Eur Spine J (2003) 12 : 400–407
DOI 10.1007/s00586-003-0548-5

ORIGINAL ARTICLE

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Do autologous growth factors enhance transforaminal lumbar interbody fusion?

Received: 12 August 2002
Revised: 18 December 2002
Accepted: 14 February 2003
Published online: 22 May 2003

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Abstract Pseudarthrosis remains a significant problem in spinal fusion. The objective of our study was to investigate the effects of autologous growth factors (AGF) in instrumented transforaminal lumbar interbody spinal fusion (TLIF). A prospective review was carried out of 23 patients who underwent TLIF with application of AGF, with a minimum 2-year follow-up. Comparison with our historical cohort (without AGF application) was performed. Mean age at surgery was 44.3 years in the AGF treatment group. Twelve had a positive smoking history. Fourteen had undergone previous spinal surgeries. Thirteen received one-level fusions and ten received two-level fusions. The radiographic results showed a fusion rate of 100% in one-level fusions and 90% in two-level fusions. There was no significant difference in pseudarthrosis rates between the AGF treatment group and historical cohort. Excluding the cases with pseudarthrosis, there was faster bony healing in patients who had been treated with AGF application. This study indicates that although AGF may demonstrate faster fusions, it does not result in an overall increase in spinal fusion rates. Further studies are needed before AGF can routinely be used as an adjunct in spinal fusion.

Keywords Autologous growth factors (AGF) · Platelet derived growth factor (PDGF) · Pseudarthrosis · Transforaminal lumbar interbody fusion (TLIF) · Transforming growth factor-beta (TGF-β)

Introduction

Pseudarthrosis remains a significant problem in spinal fusion, the incidence of which ranges from 5 to 34% in various series [14, 15, 43]. Revision surgery to attempt arthrodesis is often necessary [13]. The graft-healing rate appears to decrease in patients who smoke, are diabetic, have rheumatoid arthritis, or are chronic steroid or non-steroidal anti-inflammatory drug users [7, 8]. Allografts have also been associated with an increased pseudarthrosis rate [1].

One of the requirements for successful fusion is the presence of osteoinductive activity in the fusion site. Demineralized bone matrix has been used to enhance spinal fusion [27]. Recent studies have reported the efficacy of bone morphogenetic protein (BMP) in facilitating spinal fusion [5]. The beneficial effects of platelet-derived growth factor (PDGF) on bone formation in vitro has also been described previously [9, 10, 18, 20, 22, 34, 36, 37], while in vivo stimulation of bone formation by transforming growth factor-β (TGF-β) has been shown in animal models [20, 30, 33]. Both PDGF and TGF-β have mitogenic effects on fibroblasts, osteoblasts, and mesenchymal cells by the stimulation of DNA synthesis and cell replication [12]. PDGF and TGF-β have chemotactic and mitogenic effects on undifferentiated stem cells, causing them to multiply and secrete more growth factors [11]. These cells subsequently undergo differentiation into osteoblasts.

Platelet gel derived from buffy coat was initially used as an autologous fibrin sealant [2]. Further understanding of the healing and regenerative properties of the growth factors contained in the platelets [21, 37] led to the use of platelet gel for various healing applications. Platelet gels have also been used in mandibular and maxillary reconstruction to hold bone graft in the desired position and prevent graft migration. One study showed one-third more new bone formation in cases that had platelet-rich plasma [30]. It also reported that the platelet count in the platelet-rich plasma increased 338% as compared to the baseline.

The concept of AGF applications is to further enhance the healing properties of the platelet-rich plasma, also known as the buffy coat. This is achieved by further concentrating the buffy coat through an ultraconcentrator [2]. This process produces an increase in the platelet level of 575% compared to the baseline [30],thereby allowing greatly increased amounts of growth factors to be delivered to the fusion sites. Concentration of AGF through blood shows promise as an osteoinductive or mitogenic agent to help promote bony healing [3]. Other studies have reported that when multiple growth factors are present together at the bone formation site, they may exert synergistic effects on one another [30], which could be important for regeneration of bone cell proliferation [4]. This finding would support the concept of enhancing bony fusion by the application of AGF locally at the bone fusion sites.

In one study [29], 19 patients were retrospectively reviewed after 13 months to assess the results of AGF in lumbar spinal fusion. No impending pseudarthrosis was found on radiographs of the lumbar spine at last follow-up. They concluded that AGF offers advantages when used as an adjunct to autografts. In another study of 69 patients [35], no pseudarthrosis was noted at an average of 9 months after surgery.

However, a major concern in delivering growth factors (PDGF, TGF-β) to the fusion sites was their short systemic half-lives [32]. PDGF has a half-life of 2 minutes if injected intravenously, and TGF-β is also cleared from the blood within a few minutes. One study [33]demonstrated that the effect of TGF-β is a local one, with no effects on bone formation at distant sites. Other authors have noted that multiple growth factors are present at the same time at the site of bone formation and have a synergistic effect on one another [22]. This led to the concept of providing high concentrations of growth factors at the actual site of fusion, in order to mimic the natural process of osteogenesis as closely as possible.

We know that growth factors and bone morphogenetic proteins (BMPs) can lead to a faster union rate than autograft in femoral defects of rats, rabbits, and rodents [25]. However, when they are applied to primates, no better success was achieved than using autograft alone [6]. The growth factors may have diffused away before they were able to exert any effect. Besides, the number of progenitor cells that are responsive to these factors may be more limited in primates and humans, especially under clinical situations such as non-unions and previous surgeries, than in young animal models [24].

The objective of the current study is to prospectively evaluate the efficacy of AGF as a biological enhancer for instrumented transforaminal lumbar interbody spinal fusion (TLIF). The prospective study was started in May 1999. The results were then compared to a historical control group without the use of AGF. This historical cohort was drawn from the authors' previous operative experience [19].

Materials and methods

The prospective study was started in May 1999. All patients who received instrumented TLIF with autogenous iliac crest bone grafts were included. Exclusion criteria included patients who received isolated posterolateral fusion, anterior lumbar interbody fusion, placement of internal bone growth stimulators, or the use of allografts or local bone grafts. Patients were informed that they were to be included in a prospective study. All patients had a minimum of a 24-months follow-up. Twenty-four patients fulfilled the criteria. One was lost to follow-up. The evaluation was performed by an independent clinician throughout the study.

Technique of transforaminal interbody fusion

This technique provides anterior column support where the graft is inserted from the posterior approach. The key steps include excision of the supraspinous and inter-spinous ligaments, removal of the ligamentum flavum, unilateral facetectomy, and distraction of the inter-laminar space via the base of the spinous processes. Resection of the superior part of the inferior articular process of the facet joint is performed with a Kerrison rongeur. The caudal pedicle (e.g. L5 pedicle in L4-L5 fusion) is identified with a curved ball-tip probe. Using a soft tissue dissector, the peridural tissues including the nerve root are swept and retracted in a medial and cephalad direction. This maneuver exposes the epidural vessels, which are coagulated with a bi-polar electrocautery. The annulus fibrosus is incised sharply, and the disc material is evacuated with pituitary rongeurs. The disc space is subsequently dilated with a series of dilators, allowing removal of remnant disc material. The end-plates are prepared with a curette, ensuring complete removal of the cartilaginous portion of the end-plates. Autogenous iliac crest bone graft and AGF are packed into the disc space and impacted into the anterior one-third of the disc space by a dilator. All 23 cases had placement of cages as anterior structural support: 22 were titanium mesh cages (96%); 1 was a carbon fiber cage (4%). The cages were packed with autogenous iliac crest bone graft and AGF. Supplemental posterolateral or intertransverse fusion was also performed in all cases, using autogenous iliac crest bone graft and AGF. Posterior instrumentation was performed using rigid pedicle screw systems.

Technique of AGF preparation

After the patient was anesthetized, a central line was inserted into the internal jugular vein to obtain 450 cc of whole blood. A weighing scale (Douglas Home Corporation) was used in all cases. The whole blood was spun in the centrifuge of a cell saver machine (Haemonetics Corporation), and processed through a two-stage

platelet sequestration protocol to isolate 60 cc of buffy coat concentrate. The platelet-poor plasma and red blood cells were collected and re-infused into the patient's circulation, minimizing total blood volume loss. The buffy coat concentrate was further concentrated by removing water and low-molecular-weight molecules through a proprietary ultrafiltration platelet concentration device (Ultraconcentrator, Interpore Cross). This process obtained 20 cc of AGF concentrate. The amount obtained was the same in all the patients in the study. Upon mixing the AGF concentrate with thrombin in a 1:10 volume ratio at a concentration of 100 units/ml, a firm AGF gel was created within 30–60 s. The AGF gel would then be mixed with bone grafts for application to the fusion sites (interbody and alar transverse).

Investigations

Aliquots (1-cc samples) were taken from whole blood and AGF concentrate, and analyzed for platelet, PDGF, and TGF-β concentrations. Samples for platelet counts were analyzed using a Coulter AcT-10 Hematology Analyzer. Both PDGF and TGF-β concentrations were derived from ELISA immunoassay kits (Quantikine Immunoassays, R & D Systems). Differences were assessed using the paired *t*-test. If there was evidence of non-normality in any variable (platelet, PDGF, or TGF-β), Wilcoxon's Signed Rank test was performed.

Clinical assessment

The patients were followed up at the following time intervals: 2 months, 4 months, 6 months, 12 months, and 24 months. All patients were given preoperative and postoperative questionnaires to assess their pain level, analgesic usage, and work status. The level of pain was defined by an analog pain scale, ranging from 0 (no pain) to 10 (worst pain imaginable). A paired student *t*-test was used to compare pre- and postoperative pain scores. If there was evidence of non-normality in the score, Wilcoxon's Signed Rank test would be performed. Every patient was also asked to record all analgesic medications together with their frequency and dosage. A substantial change in medication usage included a change in drug schedule (as denoted by the Controlled Substance Act), or a change in frequency, or a change in dosage of 50% or greater. The patients were asked whether or not they were working and what their job classification was pre- and postoperatively.

Radiographic assessment

The radiographs were read by the independent clinician and a radiologist. The radiological results were all assessed in a similar way using the method described by Gertzbein et al. [17]. Briefly, fusion was considered solid if the anterior interbody area was fused, if the two posterolateral areas were fused, or if all three areas were fused. A patient would be considered to have radiographic confirmation of fusion only if both the clinician and the radiologist agreed on the radiographic finding of bony consolidation, as described by Gertzbein.

Comparison with the control group

In order to determine objectively whether AGF enhanced instrumented TLIF, a comparison with an historical control group (without AGF application) was made. The historical cohort was based on the authors' past operative experience [19]. For the purpose of this study, a sub-group of the historical cohort was used as the control group. It consisted of all patients who had undergone TLIF without the application of AGF. In this group of 111 patients, 50 patients (45%) had received a single-level interbody and posterolateral fusion. Forty-eight patients (43%) had received a two-level fusion, eight patients (7%) a three-level fusion, and 5 patients (5%) a four-level fusion.

The fusion results were compared to those of the current study population comprising of patients who received TLIF and AGF application. The two groups were similar in terms of operative techniques. Supplemental posterolateral fusion was performed in all cases with autogenous iliac crest bone graft. Rigid pedicle screw instrumentation was used in all cases. The operative levels were also similar in the two groups, since only lumbar interbody fusions were compared.

Univariate comparison of the categorical variables (sex, smoking history, medical co-morbidity, previous spine surgery, number of levels fused, and presence of pseudarthrosis) between the two groups was done using Pearson's χ^2 test. When samples were of insufficient size, Fisher's Exact test would be used. Univariate comparison of continuous variables (age, body mass index, blood loss, and operating time) between the two groups was also done, using Student's *t*-test, or, when data were non-normal, Wilcoxon's Rank Sum test.

Logistic regression procedures were used if there was evidence of significance at the univariate level. This would determine whether any variable (categorical or continuous), was independently related to pseudarthrosis, after adjustment for confounding variables.

Results

Patient demographics

There were 15 women and 8 men in the study. Average age at surgery was 44.3 years old (range 21–66 years). Mean follow-up was 25 months (range 24–27 months). Twelve patients (52%) were smokers at the time of surgery. Fourteen patients (61%) had undergone previous surgery to the spine. Seven patients (30%) had medical co-morbidities; one patient had chronic obstructive pulmonary disease; three had hypertension or coronary artery disease; three had diabetes mellitus; one had epilepsy. The body mass index averaged 27.9 kg/m^2 (range 20.4–39.4 kg/m^2). Table 1 compares the patient data of the historical cohort group with that of the AGF study group.

Diagnoses in the AGF group were: degenerative disc disease in 15, pseudarthrosis in 7, spinal stenosis in 6, spondylolisthesis in 4, herniated disc in 1 (L5-S1 herniated disc associated with spondylolisthesis), and degenerative

Table 1 Patient data[a] (*TLIF* transforaminal lumbar interbody fusion, *AGF* autologous growth factors)

	TLIF + AGF (*n*=23)	TLIF (*n*=111)
Gender: M/F	8/15	42/69
Mean age at surgery (yrs)	44.3 (21–66)	47.7 (26–81)
Mean follow-up (yrs)	2.1 (2–2.3)	2.7 (2–4)
Previous surgery	14 (61%)	68 (61%)
Mean body mass index	27.9 (20.4–39.4)	28.7 (16.3–56.7)
Co-morbidities	7 (30%)	65 (59%)
Cigarette smoking	12 (52%)	62 (56%)

[a] Figures in parentheses denote either ranges or percentages

Table 2 Patient diagnoses[a]

	TLIF (n=111)	TLIF + AGF (n=23)
Degenerative disc disease	78 (70%)	15 (65%)
Herniated disc	7 (6%)	1 (4%)
Spinal stenosis	37 (33%)	6 (26%)
Spondylolisthesis	18 (16%)	4 (17%)
Degenerative scoliosis	6 (5%)	1 (4%)
Pseudarthrosis	18 (16%)	7 (30%)

[a] Diagnoses are not mutually exclusive, i.e. patients in both groups can have more than one diagnosis each

scoliosis in 1. Eleven patients had more than one diagnosis. Table 2 illustrates the breakdown of patient diagnosis in the AGF group and the historical cohort group.

Surgical data

Thirteen patients (57%) had one-level spinal fusions. Ten patients (43%) had two-level spinal fusions. TLIF was performed on all patients, using cages packed with autogenous iliac crest bone grafts and AGF gel. The interbody fusion was supplemented by posterolateral fusion with autogenous iliac crest bone grafts and AGF gel in all cases. All patients had pedicle screw instrumentation. The mean operating time was 155 min (range 105–240 min). Estimated blood loss was 609 cc (range 200–1500 cc). After surgery, all patients wore braces for a period of 4–8 weeks for comfort and support.

Laboratory analysis

The average platelet count increased by 489% from the baseline (whole blood) to the AGF concentrate stage (Table 3). This was statistically significant, using paired student t-test (P<0.0001). Similarly, as illustrated in Table 3, a corresponding increase in PDGF and TGF-β concentrations was obtained (P<0.0001) from the whole blood to the AGF concentrate stage.

Table 3 Concentrations of platelets, platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β) in whole blood and AGF concentrate: mean values and standard deviations (SD)

	Whole blood	AGF concentrate	P-value[a]
Platelet count (cells/ml)	270,479 (55,098)	1,311,739 (54,038)	0.0001
PDGF (ng/ml)	28.9 (4)	170.9 (4.9)	0.0001
TGF–β (ng/ml)	49.6 (4.8)	199.4 (6.3)	0.0001

[a] Differences were assessed using a paired t-test. Due to some non-normality in the platelet variable, Wilcoxon's Signed Rank test was also performed, with the same P-value as the t-test

Clinical results

Overall pain scores showed a decrease from 7.7±0.47 preoperatively to 3.7±1.13 at the most recent follow-up (P<0.0001). Two patients did not report substantial improvement of pain after surgery. One had pseudarthrosis and one developed spinal stenosis at a level above the fusion after 12 months. Sixteen patients (67%) decreased their analgesic usage after surgery, five patients (21%) did not notice any substantial change in analgesic usage, and two (9%) reported increased use of analgesics.

With regard to work status, 15 patients were unemployed preoperatively. Of these, 13 patients continued to be unemployed. The remaining two patients managed to return to work, with one returning to a less physically demanding job. Three of the eight patients who were working preoperatively continued to work at a similar level. Two of the eight patients returned to a less physically strenuous job. The remaining three had claimed disability and remained unemployed.

Radiographic assessment

Serial radiographs revealed evidence of spinal fusion in 22 out of 23 patients (96%) at a minimum of 24 months follow-up. The fusion rate was 100% for single-level fusions and 90% for two-level fusions.

Comparison with historical cohort

The indications for surgery in both the AGF treatment and the historical cohort group are shown in Table 2. The different indications were present in similar proportions in the two groups, except for pseudarthrosis. The proportion of patients who underwent the surgical treatment for pseudarthrosis was higher in the AGF treatment group (30 vs 16%). A comparison of the results of TLIF with and without AGF are shown in Table 4. There was no significant difference in pseudarthrosis rates between the AGF treatment group and the historical cohort. Analysis of the 111 patients who underwent TLIF (without AGF) in the historical cohort revealed an overall pseudarthrosis rate of 6% (7 out of 111). The pseudarthrosis rate of the 23 patients in the current study who had TLIF and AGF was 4%. The non-union rate for single-level fusions was 4% (2 out of 50) in the historical cohort and 0% in the current treatment group. The pseudarthrosis rate for multiple-level fusions was 8% (5 out of 61) in the historical group and 10% (1 out of 10) in the current treatment group. None of the variables (age, sex, medical co-morbidity, smoking history, number of levels fused, previous surgery, body mass index, operative time, and estimated blood loss) was significantly related to presence/absence of pseudarthrosis/non-union, with P≥0.20. There was no

Table 4 Univariate comparison of procedures (TLIF vs TLIF + AGF). None of the variables in this table approached the significance level of $P<0.05$[a] (*BMI* body mass index, *OR* operating room, *EBL* estimated blood loss)

	TLIF only (n=111)	TLIF + AGF (n=23)
Gender		
Male	42	8
Female	69	15
Medical problems		
None	46	16
1 or more	65	7
Smoker		
Yes	62	12
No	49	11
Levels fused		
1	50	13
2 or more	61	10
Previous surgery		
Yes	68	14
No	43	9
Age: mean ± SD	47.7±11.5	44.3±11.4
BMI: mean ± SD	28.7±6.6	27.9±4.4
OR time: mean ± SD	172±46.6	155±21.5
EBL: mean ± SD	808±686.6	609±406.2

[a] Differences for categorical variables were assessed using Pearson's χ^2 tests or, when sample sizes were insufficient, Fisher's Exact test. Differences in means (medians) were assessed using Student's t-test, or, when data were non-normal, Wilcoxon's Rank Sum test

point in logistic regression, given the lack of significance at the univariate level.

Excluding patients who developed pseudarthrosis, we found faster bony healing in the current treatment group. At 4 months post-operatively, 16 out of 23 patients (70%) who had AGF application showed radiographic evidence of bony consolidation. In contrast, only 40 out of 111 patients (36%) in the historical cohort had evidence of bony healing. The difference was statistically significant ($P<0.05$), using the chi-square test. At 6 months post-operatively, 22 out of 23 patients (96%) in the AGF treatment group had bony consolidation on radiographs. This was significantly more ($P<0.05$) than the historical cohort group, who showed bony fusion in 71 out of 111 patients (64%).

Complications

Two patients had dural tears that were recognized and repaired intra-operatively. Both went on to uneventful wound and bony healing. There was one case of pseudarthrosis. This patient was a chronic smoker with previous lumbar fusion at the L4-L5 level with threaded cages that ended up with pseudarthrosis. She also had degenerative disc disease and spinal stenosis at the L5-S1 level when she presented to us. She underwent TLIF at the L5-S1 level, as well as posterolateral fusion from L4 to S1. Unfortunately, she developed pseudarthrosis from L4 to S1.

Discussion

Our study is the first prospective clinical study with a minimum 2-year follow-up on the use of AGF in spinal fusion. In our study, we obtained a 489% increase in the platelet counts from the baseline to the AGF concentrate stage. PDGF levels increased 5.9 fold from the baseline to the AGF stage. TGF-β levels increased four fold from the baseline to the AGF stage. We achieved a 100% fusion rate in single-level fusion cases. The fusion rate for two-level fusion cases was 90%. Comparison between the current group and the historical cohort revealed no significant difference in pseudarthrosis rates (4 vs 6%). The pseudarthrosis rate was noted to be lower in single-level fusions for the current group (0%) than for the historical cohort (4%). The non-union rate for multiple-level fusions was marginally higher for the current group (10%) than for the historical cohort (8%). A pseudarthrosis rate of 0% reported in earlier studies [29, 35] was not repeated in our study.

In an attempt to improve the fusion success rates in low back surgery, researchers have been investigating various alternatives to autologous bone graft. Examples are the use of allografts, osteoinductive growth factors such as BMPs, and synthetic osteoconductive carriers [40]. Others have examined and applied the use of adjunctive internal fixation (pedicle screws, cages), electrical or magnetic stimulation, and ultrasound therapy [40]. The use of spinal instrumentation [42] has become an important and popular adjunct to bone grafting in lumbar fusion surgeries, further increasing the fusion rates (to 80–90%). To reduce the need for harvesting large amounts of autogenous iliac crest bone graft, cages have been developed that function to distract a collapsed intervertebral disc, provide immediate rigidity, and act as a structural anterior column support and bone graft carrier [39]. Unlike bone grafts, there is no risk of graft collapse leading to post-operative loss of correction and pseudarthrosis [38].

Current research in bone biology has focused on the biology of osteoinduction and stem cell differentiation. We now have the ability to sequence and clone various forms of BMPs, such as rhBMP-2 and rhBMP-7 (OP-1). One study [5] reported that rhBMP-2 generates bone in humans in a predictable fashion, and the dose that works in nonhuman primates also works in humans. In recent years, a simple technique has been used to intra-operatively concentrate the patient's own platelet-rich plasma into AGF. The AGF contains various growth factors including PDGF, TGF-β, IGF, and various BMPs. There are currently two proprietary systems on the market with the ability to har-

vest AGF: Ultraconcentrator (Interpore Cross) and Symphony (Depuy-Acromed). The main advantage of AGF over synthetically derived BMPs is its easy availability and its cost-effectiveness. AGF costs about US$400 (€348) per procedure – far less than BMPs, which are expected to cost US$3,000–US$5,000 (€2612–€4353) per use [31].

Performing TLIF in conjunction with posterolateral fusion and rigid pedicle screw instrumentation (360° fusion) requires a lot of surgical effort. On top of this, preparing and adding AGF to the autogenous bone graft makes the effort even larger. There will be questions raised with regard to the justification of surgical costs related to the increased operating time and the cost of harvesting the AGF. In our practice, a cell-saver machine is utilized routinely, and it can be concurrently used to isolate buffy coat concentrate, which can then be passed through the ultraconcentrator to obtain the AGF concentrate. Thus, the only cost involved relates to the use of the ultraconcentrator, which is much cheaper than using commercially available BMPs. In our hands, prolongation of the operating time is also not a significant problem, as the preparation and mixing of the AGF with the autogenous bone graft is performed by the surgical scrub technician, leaving the surgeon and his assistant to concentrate on the preparation of the fusion bed.

In our practice, significant number of cases belong to the "high-risk category" for pseudarthrosis: previous surgery (61%), smoker (52%), and pseudarthrosis from previous surgeries (30%). Circumferential or 360° fusion (TLIF plus posterolateral fusion) gives the best chance for spinal arthrodesis success. Our fusion rates in both the AGF group and the historical cohort group compare favorably with a recent TLIF study [28]. In that study, 90% had solid fusions radiographically and 79% had excellent or good clinical outcomes. In our own previously reported study [19], we compared two techniques of circumferential fusion (anterior/posterior fusion versus transforaminal interbody and posterolateral fusion). TLIF is the preferred technique, because it is associated with a shorter operating time, less blood loss, shorter hospital stay, and lower incidence of complications. The pseudarthrosis rate for TLIF (6%) was also lower than that for anterior/posterior fusion (15%), although the difference did not reach statistical significance (P=0.07).

Though technically more demanding, interbody and circumferential fusion is preferred over traditional posterolateral fusion because of higher fusion rates and the ability to remove the disc as a pain generator [16, 23]. The higher fusion rates are due to a large surface area for fusion, and bone graft being subjected to compressive loads, which is advantageous in achieving fusion [26]. Other advantages of interbody fusion are immediate anterior column load sharing and the ability to restore the sagittal alignment while indirectly decompressing the neuroforamen [26].

The type of carrier that would be ideal for the delivery of these growth factors is yet to be defined. AGF uses thrombin to create a gel containing the growth factors for implantation onto fusion sites. We find the gel to be less than ideal as a carrier for the growth factors, as it has a tendency to fragment during implantation. It may also be suctioned away easily. Perhaps when better carriers are developed that can retain the growth factors better and for longer, then results superior to autografts alone may be achieved.

Although there is no clear-cut evidence that AGF has any statistically positive effect on fusion success rates, the application of AGF does speed up bony healing in cases that achieved eventual bony consolidation. In our study, bone healing was clearly accelerated by the application of AGF. All 22 patients who had evidence of bony healing did so within the first 6 months after surgery. Although further studies are needed to validate these findings, our experience suggests that the effects of these growth factors probably last for no longer than 6 months. AGF cannot entirely substitute for bone grafts, since growth factors lack the structural strength present in bone grafts. Increased stiffness rather than strength is the early benefit after AGF treatment [41].When used in conjunction with bone grafts, AGF may have the potential to enhance bone growth and early spinal fusion. AGF may provide a biological boost to an osteoconductive bone graft as well as autograft [41].

One of the shortcomings of this paper is that it is not a prospective randomized controlled trial. Another is the relatively small number of patients (with mixed diagnosis) in the study, which may not be large enough to detect a difference from the historical cohort of patients without AGF application. The large number of patients having previous surgeries (61%) and pseudarthrosis (30%) may also complicate the results as far as judging fusion rates and the effectiveness of the use of AGF is concerned. In these cases, the local environment for the graft is not conducive. The blood supply may not be adequate, thus limiting available oxygen, nutrients, neovascularization, and cellular migration to the fusion mass [40]. On the other hand, it is also in these unfavorable conditions that bone graft adjuncts, e.g. osteoinductive growth factors (AGF), are potentially useful.

The fact that the two group sizes are unequal does not pose a problem in statistical analysis and the value derived from it. In our analysis, sample size information is incorporated into the statistics as part of the computation of statistical precision (i.e. variance), as well as a weighting factor in the degrees of freedom computation. Rarely are group sizes equal in clinical studies, and equality of groups is therefore not a requirement for any of the statistical methods used.

Conclusion

Although the use of AGF in TLIF procedures may demonstrate faster fusions, it does not result in overall increase in spinal fusion rates. Further refinements in the techniques of AGF application must be performed, both in the laboratory and clinical settings, before it can be applied routinely in spinal fusions.

References

1. An HS, Lynch K, Toth J (1995) Prospective comparison of autograft vs allograft for adult posterolateral lumbar spine fusion: differences among freeze-dried, frozen, and mixed grafts. J Spinal Disord 8:131–135
2. Arm DM (2000) A comparison of autologous growth factors (AGF™) and platelet gel. Presented at the 16th International Symposium – Bone growth Factors and Substitutes, Coronado
3. Arm DM, Lowery GL, Hood AG, Shors EC (1999) Characterization of an autologous platelet gel containing multiple growth factors. Presented at the 45th Orthopaedic Research Society Meeting, Anaheim
4. Arm DM, Ponticiello M, Shors EC (2001) Autologous growth factors: characterization and clinical use. J Bone Joint Surg Br 83 [Suppl III]:366
5. Boden SD, Zdeblick TA, Sandhu HS, Heim SE (2000) The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 25:376–381
6. Bostrom MP, Camacho NP (1998) Potential role of bone morphogenetic proteins in fracture healing. Clin Orthop 355 [Suppl]:274–282
7. Buckwalter JA, Cruess RL (1991) Healing of the musculoskeletal tissues. In: Rockwood CA, Green DP (eds) Fractures in adults. JB Lippincott, Philadelphia, pp 181–222
8. Buckwalter JA, Glimcher MJ, Cooper RR, Recker R (1995) Bone biology. II. Formation, form, modeling, remodeling, regulation of cell function. J Bone Joint Surg Am 77:1276–1289
9. Canalis E (1985) Effect of growth factors on bone cell replication and differentiation. Clin Orthop 193:246–263
10. Canalis E, McCarthy TL, Centrella M (1989) Effects of platelet derived growth factor on bone formation in vitro. J Cell Physiol 140:530–537
11. Caplan AI (1991) Mesenchymal stem cells. J Orthop Res 9:641–650
12. Centrella M (1989) Platelet-derived growth factor enhances deoxyribonucleic acid and collagen synthesis in osteoblast-enriched cultures from fetal rat parietal bone. Endocrinology 125: 13–19
13. Curylo LJ, Johnstone B, Petersilge CA, Janicki JA, Yoo JU (1999) Augmentation of spinal arthrodesis with autologous bone marrow in a rabbit posterolateral spine fusion model. Spine 24: 434–439
14. De Palma AF (1968) The nature of pseudoarthrosis. Clin Orthop 59:113–118
15. Eie N, Solgaard T, Kleppe H (1983) The knee-elbow position in lumbar disc surgery: a review of complications. Spine 8:897–900
16. Fujimaki A, Crock HV, Bedbrook GM (1982) The results of 150 anterior lumbar interbody fusion operations performed by two surgeons in Australia. Clin Orthop 165:164–167
17. Gertzbein SD, Betz R, Clements D, Errico T, Hammerberg K, Robbins S, Shepherd E, Weber A, Kerina M, Albin J, Wolk D, Ensor K (1996) Semirigid instrumentation in the management of lumbar spinal conditions combined with circumferential fusion. A multicenter study. Spine 21:1918–1926
18. Gospodarowicz D (1983) Growth factors and their action in vivo and in vitro. J Pathol 141:201–233
19. Hee HT, Castro FP, Majd ME, Holt RT, Myers L (2001) Anterior/posterior lumbar fusion versus transforaminal lumbar interbody fusion: analysis of complications and predictive factors. J Spinal Disord 14:533–540
20. Howes R, Bowness JM, Grotendorst GR, Martin GR, Reddi AH (1988) Platelet derived growth factor enhances demineralized bone matrix induced cartilage and bone formation. Calcif Tissue Int 42:34–38
21. Joyce ME, Jingushi S, Scully SP, Bolander ME (1991) Role of growth factors in fracture healing. Prog Clin Biol Res 365:391–416
22. Kasperk CH, Wergedal JE, Mohan S, Long DL, Lau KH, Baylink DJ (1990) Interactions of growth factors present in bone matrix with bone cells: effects on DNA synthesis and alkaline phosphatase. Growth Factors 3:147–158
23. Kozak JA, O'Brien JP (1990) Simultaneous combined anterior and posterior fusion. An independent analysis of a treatment of the disabled low-back pain patient. Spine 15:322–328
24. Lane JM (2001) BMPs: why are they not in everyday use? J Bone Joint Surg Am 83 [Suppl 1]:161–163
25. Lane JM, Tomin E, Bostrom MP (1999) Biosynthetic bone grafting. Clin Orthop 367 [Suppl]:107–117
26. Lin P, Cautilli R, Joyce M (1983) Posterior lumbar interbody fusion. Clin Orthop 180:154–167
27. Lindholm TS, Ragni P, Lindholm TC (1988) Response of bone marrow stroma cells to dimineralized cortical bone matrix in experimental spinal fusion in rabbits. Clin Orthop 230:296–302
28. Lowe TG, Tahernia AD, O'Brien MF, Smith DAB (2002) Unilateral transforaminal posterior lumbar interbody fusion (TLIF): indications, technique, and 2-year results. J Spinal Disord Tech 15:31–38
29. Lowery GL, Kulkarni S, Pennisi AE (1999) Use of autologous growth factors in lumbar spinal fusion. Bone [Suppl] 25:47–50
30. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR (1998) Platelet-rich plasma. Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol 85:638-646
31. Nather A, Hee HT (2002) New frontiers in spinal surgery. In: Nather A (ed) Research methodology in orthopaedics and reconstructive surgery. World Scientific, New Jersey, pp 551–574
32. Nimni ME (1997) Polypeptide growth factors: targeted delivery systems. Biomaterials 18:1201–1225
33. Noda M (1998) In vivo stimulation of bone formation by transforming growth factor-β. Endocrinology 124:2991–2994
34. Pfeilschifter J (1990) Stimulation of bone matrix apposition in vitro by local growth factors: a comparison between insulin-like growth factor I, platelet-derived growth factor, and transforming growth factor-β. Endocrinology 127:69–75
35. Scott-Young M (2001) Spinal fusion using autologous growth factor. J Bone Joint Surg Br 83 [Suppl III]:366

36. Seppa H, Grotendorst G, Seppa S, Schiffmann E, Martin GR (1982) Platelet-derived growth factor is chemotactic for fibroblasts. J Cell Biol 92:584–588
37. Slater M, Patava J, Kingham K, Mason RS (1995) Involvement of platelets in stimulating osteogenic activity. J Orthop Res 13:655–663
38. Tullberg T, Brandt B, Rydberg J, Fritzell P (1996) Fusion rate after posterior lumbar interbody fusion with carbon fiber implant: 1-year follow-up of 51 patients. Eur Spine J 5:178–182
39. Vaccaro AR, Ball ST (2000) Indications for instrumentation in degenerative lumbar spinal disorders. Orthopedics 23:260–271
40. Vaccaro AR, Chiba K, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC (2002) Bone grafting alternatives in spinal surgery. Spine J 2:206–215
41. Walsh WR, Loefler A, Nicklin S, Arm D, Yu Y (2001) Autologous growth factors for use in spinal fusion. J Bone Joint Surg Br 83 [Suppl III]:366–367
42. Yashiro K, Homma T, Hokari Y, Katsumi Y, Okumura H, Hirano A (1991) The Steffee variable screw placement system using different methods of bone grafting. Spine 16:1329–1334
43. Zdeblick TA (1993) A prospective randomized study of lumbar fusion. Preliminary results. Spine 18:983–991