

# GLYCEROL SAFETY AND BONE VOID FILLERS

## Background: Use of Glycerol as a carrier for Demineralized Bone Matrices

The majority of demineralized bone matrices (DBM) used today are in the form of particulate powder requiring the use of a carrier to impart desirable handling properties to the graft. These carriers include glycerol, collagen, and gelatins. Glycerol, the carrier used in Grafton<sup>®</sup> DBM and Optium DBM<sup>®</sup>, does not by itself enhance the bone forming process. Therefore, it is referred to as an inert carrier. While considered inert, glycerol provides improved handling characteristics. These properties allow glycerol to offer the advantages of excellent graft handling, containment and flexibility. Additionally, since glycerol is pre-combined with the DBM, the graft requires no intra-operative preparation in the OR.

Glycerol has been used as a DBM carrier since the introduction of Grafton by Osteotech over 20 years ago, and it has a demonstrated clinical history of safety. Since its introduction, millions of cubic centimeters of DBMs containing glycerol as a carrier have been implanted.

Glycerol is a non-toxic, colorless, odorless and biodegradable viscous liquid that has been classified as a 'Generally Recognized as Safe' (GRAS) multiple purpose food substance by the FDA.<sup>1</sup> Glycerol has been on the scene for many years before its use in a DBM. It was discovered over two centuries ago, and its unique properties led to its widespread use in over 1,500 worldwide cosmetic and toiletry applications. These include toothpastes, lipsticks, mouthwash, moisturizing creams and deodorants. Glycerol is a commonly found food additive in breads, baked goods, wine, fruit punches, gum, candy, ice cream, margarine, sausages, beverages and flavor extracts. It is also a carrier for pharmaceuticals, and it can be found in gelatin capsules, ointments, and antibiotics.

Although glycerol has been used as a carrier in DBM since 1991, a 2001 study by Bostrom et al., entitled "An Unexpected Outcome during Testing of Commercially Available Demineralized Bone Graft Materials. How Safe Are the Nonallograft Components?" cast concerns on glycerol's safety:

In this study, six different bone grafting materials were evaluated in an in-vivo bone formation model using athymic nude rats. Eight rats died, all of which had received the DBM in a glycerol carrier. Upon further protocol analysis, the researchers uncovered an error in their volume of glycerol carrier material they used in the deceased rats. The researchers found they had given this glycerol carrier test **group eight times the maximum known DBM dose used in humans**. This overdose was equivalent to implanting 600ccs of the DBM in a 70kg person. Based on this very unrealistic dosage, the death of these rats has very little, if any, clinical significance. The authors acknowledge this by concluding that "although the volume of Grafton product per kilogram of body weight used in this study was approximately 8 times the maximum volume used in humans, it is unlikely that the findings from this study will have clinical implications for otherwise healthy patients." The authors also noted that it is unknown if glycerol has any similar toxic effects in humans, and that there have not been any adverse outcomes reported since the

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first DBM in a glycerol carrier had been released to the market. In addition, Bostrom et al. reported that the athymic rat model is a more susceptible and compromised host model for glycerol overdose.

Later that year, Wang et al. published a follow-up study in SPINE titled “Dose Dependent Toxicity of a Commercially Available Demineralized Bone Matrix Material.” They found that when they repeated the Bostrum overdose of 8cc/ kilograms of DBM, 100% of the rats died. At a medium dose of 4cc per kilograms, 50% of the rats died. At a low dose of 2cc per kilograms, 0% of the rats died.

Wang concludes that “clinical usage of [glycerol-carrier] putty in humans should be limited to no more than 2 milliliters per kilogram body weight.” Wang’s recommendations are equivalent to limiting putty to 140cc in a 70kg person. This is the equivalent of 14 units of the 10cc Optium DBM offering. It is extremely unlikely that 14 of the 10ccs putties would ever be implanted in one patient at one time.

### What does the clinical evidence say?

There have been several published clinical evaluations\* that shed further light on the results of these studies.

In a study by Cammisa, et al.<sup>2</sup>, “120 patients underwent posterolateral spine fusion with pedicle screw fixation and bone grafting. Iliac crest autograft was implanted on one side of the spine and a [glycerol-carrier DBM]/autograft composite was implanted on the contralateral side.” In this study, “Nearly 70% of patients (81 of 120) provided complete 24-month radiographic studies. The bone graft mass was fused in 42 cases (52%) on the [glycerol-carrier DBM] side and in 44 cases (54%) on the autograft side.” In conclusion, the authors state **“[glycerol-carrier DBM] can extend a smaller quantity of autograft than is normally required to achieve a solid spinal arthrodesis.”**

Hamadouche et al.<sup>3</sup> described their technique and preliminary results for “major acetabular reconstruction using the Kerboul acetabular reinforcement device with allograft bone and [glycerol-carrier] DBM.” The authors’ technique is based on the glycerol-carrier DBM, which they describe as “easy to handle and place in [the] acetabular cavity.” In conclusion, the authors state **“that fibre-based [sic] DBM could enhance allograft bone incorporation and remodeling in major acetabular reconstruction.”**

Kang, et al.<sup>4</sup> published a randomized, multi-center study that investigated glycerol-carrier DBM in 28 patients and iliac crest bone graft (ICBG) in 13 patients for a single-level instrumented posterior lumbar fusion. After a two year follow-up, the authors found similar fusion rates between the two groups. Furthermore, the authors concluded **“the [glycerol-carrier DBM] group showed slightly better improvement in ODI [Oswestry Disability Index]...consistently higher physical function scores at 24 months...[and] there was a statistically significant greater mean intraoperative blood loss in the ICBG group.”**

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In a prospective study, Park, et al.<sup>5</sup> treated 31 patients “with ACDF [anterior cervical discectomy and fusion] using the PEEK [polyetheretherketone] cage and DBM [glycerol-carrier DBM]... at 42 levels,” including 1, 2, and 3 levels. After a 12 month follow-up, the authors noted **“using the Solis cage packed with [glycerol-carrier DBM] demonstrated good clinical and radiologic outcomes... [and] is a safe and effective alternative to the gold standard of autologous iliac bone grafts.”**

In a study published by Pieske et al.<sup>6</sup>, “twenty patients had ununited diaphyseal fractures of long bones and were treated by ORIF [open reduction and internal fixation] combined either by ICABG [iliac-crest-autologous-bone-grafting] (n = 10) or DBM-augmentation [demineralized-bone-matrix] (n = 10).” After a multi-year follow up, the authors concluded “that the application of DBM compared to ICABG **led to an advanced outcome in the treatment of non-unions and simultaneously to a decreased quantity of adverse effects.”** Furthermore, **“patients treated with DBM were more satisfied with the surgical procedure (p = 0.031).”**

In a study reported by Sassard, et al.<sup>7</sup> “Mineralization and integrity of the bone graft mass were evaluated among patients having posterolateral fusion. Grafting consisted of a composite of [glycerol-carrier DBM] and “local” autologous bone (n=56) or iliac crest autograft alone (n=52). Mineralization was rated radiographically at baseline and at 3, 6, 12, and 24 months. Integrity was judged as fused or not fused. Mineralization ratings did not differ significantly between groups at any postoperative interval (P values of .25-1.00). **The percentage of patients fused was similar in both groups (60% and 56% for glycerol-carrier DBM and controls, respectively; P=.83).”**

Thalgott, et al.<sup>8</sup> reported on treating “difficult to fuse patients, such as smokers [and] elderly patients with poor bone quality” who required posterolateral fusion. As an alternative to autogenous fusion, the authors used coralline hydroxapatite in 40 patients along with glycerol-carrier DBM “as a bone graft extender” in 28 of these patients (70%). The authors found an overall fusion rate of 89.3% in the patients that received [glycerol-carrier DBM]. **The high fusion rate is especially significant when the challenging patient population is taken into account.**

Thoradarson and Kuehn<sup>9</sup> investigated “Sixty-three patients who underwent complex ankle or hindfoot fusion” and were divided into two groups, each receiving a demineralized bone void filler to stimulate fusion. The authors found similar fusion rates in both groups “compared to historical controls [10%]” and **it should be noted these comparable rates of fusion were reached without the donor site morbidity and pain of autografts.**

Weinzapfel, et al.<sup>10</sup> performed a study “To compare fusion rates between allograft bone and [glycerol-carrier DBM] following VATS using standard standing lateral spine radiographs.” In studying 40 patients

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with one or more year follow-up with morselized graft and 28 with [glycerol-carrier DBM] , “interbody fusion was assessed on standing lateral radiographs using the Newton et al. 4-level grading scale.” They found “At most recent assessment, 60 of 73 disc spaces (82%) in the Allograft group and 100 of 109 disc spaces (92%) in the [glycerol-carrier DBM] group were rated as radiographically fused” and concluded that “Demineralized bone matrix (**[glycerol-carrier DBM]**) seem to be an effective bone graft substitute in thoracoscopic surgery for idiopathic scoliosis.”

**In summary, the positive clinical experience with glycerol-carrier DBM supports their wide use in bone void filling clinical applications.**

#### References:

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**The use of glycerol as a carrier for DBMs is well known and accepted.**

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