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Recombinant bone morphogenetic protein-7 as an intracorporal bone growth stimulator in unstable thoracolumbar burst fractures in humans: preliminary results

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Abstract The study presented here is a pilot study in five patients with unstable thoracolumbar spine fractures treated with transpedicular OP-1 transplantation, short segment instrumentation and posterolateral fusion. Recombinant bone morphogenetic protein-7 in combination with a collagen carrier, also referred to as OP-1, has demonstrated ability to induce healing in long-bone segmental defects in dogs, rabbits and monkeys and to induce successful posterolateral spinal fusion in dogs without need for autogenous bone graft. Furthermore OP-1 has been demonstrated to be effective as a bone graft substitute when performing the PLIF maneuver in a sheep model. Five patients with single-level unstable burst fracture and no neurological impairment were treated with intracorporal OP-1 transplantation, posterior fixation (USS) and posterolateral fusion. One patient with osteomalacia and an L2 burst fracture had an additional intracorporal transplantation performed proximal to the instrumented segment, i.e. OP-1 into T 12 and autogenous bone into T 11. Follow-up time was 12–18 months. On serial radiographs, Cobb and kyphotic angles, as well as anterior,

middle and posterior column heights, were measured. Serial CT scans were performed to determine the bone mineral density at fracture level.

In one case, radiographic and CT evaluation after 3 and 6 months showed severe resorption at the site of transplantation, but after 12 months, new bone had started to fill in at the area of resorption. In all cases there was loss of correction with regard to anterior and middle column height and sagittal balance at the latest follow-up. These preliminary results regarding OP-1 as a bone graft substitute and stimulator of new bone formation have been disappointing, as the OP-1 device in this study was not capable of inducing an early sufficient structural bone support. There are indications to suggest that OP-1 application to a fracture site in humans might result in detrimental enhanced bone resorption as a primary event.

Key words Thoracolumbar burst fractures · Recombinant human bone morphogenetic protein-7 · Transpedicular transplantation · Clinical results · Bone graft substitute

Introduction

The goals of the treatment of unstable thoracolumbar fractures include anatomic reduction, rigid fixation, solid fusion

and early rehabilitation [1, 2, 8, 9, 12]. Numerous techniques of stabilization have been developed to facilitate fracture reduction and to create immediate stability. However, osteogenesis and fracture healing are biological processes, which are facilitated but not replaced by instru-

mented fixation. The development of new techniques for exploring mechanisms in cellular and molecular biology have led to better understanding of the basic events that regulate the repair of bone fractures and have directed focus toward biological considerations, i.e. the quality of the bone graft, osteoinductive growth factors, and bone graft substitutes [7, 10, 11, 15, 17, 19]. Development of methods for local stimulation of fracture healing involves not only the identification and manufacturing of specific molecules that stimulate the fracture healing process, but also design of appropriate delivery systems [10]. The successful isolation and purification of bone morphogenetic proteins (BMP's) and the demonstration that recombinant human BMP (rhBMP) can induce the entire cascade of endochondral osteogenesis [17] have led to the development of the OP-1 device. The OP-1 device, consisting of 2.5 mg human recombinant bone morphogenetic protein-7 (BMP-7) in conjunction with 1 g of bovine bone-derived type 1 collagen may enhance healing by two mechanisms: The BMP-7 has an osteoinductive potential, which triggers the active recruitment of host pluripotent cells that differentiate into chondroblasts and osteoblasts [17, 18]. The collagen carrier has an osteoconductive potential, as it serves as a scaffold for the ingrowth of sprouting capillaries, perivascular tissues, and osteoprogenitor cells from the recipient host bed [17]. In vivo animal studies have suggested that the OP-1 device can be used as a bone-graft substitute in spinal fusion, [4, 7, 13, 17] in long-bone segmental defects [3, 5, 17] and to promote osteointegration during metal-prosthesis fixation in orthopedic and dental procedures [6, 15, 16, 19].

The purpose of the present study was to investigate the clinical use of recombinant human BMP-7 (rhBMP-7) in conjunction with a bovine bone-derived collagen type 1 carrier as a bone graft substitute in transpedicular transplantation of unstable thoracolumbar burst fractures.

Materials and methods

In the period July 1997 to May 1998, four males and one female were assigned to this pilot study. Inclusion was limited to patients presenting an acute unstable [9], single-level, non-pathologic burst fracture at the thoracolumbar junction and no neurologic impairment. The National Board of Health in Denmark had certified the OP-1 device for clinical use, and this study was approved by the Regional Scientific Ethics Committee. All patients gave their informed consent prior to their inclusion in the study.

Surgical technique

The levels above and below the fracture were exposed using a standard posterior approach with the patients placed in prone position on bolsters with hip flexion and the site of the fractured spine in an extended, lordotic position. Under C-arm image intensifier control, titanium USS pedicle screws were inserted into the pedicles one level above and below the fractured vertebra, followed by reduction, i.e. lordosing and distraction, of the instrumented spinal segment. A probe was inserted through the right pedicle of the fractured vertebra to elevate the depressed superior endplate. Under flu-

oroscopic control, transpedicular transplantation of the fractured vertebra was performed through a metal funnel. After transplantation the pedicle was sealed by a collagen sponge in case 1 and by autogenous bone in the remaining four cases. At this stage, myelography was carried out. Finally, a standard bilateral posterolateral autogenous bone transplantation was performed with material from the iliac crest. The patients were mobilized on the 3rd day. Two patients with poor bone quality were braced in a thoracolumbar orthosis for 3 months.

Radiographic evaluation

Measurements of kyphotic angles, anterior, middle and posterior vertebral column heights were performed at the time of injury, and values were compared with similar measurements performed immediately postoperatively and after 3, 6, and 12 months. Vertebral compression was estimated by comparison of the anterior, middle, and posterior vertebral height with the mean of the value for the two adjacent vertebrae. Kyphotic angle was measured as described by Crawford and Askin [8]. Bone-mineral density measurements at the fractured level and at a control level (L4) were performed by quantitative CT scans (QCT) in four patients postoperatively and at follow-up.

Case 1

A previously healthy 35-year-old man sustained a burst fracture of L1 after a fall 6 m down from a roof (Fig. 1 A). Immediately after surgery, a good correction was obtained at the fracture level (Fig. 1 B, Tables 1, 2), but at the 3- and 6-months follow-up, severe resorption at the site of transplantation was seen (Fig. 2 A). MR scans and blood-tests did not reveal any signs of infection. Despite the poor radiological result, the patient reported no pain and had returned to full-time work as a locksmith at the 6 months follow-up. At 12 months, the contour of the vertebra could again be seen as a result of new bone-formation at the site of initial resorption (Fig. 2 B).

Case 2

A 48-year-old man suffered an L2 burst fracture in a traffic accident. The preoperative radiographs revealed poor bone quality, which made it necessary to advance the pedicle screws through the anterior cortex. The poor bone quality was caused by osteomalacia documented by a preoperative bone biopsy. At fracture level, transpedicular transplantation was performed by a combination of the OP-1 device and autogenous bone graft. In addition, an intracorporeal transplantation with the OP-1 device was performed at T 12 and an intracorporeal autogenous bone transplantation at T 11. The initial correction was lost during follow-up (Tables 1, 2). The bone-mineral density (BMD) at fracture level increased postoperatively and up to the 3 months follow-up and decreased minimally at 6 and 12 months follow-up. At T 12 and the L4 reference level, BMD decreased during the first 6 months, but was increased at the 12 months follow-up (Table 3). The patient suffered tiredness in his back during follow-up, and at the 12 months visit he reported incidences of back-pain. Radiographic evaluation revealed loosening of one screw and the patient had the instrumentation removed after 18 months.

Case 3

A 28-year-old man sustained a burst fracture at L1 (fall accident, 4 m down).

A pure intracorporeal OP-1 transplantation was performed at the fracture level and the correction that was obtained postoperatively was satisfactory. At the 3- and 6-months follow-up, the correction

Fig. 1 **A** Preoperative CT scan, **B** post-operative lateral radiograph

Fig. 2 **A** Three-month follow-up radiograph shows severe resorption of the anterior column. **B** Twelve-month follow-up: the contour of the vertebrae can be seen again

Table 1 Anterior and midcor-poral compression at the frac-ture level (*mo.* month)

Case	Anterior compression (%)					Midcor-poral compression (%)				
	Preop.	Postop.	3-mo.	6-mo.	12-mo.	Preop.	Postop.	3-mo.	6-mo.	12-mo.
1	30	0	•	•	28	22	0	19	19	33
2	23	11	18	24	24	36	19	33	27	28
3	51	7	14	19	19	32	6	12	18	18
4	33	15	39	39	47	31	12	39	57	58
5	44	12	11	18	20	28	19	12	18	29

(•) No measurements because of resorption

Table 2 Angle at the fracture level (degrees). Negative values represent lordosis

Case	Preop.	Postop.	3-mo.	6-mo.	12-mo.
1	0	-14	-11	-11	-2
2	9	-16	-9	0	0
3	13	-13	-12	-10	-10
4	9	-9	5	7	8
5	6	-11	-5	-2	-2

was only partly lost (Tables 1, 2) and was stable after 6 months. BMD was increased at the fracture level, but decreased at the L4 reference level (Table 3). The patient had no complaints at the follow-up visits.

Case 4

A 76-year-old man had an unstable L1 burst fracture after a fall accident (0 m). Intracorporeal OP-1 transplantation was performed at the fracture level, and the pedicle screws were advanced to the anterior cortex because of poor bone quality. During follow-up the correction was lost and compression at the fracture level increased beyond the preoperative value (Tables 1, 2). BMD at the fracture level initially increased, but decreased at the L4 reference level (Table 3). The patient reported no back pain, but often felt tiredness in his back.

Case 5

In the last case, a 60-year-old woman with an L1 burst fracture (traffic accident) partly lost the correction during follow-up (Tables 1, 2). The BMD at 6-months follow-up was increased at the fracture level and decreased at the reference level (Table 3). During follow-up, the patient had no back-related complaints.

Discussion

These are the first preliminary clinical results after intracorporeal OP-1 transplantation in unstable thoracolumbar spine fractures in humans. Fundamental to any clinical application of rhBMP-7 is proof that the molecule is biologically active in humans. Information is scarce concerning the safety and efficacy of rhBMP-7 in humans. Therefore we approached this problem in a pilot study. The patient group was planned to be heterogeneous with respect to age and bone quality, as we wanted to look at the potential of OP-1 as an inducer of new bone formation in both the

young and the elderly, and in patients with normal as well as osteoporotic bone. The intracorporeal application of OP-1 described in this study we find superior to other locations, since the intracorporeal compartment is controlled without risk of removing OP-1 by suction drainage.

Sagittal correction

In all cases we observed a loss of kyphotic angle correction from postoperative measurements to the latest follow-up, (median 12°, range 3°–16°), and this loss of angle correction might be more prominent in comparison to our previous results in 78 patients after transpedicular autogenous bone transplantation (median loss 6°, range 0°–17°) [12]. The anterior and middle column height correction achieved postoperatively was also partly lost in all patients at the latest follow-up, and in a 76-year-old man with poor bone quality, the anterior and middle compression at fracture level even increased beyond the preoperative value. However, we have also observed this phenomenon in a few patients with poor bone quality after autogenous intracorporeal bone transplantation [12]. The results so far regarding maintenance of the sagittal correction achieved postoperatively have been disappointing, because the OP-1 device in this study was not capable of inducing a sufficient early biomechanical bone support.

BMD

The BMD at the fracture level after 3 and 6 months was increased in all patients compared to the postoperative value, while the opposite phenomenon was observed at the reference level.

Whether the increased BMD at the fracture level after 3 and 6 months was caused by the increasing compression at that level or a combination of compression and new bone formation can not be determined from the present results. The drop in BMD at the reference level after 3 and 6 months was expected as a consequence of the regional acceleratory phenomenon and the relative immobility of the patients. At the 12 months visit we observed in the patient with osteomalacia, in contrast to the rest of patients, that BMD at the reference level had increased from 6 to 12 months and was even higher than the postoperative

Table 3 Bone mineral density (mg Ca-Ha/ml) at the fracture level and at a reference level (missing values are due to technical problems with the CT scanner)

Case	BMD at fracture level				BMD at L4 (reference level)			
	Postop.	3-mo.	6-mo.	12-mo.	Postop.	3-mo.	6-mo.	12-mo.
2	155	194	186	174	96	72	71	106
3	219	279	280	278	212	177	180	–
4	131	224	201	191	159	155	148	136
5	169	–	210	169	167	–	133	130

level. This could be a result of the medical treatment (calcium and D-vitamin) which was initiated in this patient 3 months after surgery.

Complications

So far there have been two complications. One was a case of screw loosening seen in the patient with osteomalacia, which could be expected because of the very poor bone quality. The second, in a previously healthy 33-year-old man, consisted of resorption of the whole anterior column at the fracture level. This kind of complication has not previously been reported after transpedicular autogenous bone transplantation, but the resorption could be explained by findings in preclinical studies. A recent study by Jensen et al. [11] using impacted mixtures of allograft and OP-1, in a gap model around implants in dogs, demonstrated extensive effects on new bone formation by OP-1, but also accelerated graft resorption. Salkeld et al. [16], using both auto- and allograft with OP-1, obtained similar results; they found an accelerated resorption of the graft material but also significant formation of new bone. The results from these animal studies suggest that OP-1 initially enhances the osteoclast activity; this could explain the excessive resorption phenomenon and the late restoration of the vertebra seen in our case. However, we only observed

severe resorption in this one case, and an additional explanatory reason might be the severity of that fracture, as the preoperative CT scan revealed a total dislocation of the anterior fracture fragment.

Based on the data obtained and presented here, we have by ethical obligation discontinued and redesigned the study. The OP-1 device has been shown to have an osteogenetic potential in many experimental studies [3–7, 11, 13, 14, 16–19]. However, in clinical situations where an early biomechanical support is mandatory, it's perhaps too optimistic to use the OP-1 device in the former composition with a bovine collagen carrier. Furthermore, important questions still remain to be answered – most importantly, the optimal dose of rhBMP-7 to be applied in humans, the best carrier in humans, the containment of rhBMP-7 and the long-term effect of rhBMP-7 in humans.

In conclusion, the present pilot study on the use of OP-1 as a bone graft substitute and stimulator of new bone formation has been disappointing, as the OP-1 device in this study was not capable of inducing a sufficient early structural bone support. There are indications to suggest that application of OP-1 at a fracture site in humans in some cases may result in inappropriate enhancement of bone resorption as a primary event.

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