OP-1 for cervical spine fusion

Bridging bone in only 1 of 4 rheumatoid patients but prednisolone did not inhibit bone induction in rats

Charlotte Jeppsson[1], Hans Säveland[2], Urban Rydholm[1] and Per Aspenberg[1]

We used OP-1 (also called BMP-7) on a collagen type-1 carrier in atlanto-axial posterior fusions to promote bony healing after wire fixation. 4 patients who had instability between the atlas and axis due to rheumatoid disease received the implants. The patients were examined with conventional radiography postoperatively at 2, 6 and 10 months. In 3 patients, no new bone formation was detectable. In 1 patient, new bone bridged the fusion site at 6 months. 3 patients were on chronic steroid treatment, including the patient in whom bone formation was detected. To determine whether steroid treatment could be responsible for the low rate of bone induction, 24 rats each received OP-1 implants in an abdominal muscle pouch. They were divided into 3 groups receiving saline, 0.1 or 1.0 mg/kg BW of prednisolone daily until they were killed 3 weeks postoperatively. Specimens were decalcified for histology and the amount of calcium in the decalcifying solution was measured. All groups showed ossicles induced by OP-1, and no effect of prednisolone was detected. Thus the failures in the patients may have causes other than prednisolone treatment.

Departments of [1]Orthopedics and [2]Neurosurgery, Lund University Hospital, SE-221 85 Lund, Sweden.
Tel +46 46–17 15 26. Fax –13 07 32
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Since 1988, when the first bone morphogenic proteins (BMPs) were identified (Wozney et al. 1988), almost 20 BMPs have been identified and are referred to as a family in the TGF-ß superfamily of growth factors (Wozney 1992). The various BMPs have slightly different properties, but most of them are considered to induce bone formation by stimulation of mesenchymal pluripotent precursor cells. When combining BMPs with an osteoconductive carrier, a device is created, which is theoretically both bone conductive and inductive (Cook and Rueger 1996). A device with such properties should be useful in several clinical situations such as osteoporotic fractures, pseudarthrosis or spinal fusions. Many studies have shown their efficiency for healing critical size defects in rodents and nonhuman primates (Tourimi et al. 1991, Yasko et al. 1992, Cook et al. 1994a, b).

Spontaneous atlanto-axial instability is a complication of rheumatoid disease. The patients suffer from neck pain and/or a wide variety of neurological symptoms. There is a high mortality rate due to medullary compression, if the joint is not stabilized. The standard operation for these patients at Lund University Hospital is a posterior fusion between the atlas and axis vertebrae with three wires (Figure 1) and a bone graft from the posterior iliac crest. This is a modification of the Gallie (1939) operation. This operation is designed so that the short-term clinical outcome does not depend on bony

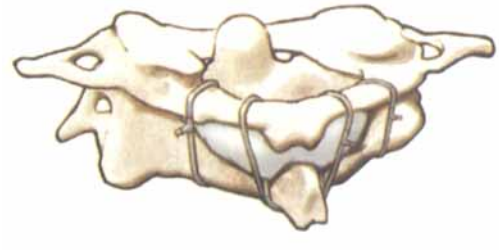

Figure 1. Operating technique using three wires for fixation between axis and atlas.The wires form a cage which protects the OP-1 device from being squeezed away by the surrounding tissues.

fusion. Since the bone transplant is often of poor quality and quantity in rheumatic patients, and complications are common from the donor site (Summers and Eisenstein 1989), a BMP device would be of great value, if it made transplantation unnecessary.

OP-1 on collagen granules was commercially available as an implant device. We planned to use this device in 10 patients undergoing stabilizing surgery, thereby avoiding the bone transplantation procedure. As no bone formation was detectable after 2 months in the first 4 patients, we decided not to treat any more patients until the final outcome in these 4 was evaluated.

One reason for the unexpected absence of bone induction might be that 3 of these 4 patients were on chronic steroid treatment. We therefore studied the effects of glucocorticoids on bone induction by OP-1 in rats.

Material and methods

Patients

4 consecutive patients with a rheumatoid disease—3 with rheumatoid arthritis (RA) and 1 with psoriatic arthritis—were operated on at the neurosurgical department of Lund University Hospital. All showed instability of the atlanto-axial joint and all suffered from neurological symptoms. The 3 RA patients were taking 5, 7.5 and 10 mg prednisolone daily. The patient with psoriatic arthritis had no steroid treatment.

Implants. The recombinant OP-1 device was bought from Stryker Biotech (Natick, MA, USA). It was delivered as dried sterile granules of bovine bone collagen with OP-1. Prior to implantation, the granules were moistened with physiological saline solution, turning it into a malleable mass, similar to wet sand.

Surgical technique (Figure 1). The patients were placed on a Stryker frame and intubated in the supine position. Then, skull traction with a Gardner-Wells tong was applied, and the patients were placed in the prone position. A midline incision was made from the inion to the spinous process of the 4th cervical vertebra. The laminae of the atlas and axis vertebrae were dissected. The cortical bone was freed from fibrous tissue and a drill burr was used to decorticate the laminae of the atlantis and axis vertebrae. We used three wires. Two were passed below the laminae of the atlas and axis bilaterally and one was passed under the lamina of the atlas twice, close to the spinous process, and looped around the spinous process of the axis. 2.5 mg OP-1 on 1 g of collagen was placed on the roughened cortical surface between the spinous processes of the two verebrae. The wires acted as a cage, surrounding the OP-1 device, protecting it from being squeezed away by the muscles. The wound was closed in layers and the skull traction was removed. The patients were mobilized in a semi-rigid collar on the day after the operation. The collar was kept on for 6–8 weeks.

Evaluation. The patients were examined with radiography in the first week postoperatively and at 2, 6 and 10 months after surgery, to detect visible bone formation between the spinous processes of the atlas and axis vertebrae. All patients were examined and interviewed by the neurosurgeon at 2 and 6 months postoperatively, concerning their neurological symptoms and neck pain.

Animals

24 female Sprague-Dawley rats (200 g) were obtained from Möllegård (Köge, Denmark).

Implants. The recombinant OP-1 device was a gift from Stryker Biotech (Natick, MA, USA). It was identical with the clinically used material. Prior to implantation, the dried collagen granules were moistened with physiological saline.

Surgical technique. The rats were anesthetized with peritoneal injections of 0.4 mL of a solution containing 15 mg pentobarbital and 2.5 diazepam per mL. Under aseptic conditions, a longitudinal incision was made in the abdominal wall and 20 mg of the OP-1 device (equivalent to 50 μg OP-1) was implanted subfacially in a muscular pouch. The wounds were closed in layers.

Experimental design. The rats were divided into 3 groups of 8 in each. Starting on the day of implantation, all received subcutaneous injections of physiological saline or prednisolone daily for 3 weeks. The two prednisolone groups received 1.0 or 0.1 mg/kg BW, respectively. The rats were killed with an overdose of pentobarbital after 3 weeks, and the implants were retrieved.

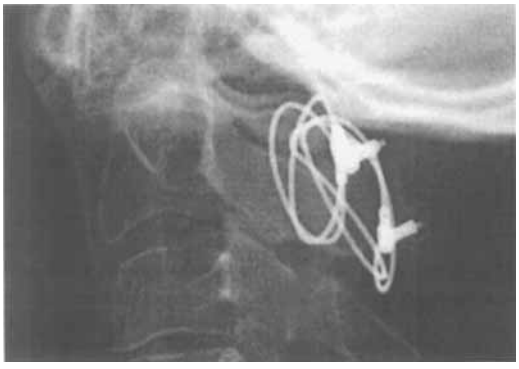

Figure 2. Radiographic bone formation at the implantation site at 6 months. This patient was on 7.5 mg prednisolone daily. Bone formation was found after partial redislocation.

Evaluation. The retrieved implants were processed for decalcified histology and the decalcification solution was analyzed for calcium content, using atomic absorption. Results were analyzed by Anova. Qualitative histology was used for confirmation.

Results

All postoperative radiographs showed adequate realignment of the atlanto-axial joint and the wires were correctly placed (Figure 2). No patient used the neck collar after 8 weeks. At examination 2 months postoperatively, all patients reported regress of neurological symptoms and neck pain. One patient complained of impaired motion of the neck and had removed the collar at home after 6 weeks. At 2 months postoperatively, no patient showed radiographic bone formation. In the radiographs from the patient who had removed the neck collar at home, an 8 mm redislocation was found. The joint appeared stable when examined with radiography in flexion and extension. At 6 months, only this patient showed bone formation at the site of the OP-1 device (Figure 2). He was taking 5 mg prednisolone daily and radiographs from his bilaterally operated hip prostheses showed ectopic bone formation. At 10 months postoperatively, still no detectable bone formation was found in the 3 remaining patients, and no additional bone formation had occurred in the one with bone formation at 6 months.

Calcium content in retrieved OP-1 implants (mg) after daily prednisolone injections in rats

Prednisolone mg/kg BW/day	n	Mean	SD
0.0	8	0.75	0.28
0.1	8	0.70	0.31
1.0	8	0.68	0.20

The rats showed extensive bone formation in the muscular pouch in all 3 groups. No difference in calcium content was found between the 3 groups (Table). Histologically, mature bone was found at the place of implantation in all rats.

Discussion

We found bone formation in 1 of 4 patients treated with OP-1 instead of autologous bone. The bone formation occurred later than 2 months postoperatively, and this patient also showed ectopic bone formation around his bilateral hip arthroplasties. The confidence interval for 1 of 4 (exact calculation) implies that a healing rate in a large series has a less than 5% probability of exceeding 75%. Therefore, the planned series was stopped.

The bone fusion rate in rheumatoid neck atlanto-axial fusion in various reports using autografts ranges from 50% (Santavirta et al. 1991) to 100% (Boden et al. 1993). In other series published since 1980 concerning atlanto-axial fusions, 75% of 250 patients showed bony fusion (Conaty and Mongan 1981, Meijers et al. 1984, Thompson and Meyer 1985, Larsson and Toolanen 1986, Fehring and Brooks 1987, Zoma et al. 1987, Heywood et al. 1988, Clark et al. 1989, Milbrink and Wigren 1989, Grob et al. 1990, Santavirta et al. 1991, Vanden Berge et al. 1991, Chan et al. 1992, Stirrat and Fyfe 1992, Boden et al. 1993, Zygmunt et al. 1995). However, since bad results are often not published, a true average result is probably lower than 75%.

Why did we have 3 failures in 4 patients with a device that is so successful in dogs (Cook et al. 1994 b) and baboons (Ripamonti et al. 1996)? One explanation may be that the effect of BMPs is sometimes dependent on a certain degree of mi-

cromotion. In a rabbit bone chamber model, BMPs had an inhibitory effect on bone formation, but this was changed to stimulation when micromotion was added to the system (Boström et al. 1998). Some studies in humans (Johnson et al. 1988 a,b) are hard to evaluate, due to heterogeneous patient groups and the impurity of the BMPs used, but one prospective controlled study in humans (Geesink et al. 1999) showed healing in 5 of 6 fibular osteotomies treated with OP-1 compared to none of the 6 controls. The fibular osteotomies were left without osteosynthesis, thereby providing a site with a certain degree of micromotion. Correspondingly, those of our neck fusions that did not heal were successfully fixated, whereas the patient who produced bone had a minor fixation failure.

The upper neck location itself may be a suboptimal site for bone induction by OP-1 in humans, possibly because BMP receptor expression may vary between different sites in the body. In squirrel monkeys, the effect of BMP-2 in extraskeletal sites is weak, but clearly dependent on the implantation site (Aspenberg 1996). Another uncertainity is, of course, the glucocorticoid treatment.

The patient who showed bone formation was taking 5 mg prednisolone daily, as compared to the three patients with no signs of bone formation, who were on daily doses of 0, 7.5 and 10 mg. Glucocorticoid treatment may impair bone formation and glucocorticoids induce osteoporosis both by inhibiting bone formation and by increasing bone resorption (Rude et al. 1993).

We used a subcutaneous model in the rats, but the effect of cortisone on osteoinduction might be different close to the spine. Prednisolone did not affect bone induction in the rats and our prednisolone doses were not too low. Methylprednisolone acetate in as low a dose as 0.1 mg/kg B.W. s.c. 3 days per week for 2 weeks induces osteopenia in rats (Nakamuta et al. 1996). This, and the finding that the patient who healed with bony fusion was on steroid treatment indicates that glucocorticoids are probably not the reason for the failure in 3 of 4 patients.

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