MP at the moment of surgery, because it has been reported that these patients with SCI have slower clearance (with a longer effect) of MP [31].

Our study found that high-dose MP reduced the success of fusion compared with controls, although without a statistically significant difference between the two groups. That lack of statistical difference may be secondary to a type II error; the minimum number required to demonstrate a significant difference based on the fusion success observed would be 40 rabbits in each group. Moreover, for animals that received MP the success of fusion was lower than for control animals in previous reports with this model using autograft, for which fusion success in controls was from 42 to 77% [22, 32, 33].

Although the manual palpation test is the gold standard to determine fusion, an anteroposterior X-ray showing a continuous bone bridge was also required to consider a specimen as fused; in this work, therefore, stricter criteria were used to establish that a solid fusion is achieved. However, we did not perform computed tomography or histological studies; this could be regarded as a limitation of our study.

High-dose MP reduced the success of fusion in a lumbar spinal arthrodesis model in rabbits; however, our data did not reach statistical significance. As with other drugs, the dose and the specific drug administered are factors that may affect fusion healing. Future studies should help to define the role of different corticosteroids and their doses on spinal fusion in experimental models, and how they transfer to patients.

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**Conflict of interest** The authors do not have any commercial affiliations, consultancies, stock ownership, or patent-licensing arrangements that could be regarded as posing a conflict of interest regarding this article. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this study.

**References**


