REVIEW ARTICLE

Bone Graft Substitutes for Anterior Lumbar Interbody Fusion

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The procedure of anterior lumbar interbody fusion (ALIF) is commonly performed on patients suffering from pain and/or neurological symptoms associated with disorders of the lumbar spine caused by disc degeneration and trauma. Surgery is indicated when prolonged conservative management proves ineffective. Because an important objective of the ALIF procedure is solid arthrodesis of the degenerative spinal segment, bone graft selection is critical. Iliac crest bone grafts (ICBG) remain the "gold standard" for achieving lumbar fusion. However, patient dissatisfaction stemming from donor site morbidity, lengthier operating times and finite supply of ICBG has prompted a search for better alternatives. Here presented is a literature review evaluating available bone graft options assessed within the clinical setting. These options include autografts, allograft-based, synthetic and cell-based technologies. The emphasis is on the contentious use of recombinant human bone morphogenetic proteins, which is in widespread use and has demonstrated both significant osteogenic potential and risk of complications.

Key words: Allograft; Anterior lumbar interbody fusion; Autograft; Bone graft substitutes

Introduction

The earliest report of anterior lumbar interbody fusion (ALIF) was in 1932 by Capener, who described its use in surgical management of spondylolisthesis[1] Subsequent reports were by Mercer for the treatment of disc pathology[2] and Burns in 1933[3]. Its many advantages over posterior fusion, such as avoidance of paraspinal muscular injury, have resulted in increasing popularity of ALIF procedures. Although abundant clinical studies assessing bone graft alternatives for anterior cervical discectomy and fusion have been published[4], grafting options for ALIF are not well documented in the literature.

Successful arthrodesis depends on numerous surgical and host factors, including selection of a bone graft with elements critical for bone regeneration. Osteogenic properties of a graft enable it to provide stem cells and osteoblasts directly to regenerating bone, whereas osteoinductive factors such as bone morphogenetic proteins (BMPs) and other growth factors stimulate differentiation of progenitor cells into osteoblasts and osteocytes for new bone formation. An osteoconductive scaffold containing hydroxyapatite and collagen facilitates neovascularization that supports and maintains bone growth[4–6]. For fusions of the lumbar spine, autologous bone is the "gold standard" with which graft alternatives are compared because it encompasses these ideal properties, whilst also conferring minute risk of infection or host rejection and having excellent fusion rates. However, its disadvantages include donor site pain, blood loss, neurovascular injury, increased duration of hospital stay and limited availability[7–9]. To bypass these complications, many alternatives with potential for better patient outcomes are emerging (Table 1). Unfortunately, a lack of published clinical trials specifically assessing ALIF procedures limits the number of graft options accepted as safe alternatives to autografts. Also of note is that authors' definitions of "successful fusion" vary, which can influence claimed study outcomes.

Bone graft materials can be used as stand-alones or supplement other grafts or synthetic cages[10–14]. Such materials include graft enhancers, which strengthen the fusion mass, and graft extenders, which help achieve fusion with a reduced primary graft component[15]. For the purpose of this review, our

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TABLE 1 Summary of bone graft alternatives in ALIF procedures

Graft option	Fusion rates (%)	Type of graft	Properties				Advantages	Disadvantages	Complications with graft	Cost†
			Osteogenesis	Osteoconduction	Osteoinduction	Strength				
Autograft	51.9–100	Cancellous bone	+++	+++	++	–	Host tissue; natural biological properties	Finite supply, increased surgical time, blood loss, pain	DSM	Nil
		Cortical bone	+	+	+	–				
Allograft	42.8–100						No DSM, abundant supply, versatility as extender and/or graft	Risk of bacterial contamination, viral transmission, host rejection.	Graft collapse	++
Cancellous		Fresh-frozen	–	++	+	–				
		Freeze-dried	–	++	+	–				
Synthetic										
DBM	90*		–	+	++	–	No DSM, useful as bone extender	Lacks strength, only one ALIF clinical trial	Graft collapse	++
Ceramics	79.3–100		–	+++	–	+	No DSM	Not effective as stand-alone, lack of ALIF clinical trials	Cage subsidence	+
rhBMP-1	44–100		–	++	+++	++	No DSM, very potent osteoinductive properties, high fusion rates	Rare, costly, uncertainty surrounding appropriate clinical dosage	Heterotopic bone formation, early osteolysis, graft subsidence, inflammation	+++

*only one clinical study on application of DBM to ALIF has been conducted; †cost of grafts are approximate and relative only. DBM, demineralised bone matrix; DSM, donor site morbidity; *rhBMP-2*, recombinant human bone morphogenetic protein 2; "+" and "–" represent relative strengths of properties, with "+" meaning the presence of the property, and "–" meaning its absence.

focus is the various bone graft options currently available for ALIF procedures and their efficacy in achieving successful arthrodeses. Because of the diversity in ALIF techniques, internal and external instrumentation, cage technologies and surgical techniques are beyond the scope of this review.

Methods

A systematic search was conducted on the Medline database (January 1980 to July 2012) using key words and MeSH terms for autograft, autologous harvest, iliac crest, allograft, demineralized bone matrix, ceramics, hydroxyapatites, calcium phosphates, BMPs (rhBMP-2, InFuse) with ALIF, lumbar fusion, spinal fusion and fusion rates. Only English language and human studies were evaluated. Related articles were also assessed, and original articles are cited where possible. Only studies on ALIFs are included.

Autografts

Because of its potent biological properties, autologous bone graft harvested from the patient's own iliac crest has been widely accepted by surgeons for lumbar arthrodesis for many decades[11–14]. Although cortical grafts provide better structural support to the spinal column than does cancellous bone, most autografts used are composed of cancellous bone. In addition to imparting greater osteoconductivity, which helps achieve consolidation of arthrodesis, less surgical exposure is required for harvesting of cancellous graft[6].

Rates of successful fusion for autologous iliac crest bone grafts (ICBG) vary widely in published reports. Most current ALIF studies claim arthrodesis rates for single-level un-instrumented fusions varying from 78.8%–100%[15–20]. It is important to note that in one study that combined allografts with autograft bone dowels with the objective of reducing donor site morbidity (DSM), differences in fusion outcomes were statistically insignificant compared with stand-alone autografts[16]. Other studies in which ICBG was combined with posterior fixation in either single or double-level fusions have fusion rates of 71%–98.6%[21–23].

Autografts are now often used in combination with "cages" or femoral ring allografts (FRA); this places less pressure on graft harvesting, making stand-alone autograft dowels less desirable nowdays. Fusion rates using threaded titanium based devices have generally been high, particularly with posterior instrumentation: 93%–98% in stand-alone procedures[24,25] and 98.6% with posterior fixation[23]. A study using carbon-fiber cages reported a fusion rate of 73% at 24 months follow-up[26,27]. Other studies that examined stand-alone hybrid grafts have reported fusion rates fluctuating from 51.9%–75%[25,27–29]. These lower arthrodesis rates are apparently attributable to the use of FRA as cage constructs because allografts are associated with slower rates of bone remodeling and increased resorption than autografts[30]. FRAs also lack rotational stability[31]. Extra fixation (including posterior pedicle screws) has been cited in published reports as achieving superior fusion rates ranging from 98%–100%[27,28,31,32].

Published studies report suboptimal fusion rates with the use of translaminar screws. A prospective randomized blinded study conducted by Thalgott *et al*. assessed FRA in combination with translaminar screws in patients undergoing circumferential ALIF procedures and reported a suboptimal fusion rate of 71.4% at 24 months[33]. Moreover, another study comparing stand-alone ALIF and supplementary stabilization with translaminar screws reported no significant difference in the number of levels fused ($P = 0.38$), the fusion rates being 55% and 58%, respectively[34]. However, pedicle screw stabilization provided a significant improvement in rates of arthrodesis (88% fusion rate, $P < 0.01$), with no significant difference between unilateral and bilateral pedicle screws in fusion rates ($P = 0.44$).

It appears that autografts can yield favorable fusion results, especially when used in conjunction with posterior fixation devices. Despite this, graft harvesting inevitably contributes to a greater incidence of medical complications, particularly in older patients. A retrospective review of 414 lumbar surgeries involving ICBG reported 5.8% and 10% major and minor complications, respectively[35]. Major complications include abdominal herniation, vascular trauma, deep infections and iliac wing fractures, whereas minor complications include superficial infections, hematoma formation and uncomplicated seromas. Likewise, in a recent systematic review of 6449 patients who had undergone ICBG harvesting, Dimitriou *et al*. reported an overall complication rate of 19.37%, the rates of minor complications differing significantly between anterior and posterior iliac crest donor sites: rates of infections, hematomas and hypertrophic scars were significantly higher when the anterior iliac crest was used[36]. Although the study cohort was large, because outcomes were collected from all ICBG harvests, the findings are not specific to ALIF procedures. Another concern is chronic persistent pain at the donor site; Sasso *et al*. reported an incidence of 31% in a prospective study of 202 patients[37]. Summers and Eisenstein also reported that 25% of patients had "significant" graft site pain following ALIF[8]. Other reported disadvantages of ICBG include graft collapse, adjacent disc degeneration, neurological injury, pelvic fracture, gait disturbance, cosmetic deformity and hip subluxation[15–18,38]. However, the primary deterrent to ICBG harvesting for patients and surgeons is the subjective perception that harvesting is the most formidable part of the fusion procedure[39].

Trials of harvesting autologous bone grafts from alternative locations such as adjacent vertebral bodies have been promising, with reduced donor site morbidity rates and no adverse events[40,41]. However, these autograft are used in conjunction with cages and posterior fixation.

Allografts

Allogenic cancellous bone can be obtained from cadaveric femora or iliac crests and has traditionally been used as an alternative to autografts[42]. In ALIF procedures, allografts are versatile, acting as graft extenders in combination with autografts or threaded fusion devices[38]. In terms of biomechanical properties, allograft bone is biologically inferior to autologous bone because of its lack of osteoinductivity and

osteogenic strength. However, compared to autologous grafts, allograft bone is readily available and circumvents issues associated with autografts such as prolonged operating time, increased blood loss and donor site morbidity[5,43,44]. Another advantage is its long shelf life[45]. Furthermore, allograft bone has biological advantages over metallic devices because of its natural elasticity and greater potential for graft incorporation through resorption via Haversian canals[46,47]. These advantages have led to the creation of "biological cages" such as FRAs, which also act as structural supports. Limitations to the use of allografts include possible risk of host rejection, bacterial contamination and inter-individual transfer of infectious agents such as HIV and hepatitis virus in the absence of inactivation procedures. The risk of HIV transmission in thoroughly screened allograft bone is 1 in 1.6 million[48]. This risk is lower in freeze-dried preparations than in fresh-frozen bone because of the additional processing of the former[5,6]. Although processing decreases the antigenicity of allografts by reducing osteogenetic and osteoinductive factors, it is still a suboptimal alternative to autografts.

Several clinical studies have evaluated the efficacy of allografts in ALIF procedures. In a retrospective study conducted by Sarwat *et al*. in which FRA with cancellous allograft chips were used as fillers, fusion rates were reportedly 100%, 97.7% and 91.7% for one, two and three level fusions, respectively[49]. Favorable fusion rates of 83%–100% have also been reported for other allograft studies[50–53]; however, a suboptimal rate of 79% was reported for one study[54]. Further, Loguidice *et al*.[55] and Dennis *et al*.[56] retrospectively compared cadaveric allografts and autografts and found no statistically significant differences in fusion rates. One study using freeze-dried allogenic corticocancellous bone in polyetheretherketone cages in stand-alone ALIF procedures reported unfavorable fusion rates of 70.6%[57], whereas other studies that have evaluated the use of allografts in cages in conjunction with percutaneous pedicle fixation have reported fusion rates as high as 87.5%–100%[58–62]. Moreover, donor site complications are avoided with the use of allografts. However, several studies have demonstrated that allografts are inferior to autografts for ALIF. Kumar *et al*. reported a poor union rate of 66% when using femoral strut allografts[63]. These results were similar to those of a retrospective study of 11 ALIF cases using fibular allografts conducted by Vamvanij *et al*. in which only 60% of allograft cases achieved fusion[64]. These reports indicate that using FRAs with cancellous allograft filler provides arthrodesis rates that are comparable to fusion with autografts and superior to those of other forms of allograft including stand-alones. This superiority may be attributable to the potent osteoconductive factors in cancellous bone that provide a bony matrix to support fusion processes.

Demineralized Bone Matrices

Demineralized bone matrices (DBMs) are created by acid extraction of allograft bone, a process that isolates type 1 collagen proteins, in addition to numerous growth factors including BMPs. Although DBMs lack structural strength, their possession of osteoconductive and osteoinductive properties makes them effective bone graft extenders for use in spinal fusion procedures.

The efficacy of DBMs as a graft substitute in ALIF procedures has not yet been elucidated because there is are few clinical studies exploring its use. Thalgott *et al*. published a case series study on ALIF procedures evaluating the use of DBMs in conjunction with titanium mesh cages and coralline hydroxyapatite (HA)[65]. Fusion rates were 90% and it was concluded that DBM is effective when used in circumferential ALIF applications in combination with rigid instrumentation. Currently, DBMs are recommended as graft substitutes for ALIF only in conjunction with structural carriers. The higher rate of graft collapse and pseudoarthrosis in anterior cervical fusion found in a prospective Level 1 study conducted by An *et al*.[66] shows the need for further clinical studies to determine the safety and efficacy of DBMs as graft substitutes in ALIF procedures.

Ceramics

To date, few clinical studies have reported the use of ceramics as graft alternatives in ALIF procedures. Ceramics can be ideal graft extenders or substitutes because they are non-immunogenic and contain no risk of disease transmission. An example of commercially available ceramics for ALIFs is Pro Osteon Coralline Hydroxyapatite (Interpore Cross International, Irvine, CA, USA).

Coralline HA is processed from sea coral made of calcium carbonate and is completely non-immunogenic[67]. The microstructure of HA is similar to that of cortical bone; its porous structure contributes to its potent osteoconductive properties. The only study on the application of coralline HA (Pro Osteon 200) in human ALIF procedures was a retrospective review of 20 patients performed by Thalgott *et al*.[67] The rate of arthrodesis was 93.8% by level, and 90% by patient numbers at a mean follow-up of 48 months. Clinical outcomes were also favorable, 80% of patients having reported "good or excellent" pain relief. Although the ALIFs were a component of circumferential fusions, these findings provide a good safety and efficacy profile for coralline HA and indication of its possible role in future ALIF procedures. Unfortunately, Pro Osteon contains no osteoinductive or osteogenic properties; however, when loaded in compression with posterior fixation, solid arthrodesis can be achieved. According to Thalgott *et al*., Pro Osteon 200 achieves 100% resorption in 15–20 years as evidenced by identification of bony ingrowth in most postoperative radiographs.

The use of synthetic calcium phosphates has also been a relatively new frontier in ALIF procedures. In a small retrospective study of five patients who had undergone ALIF with pedicle-screw fixation, Linovitz and Peppers documented the use of β-tricalcium phosphate (β-TCP) in combination with venous blood as a bone graft extender inside FRA constructs[68]. All patients achieved 100% fusion at 3–6 months follow-up and there were reportedly no problems with the grafts. β-TCP is osteoconductive and resembles the structure of cancellous

bone. However, because of its lack of osteoinductive or osteogenic properties, supplementation by venous blood is essential for arthrodesis. Another study conducted by Pimenta *et al.* using a combination of HA and β-TCP achieved similar results with a reported fusion rate of 95.83% at 12 months follow-up[69]. However, a similar study to that of Linovitz and Peppers with a larger cohort of 29 patients of mean age 65 years (range, 61–71) reported unfavorable fusion rates of 79.3% despite translaminar screw fixation[70]. The authors noted that although posterior augmentation can provide superior spinal stability in comparison to stand-alone ALIF procedures, factors such as multilevel fusion or severe osteoporosis associated with significant cage subsidence can compromise fusion rates. The conflicting outcomes produced by these studies indicate the need for further clinical trials to confirm the efficacy and safety of these synthetic graft materials in all ALIF procedures.

Bone Morphogenetic Protein

Since the discovery of growth factor BMP by Urist in 1965, the availability of this protein, a member of the transforming growth factor-beta superfamily, has evolved dramatically from finite yield extraction from cadaveric bone to using recombinant gene technology to produce adequate amounts of rh-BMPs[71]. These are currently considered the most successful autograft alternative because they possess potent osteoinductive properties and reportedly have a high rate of early post-surgical fusion. BMPs are reportedly effective as both bone graft extenders and substitutes. These proteins induce bone growth by triggering the differentiation of pluripotent mesenchymal cells into osteoblasts to generate a bony lattice[72]. Despite their osteoinductive potential, BMPs remain costly and rare, and have a high risk of complications.

RhBMP-2 (Infuse, Medtronic, Minneapolis, MN, USA) and rhBMP-7 (OP-1, Olympus, Tokyo, Japan) are the only BMPs that have so far been evaluated in human clinical trials. In July 2002, the Food and Drug Administration approved rhBMP-2 (Infuse, Medtronic) for use within titanium cages in ALIF procedures[73,74]. The clinical success of rhBMP-2 has been demonstrated through multiple centers; compared to patients with ICBG it is associated with shorter operative times and hospital stays and decreased blood loss[73,75].

Clinical Trials with Bone Morphogenetic Protein

Burkus *et al.* reported superior fusion rates with rhBMP-2 compared to ICBG in the largest published prospective randomized control study[73]. The two year fusion success rate was 94.5% in 143 patients who underwent ALIF with rhBMP-2 (InFuse 1.5 mg/mL: 4.2–8.4 mg) combined with collagen and interbody fusion cages. In comparison, the ICBG control cohort of 137 patients achieved a fusion rate of 88.7%. Furthermore, 5.9% of patients in the control group experienced adverse events related to ICBG harvesting, including neurological injury, hematomas and infections. Another 32% of control patients reported persistent donor site pain 24 months post-surgery, which further emphasizes the problem of donor site morbidity. The same author produced another prospective non-blinded study using threaded cortical allograft dowels with either InFuse (Medtronic, 24 patients) or autologous grafts (22 patients) in single level un-instrumented ALIF procedures[29]. The fusion rate was 100% for InFuse (Medtronic) and only 89.5% and 68.4% for patients in the control autograft group at 12 and 24 months, respectively. In addition to superior fusion rates, rhBMP-2 provided greater relief of back and leg pain in participants with degenerative lumbar disc disease than in the control group, and a faster recovery time as suggested by Oswestry Disability Questionnaire scores. In contrast, members of the control group reported hip pain throughout the study period, demonstrating an advantage of rhBMP-2 in that it obviates the need for autografts and their associated donor site morbidity.

Furthermore, other comparison studies with allografts or autografts have reported 100% fusion rates with InFuse (Medtronic)[50,75–77]. Despite published reports supporting the use of rhBMP-2 as a good alternative to autografts in ALIF procedures, because many of these studies were very small, their results should serve as examples of successful cases rather than a comprehensive approval of the efficacy of BMPs.

In addition, higher non-union rates have been reported with rhBMP-2 than with ICBG. Highlighting the need for more large studies, in a similar prospective study led by Pradhan *et al.* using femoral ring allografts with either rhBMP-2 or autografts, the non-union rate in patients who received rhBMP-2 (in the same concentrations as above) was higher than that in control patients[78]. At similar follow-up times as in the Burkus *et al.* study, only 44% of the group in whom rhBMP-2 had been used fused, whereas 63% of the control group achieved fusion. However, the findings were not statistically significant because of the small number of patients (9).

Complications with the Use of rh-Bone Morphogenetic Protein-2 in Anterior Lumbar Interbody Fusion Procedures

Since its introduction, complications of the increasing use of rhBMP-2 in spinal fusions have been reported. This is attributable to uncertainty about the appropriate clinical dosage for ALIF procedures. Most adverse effects fall into three categories: ectopic bone formation; bony osteolysis from excessive osteoclastic activity[79–81], leading to graft subsidence and mechanical failure; and post-surgical soft-tissue inflammatory and edematous reactions[80,82,83]. Other unwanted effects include graft resorption and interbody cage migration[80,84].

Bone resorption or osteolysis is part of the natural remodeling process of fusion[80]. However, severe osteolysis results in graft subsidence, which can require reoperation. In a study with a 6-year follow up period, Burkus *et al.* reported seven of 279 patients developed graft subsidence (5.4%), four of whom required additional surgery[85]. Another study by Vaidya *et al.* reported a high incidence of subsidence (70% of ALIF levels) with rhBMP-2 compared to a 6% subsidence rate without rhBMP-2.

Retrograde ejaculation (RE) is another complication associated with rhBMP-2. *In vitro* studies have suggested that inflammation and ectopic bone formation associated with

rhBMP-2 exposure in lower lumbar levels during ALIF procedures can damage the superior hypogastric plexus[86], which crosses ventral to the interbody cages containing rhBMP-2. This plexus innervates the internal vesical sphincter that is responsible for contracting during ejaculation. Damage to this plexus may result in failure of the internal vesical sphincter to contract during ejaculation, leading to RE. This inflammatory response is associated with the release of cytokines preceding the bone induction cascade[87,88]. In a randomized controlled trial comparing rhBMP-2 to autologous bone grafts in ALIF procedures, Burkus *et al*. reported an overall rate of RE of 4.1%[73]. However, when Smoljanovic *et al*. reanalyzed the data of the same cohort, they reportedly found a significantly higher rate of RE associated with the rhBMP-2 cohort (7.9% compared to 1.4% in the control ICBG group; Fisher's exact test, $P = 0.05$)[89]. Similarly, in a retrospective analysis of men who had undergone one- and two-level ALIF procedures, Carragee *et al*. found the patients who had received InFuse (rhBMP-2 group) had a 7.2% incidence of RE compared with 0.6% in the ICBG group[90]. Other studies have also reported similar rates of RE[91,92]. Although the incidence of RE varies according to surgical approach, levels operated on and comorbidities such as diabetes, there is a statistically significant strong correlation between rhBMP-2 and RE. The risk of sterility post-surgery is an important consideration for men and their families, underscoring the importance of counseling men about this risk before performing ALIF procedures.

Cancer has also been associated with exposure to BMP. In late 2004, clinical trials of rhBMP-2 used in ALIF procedures conducted by Wyeth (Five Giralda Farms, Madison, NJ, USA [now under Pfizer]), the manufacturer of rhBMP-2, identified an unexpected excess of cases of pancreatic cancer[93]. To evaluate whether rhBMP-2 exposure is associated with an increased risk for pancreatic cancer, a retrospective study of 93,654 elderly patients who had undergone ALIF surgery was conducted using Medicare claims data[94]. After a mean 17 month follow-up, 91 patients had been diagnosed with pancreatic cancer (8 in the BMP, and 83 in the control non-BMP cohort). Compared to the control group who had not received BMP, this study found the use of BMP did not increase their risk of pancreatic cancer (adjusted hazard ratio, 0.70; 95% confidence interval, 0.34–1.45). Nonetheless, this study does not exclude possible long-term effects of BMP on cancer risk because the follow-up was too brief. Thus, whether BMP hastens the growth of malignant cells remains unknown.

Another disadvantage of the use of rhBMP-2 in ALIF procedures is the large expense incurred. In a cost-effective analysis, Glassman *et al*. found that the hospital cost associated with use of InFuse was higher ($24,736) than that of the autograft group ($21,138) because of the substantial cost of the implant[95]. Nonetheless, studies have suggested that rhBMP-2 is cost-effective compared with autologous grafting post-surgery if the financial burden of revising complications and malunions with the associated extended hospital stays, rehabilitation, and pain management that is associated with the latter is taken into account[82,96–98].

Infuse has shown considerable potential as a bone graft alternative, with high fusion rates comparable to those in trials using autologous bone harvesting. However, it is of interest that no prospective clinical trial comparing rhBMP-2 with autograft harvesting has found statistically significant differences between these two groups a few months postoperatively in Oswestry Disability Index or the Short Form-36, measures of patient experience of pain. Thus, given its adverse effects and high cost, rhBMP-2 as an alternative to autologous bone grafts may be little more than a surgical convenience. Further larger clinical studies comparing patient outcomes of autografts and rhBMP-2 must be conducted for comprehensive evaluation of the safety and efficacy of rhBMP-2.

Conclusion

The use of bone graft alternatives in ALIF surgery remains a tentative topic in need of further clinical studies. It appears that autologous graft remains the ideal bone grafting option in ALIF surgery. Informed evaluation of the efficacy and safety of the various graft options are difficult to make amidst suboptimal study designs that are limited by factors such as small cohort, and retrospective, non-randomized or non-blinded studies. Patient risk factors, including body mass index, smoking, age and sex, also contribute to the diversity of study groups. Because we only assessed studies published in English, we would have excluded the data of clinical trials in non-English-speaking countries. Further, many of the studies investigated bone grafts in conjunction with posterior fixation, which yields higher fusion rates than stand-alone procedures. These variations of standard ALIF procedures make it difficult to define the true effectiveness of grafts. Moreover, the absence of standardized fusion criteria and evaluation of both clinical and radiological outcomes create heterogeneity of studies, making it difficult to compare and contrast bone graft alternatives. We have drawn the following conclusions regarding bone graft substitutes for ALIF surgery:

1 **Autografts** remains the "gold-standard", naturally possessing the essential properties of a good bone graft. However, they will always be associated with significant donor site morbidity.
2 **Allografts** have favorable fusion rates comparable with fusion rates with autografts, especially when used in conjunction with supplementary posterior pedicle screw fixation.
3 **Ceramics** have also achieved excellent fusion rates. Despite ample animal study data, very limited clinical data with small cohort sizes has been reported for ALIF procedures. Ceramics is therefore a provisional graft option and must be used with caution.
4 **BMPs** are considered the optimal bone graft option and have very high fusion rates. However, there have been conflicting reports about complications and financial burden associated with the use of BMPs, suggesting it should only be used after careful consideration by surgeons and patients.

5 **New graft technologies** are currently being investigated; however, it will be some time before data is available for comparison.

Even now, no graft substitute has been proven superior to autologous bone grafts[6,99–101]. It appears that the use of rhBMP-2 can significantly improve rates of successful fusion and simultaneously decrease the rate of reoperation. The reported complications surrounding this potent graft substitute mean that surgeons should cautiously weigh the advantages and disadvantages of rhBMP-2 as an alternative to ICBG in ALIF. In addition, because significant industry support was provided to many of the studies of rhBMP-2, there is possible bias in reporting results of radiological outcomes compared with graft substitutes[73,74]. Minimal industry support has been documented for studies of other graft substitute. It is important that great effort be made to ensure that patients make well-informed decisions based on the clinical efficacy and safety of each grafting option.

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