

Complications of Anterior Cervical Fusion using a Low-dose Recombinant Human Bone Morphogenetic Protein-2

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Objective: There are several reports, which documented a high incidence of complications following the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in anterior cervical fusions (ACFs). The objective of this study is to share our experience with low-dose rhBMP-2 in anterior cervical spine.

Methods: We performed a retrospective analysis of 197 patients who underwent anterior cervical fusion (ACF) with the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) during 2007-2012. A low-dose rhBMP-2 (0.7 mg/level) sponge was placed exclusively within the cage. In 102 patients demineralized bone matrix (DBM) was filled around the BMP sponge. Incidence and severity of dysphagia was determined by 5 points SWAL-QOL scale.

Results: Two patients had prolonged hospitalization due to BMP unrelated causes. Following the discharge, 13.2% (n=26) patients developed dysphagia and 8.6% (n=17) patients complained of neck swelling. More than half of the patients (52.9%, n=9) with neck swelling also had associated dysphagia; however, only 2 of these patients necessitated readmission. Both of these patients responded well to the intravenous dexamethasone. The use of DBM did not affect the incidence and severity of complications ($p>0.05$). Clinico-radiological evidence of fusion was not observed in 2 patients.

Conclusion: A low-dose rhBMP-2 in ACFs is not without risk. However, the incidence and severity of complications seem to be lower with low-dose BMP placed exclusively inside the cage. Packing DBM putty around the BMP sponge does not affect the safety profile of rhBMP-2 in ACFs.

Key Words: Anterior cervical fusion • rhBMP-2 • Complications • Dose • Delivery methods

INTRODUCTION

Anterior cervical fusion (ACF) is a commonly performed surgical procedure to treat degenerative disorders of the cervical spine⁹. Although the use of tricortical iliac crest bone graft in ACFs is associated with the excellent outcomes, the risk of donor site related complications have always incited the spine surgeon to use various contemporary graft substitutes. In 1965, Urist¹⁴ discovered a subset of protein extract, which had a significant potential of inducing new bone formation even at the non-osseous tissues. The proteins were termed bone morphogenetic proteins (BMPs). Recombinant human bone mor-

phogenetic protein-2 (rhBMP-2) is a member of this family, which has gained a widespread popularity for its application in spinal fusions. Although, their role in lumbar fusions is well established, the safety profile of rhBMP-2 in ACFs is yet to be defined^{10,11,13}.

Baskin et al.¹ were the first authors who conducted a prospective randomized controlled trial and reported that the use of rhBMP-2 in ACFs is a safe and effective technique. Conversely several other authors reported a high incidence of neck swelling and dysphagia associated with the use of rhBMP-2 warranting either prolonged stay in the hospital or readmissions of the patients^{6,10,11,15}. Despite the high fusions rates, some authors have even abandoned the use of rhBMP-2 for ACFs due to its cost, side effects and availability of safer alternatives¹⁵. On the basis of results of earlier trials, Food and Drug Administration (FDA) issued a warning in 2008 against the use of rhBMP-2 in ACFs until the sufficient evidence is available about its safety.

Shields et al.¹⁰ reported a high rate of complications and attributed it to the use of greater amount of BMP dose (2.1 mg/level) placed both inside and outside the cage. Further emphasis on the influence of the dose and delivery method of rhBMP-2 in ACFs was given by Dickerman et al.⁴ and in their letter they proposed that the containment of low dose (1.05

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mg) rhBMP-2 within the cage and placing demineralized bone matrix (DBM) putty surrounding the INFUSE ensures a controlled delivery of rhBMP-2 in the vicinity of desired fusion site, which therefore is associated with excellent fusion rates with no adverse effects related to rhBMP-2. The purpose of our study is to share our clinical experience with low-dose of rhBMP-2 in ACF. We also aim to elucidate the impact of dose and delivery techniques of rhBMP-2 on the safety profile of its use in ACFs based on our clinical experience and review of the literature.

MATERIALS AND METHODS

We performed a retrospective analysis of 197 patients who underwent ACF with the use of rhBMP-2 during 2007-2012. ACFs included mainly anterior cervical discectomy and fusion (ACDF, n=191), although few patients underwent anterior cervical corpectomy and fusion (ACCF, n=4). The remaining 2 patients underwent both ACDF and ACCF performed at different levels. All the surgeries were performed by the senior author. Institutional review board approval was taken to conduct this study. There were 80 males (40.6%) and 117 (59.4%) females included in our study. Surgeries were performed for herniated disc prolapsed in 91 patients, for spondylosis with or without instability in 104, and for pseudoarthrosis in 2 patients (revision ACF was performed in both these patients). Most common presenting symptom was neck pain (n=175), followed by arm pain (n=163), sensory deficit (n=102) and motor weakness (n=87). Other conditions affecting the outcome were evaluated. History of cigarette smoking was present in 53 patients (26.9%) and diabetes mellitus in 21 (10.65%). Thirty nine patients had a history of previous neck surgery, most of which had undergone discectomy or nerve decompression by foraminotomy (n=37) and 2 patients had anterior fusions performed at different levels.

1. Implants and BMP

In the majority of cases (n=191) polyetheretherketone (PEEK) cages were used as a spacer device and the construct was supplemented with anterior cervical plate. In 6 patients, PEEK prevail (Medtronic Sofamor Danek) device was used, which has inbuilt slots for self drilling screws. Cages were filled with INFUSE bone graft substitute, which has 2 components: a reconstituted solution containing recombinant human bone morphogenetic protein-2 (rhBMP-2) and an absorbable collagen sponge (ACS). 1.4 mL of rhBMP-2 containing 2.1 mg was soaked with ACS measuring 5.08×2.54×0.5 cm. We placed only 1/3 of sponge within the cage (measuring 1.7×2.54×0.5 cm), which would deliver 0.7 mg of rhBMP-2 per level considering a homo-

genous distribution of this protein within the sponge (Fig. 1A). No additional ACS was filled around the cage. In a large number of the patients (n=102), we also used demineralized bone matrix (DBM), which was placed from the top and the bottom over the centrally located INFUSE within the PEEK cage (Fig. 1B).

2. Surgical technique

Unless contraindicated, intravenous dexamethasone (8 mg) was administered at the start of the procedure in all cases. Surgery was performed with the standard anterior approach. After achieving the decompression, interbody spaces were prepared for cage placement, which were filled with INFUSE substitute in a proportion already discussed. Anterior plate fixation was supplemented in all patients except in those in which Prevail PEEK device was used (n=6). In the patients with major anatomical deformities, a corpectomy was performed. A larger cage was impacted between the adjacent vertebral endplates following corpectomy. The amount of INFUSE was the same even if a larger spacer was placed after ACCF. Wound irrigation was avoided after the placement of cage. Closure was performed in layers without placing any drain. Unless it was contraindicated, all patients were given methylprednisolone orally (4 mg) in taper doses during the first week of postoperative period.

3. Post-operative evaluation and dysphagia calculation

Plain x-ray of the cervical spine was taken within few hours of surgery to document the appropriate placement of hardware. During hospitalization, any events such as dysphagia, neck hematoma, incisional swelling, and vocal cord palsy were recorded. The majority of the patients were discharged within 24 hours of surgery and the patients hospitalized beyond 48 hours were considered to have a prolonged stay. After discharge, the patients were evaluated at 2 weeks, 6 weeks, 3 months, 6 months, 12 months and 24 months after surgery. Clinical and radiological

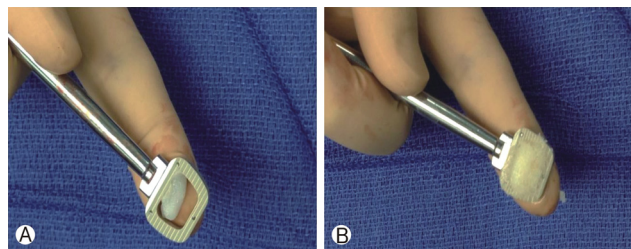


Fig. 1. (A) We used only 1/3 of sponge (measuring 1.7×2.54×0.5 cm), which would deliver 0.7 mg of rhBMP-2 per level. BMP sponge was placed exclusively within the cage. (B) In more than half of the patients (n=102) BMP sponge was surrounded by DBM.

assessments were carried out during each post-operative visit. Fusion was assessed with flexion/extension radiographs at 3 and 6 months postoperatively.

Incidence and severity of dysphagia was retrospectively determined by the 5 point SWAL-QOL scale⁷. Score 1 indicates the patient almost always had difficulty; score 2 indicates the patient often had difficulty; score 3 indicates the patient sometimes had difficulty; score 4 indicates the patient hardly had any difficulty; score 5 indicates the patient never had difficulty. For the statistical analysis, patients with dysphagia were grouped into minimal (score 3-5) and substantial (score 1-2) dysphagia.

4. Statistical analysis

All statistical analyses were performed using the SPSS software, version 21.0 (IBM Corp., Armonk, NY). The data was analyzed for descriptive and inferential statistics. Descriptive statistics were conducted for frequencies, percentages and proportions. The comparison of incidence and severity of complications between DBM and non-DBM was performed by using Fisher's exact test.

RESULTS

A total of 197 patients with the mean age of 51.3 years and male to female ratio of 1.01 were included in the study. The mean duration of follow-up was 27.5 months (range 9-43 months). The majority of patients underwent single level ACFs (n=110, 55.8%), while 2, 3, 4 levels ACFs were performed in 72 (n=36.5%), 13 (6.6%), 2 (1%) patients respectively.

Hospital stay for the majority of patients was uneventful except in 2 patients who had prolonged hospitalization. An 83 year old patient, who underwent 2 levels ACDF, developed severe postoperative dysphagia on 2nd day of surgery. The cli-

nico-radiological assessment did not reveal any neck swelling or hematoma, but the patient failed swallow tests. The patient was inserted a percutaneous endoscopic gastrostomy (PEG) tube until he started tolerating oral feeds over the next few weeks. The other patient was a 70 year old male with an existing pulmonary dysfunction, who underwent 3 levels ACDF, developed acute respiratory failure on the day of surgery. The patient was reintubated; however, no hematoma or fluid collection in the neck was detected.

A total of 26 (13.2%) patients complained of dysphagia and the mean duration of onset was 9.2 (range 2-21) days. Of these patients, 15 patients had minimal discomfort (score 3-5) and the remaining 11 patients complained of a substantial degree of discomfort (score 1-2). Seventeen patients (8.6%) reported neck swelling following ACFs. Neck swelling occurred on average postoperative day 5.4 (range 2-12 days). In 9 (34.6%) patients with dysphagia, there was also an associated visible neck swelling. On the other hand, more than half (n=9, 52.9%) of the patients with neck swelling had associated dysphagia. In a large number of the patients these adverse events resolved spontaneously (Table 1). However, several other patients were given oral methylprednisolone as an outpatient; only few required either prolonged hospitalization or readmissions. As already discussed, one patient with severe dysphagia who was found to have swallowing dysfunctions received a PEG tube and therefore, had an extended hospital stay. Two patients with neck swelling were readmitted for the management of associated dysphagia and respiratory difficulty (Fig. 2). Resolution of the

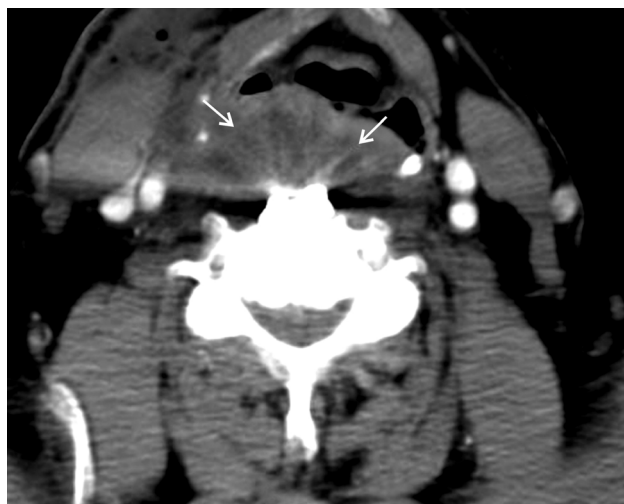


Fig. 2. Gadolinium-enhanced cervical computerized tomography of a 57-year old male patient at 7th postoperative day following a 3-level ACDF. A large hematoma is visible in the prevertebral space, causing compression and displacement of the trachea and esophagus anteriorly. The patient responded well to intravenous steroids administered over 48 hours of admission.

Table 1. Outcomes of the patients with rhBMP-2 related complications*

Outcome	Dysphagia	Neck swelling
Resolved spontaneously	9	10
Resolved by oral Medrol	14	5
Prolonged hospitalization		
Medical management	0	0
Surgical evacuation	0	0
PEG tube insertion	1	0
Readmission		
Medical management	2	2
Surgical evacuation	0	0
Total	26	17

*Some patients had both dysphagia as well as neck swelling.

Table 2. Outcomes with or without use of DBM around rhBMP-2 sponge

Outcomes	DBM N (%)	Non-DBM N (%)	p-value
Overall dysphagia	10 (9.8)	16 (16.8)	0.14
Substantial dysphagia	4 (3.9)	7 (7.4)	0.29
Neck Swelling	7 (6.8)	10 (10.5)	0.54
Spontaneous resolution			
Dysphagia	3 (30)	7 (43.8)	0.48
Neck swelling	5 (50)	7 (71.4)	0.35
Prolonged hospital stay*	1 (1)	1 (1.1)	-
Readmission*	1 (1)	1 (1.1)	-

* Due to small numbers of patients in these groups, statistical analysis was not performed

symptoms could be achieved in both patients by administering intravenous dexamethasone, and the patients were also given oral methylprednisolone for 5 days following discharge. None of the patients necessitated surgical management for the aforementioned complications. In 102 patients DBM was placed around the INFUSE sponge. Overall the incidence of dysphagia, substantial dysphagia and neck swelling was lower in the patients who were inserted DBM putty around INFUSE. On the contrary, the rate of spontaneous resolution was more in the non-DBM group; although, none of these observations reached statistical significance (Table 2). There was no difference in the incidence of prolonged hospitalization and readmissions in two groups.

Apart from the aforementioned events, we also observed other complications in this cohort. Four patients (2%) developed vocal cord palsies, which were transient and subsided over the period of few weeks in all of these patients. Pseudoarthrosis was seen in 2 patients. In the first patient, who was 50 year female with a 3 level ACDF, the fusion did not occur in the lower most vertebral segment. Patient deferred to any further intervention for the persistent symptoms arising from the involved segment. The second patient was a 66 year female, who underwent a single ACDF for the traumatic subluxation of C5/6 region. This patient underwent posterior fusion and stabilization due the radiological presentation of implant loosening and impending loss of fusion at 1 month. One patient developed postoperative deltoid weakness, which subsided spontaneously over the next few months.

DISCUSSION

The reports of high incidence of complication following its use in ACFs invoked the debate on the safety profile of rhBMP-2 in these procedures. One of such reports was from Schilds et al.¹⁰, who documented a significant rate of complications resul-

ting after the use of a high dose rhBMP-2 in ACFs. Interestingly, the incidence of the adverse events in the literature ranges from none to very high rates of complications (Table 3)^{1-3,5,6,10-13,15}. Lower incidence of the complications in some of the studies has been correlated with the lower dose of rhBMP-2 and methods of delivery^{2,4,10,13}.

Boakye et al.² produced the first report of rh-BMP-2 filled in a PEEK spacer, which is what we use at our institution. The authors studied 24 patients that underwent ACDFs with PEEK implants and rh-BMP-2. Two patients were found to have transient dysphagia. Three patients were found to have heterotopic bone formation, while the authors were using half of the amount of a small INFUSE kit (2.1 mg rhBMP-2/level). Subsequently, the authors decided to use one-fourth of the sponge (1.05 mg rhBMP-2/level) and found no heterotopic bone formation. The results of BMP in ACFs were convincing until Schilds et al.¹⁰ presented their study, which documented alarmingly high incidence of complications. However, one glaring difference was the amount of rh-BMP-2 used per level (2.1 mg). They also suspected that higher amount of INFUSE used in vertebrectomies led to a greater risk of the adverse events (7.9% vs 38.8% hematoma). The impact of BMP dose was also evident from the study by Tumialan et al.¹³, who were initially using 2.1 mg/level. The authors noticed excess interbody bone formation in the first 24 patients and subsequently reduced the dose to 1.05 mg of rh-BMP-2 per level in the next 93 patients. The authors went on to reduce the dose even more (0.7 mg/level) as more studies supported using a smaller dose.

Recent attention has also been directed to the methods of delivery. While reviewing their results, Schilds et al.¹⁰ pointed out that the placement of BMP sponge outside the cage could be related to the high incidence of complication in their series. Some surgeons have also used thrombin glue to control the diffusion of BMP into the surrounding tissues⁵. The influence of delivery techniques gained more ground when Dickermann et al.⁴ shared their experience with using DBM around BMP sponge to minimize its leakage. The authors reported excellent results with no adverse effects of using rhBMP-2 in ACFs.

In the present study, we used a low-dose rhBMP-2 (0.7 mg/level) and placed it exclusively inside the cage. In approximately half of the patient, we also used DBM around the BMP sponge. The incidence of dysphagia and neck swelling in our series was 13.2% and 8.6% respectively. Only 2 patients necessitated readmission and both of them responded well to the intravenous dexamethasone. Surgical evacuation was not required in any of the patients. The incidence and severity of complications were lower in the patients, in whom DBM was used, though these observations were not statistically significant. Interestingly, in a large number of the patients, the aforementioned symptoms resolved spontaneously.

A careful evaluation of previous studies also gives a clue to the effect of dose and delivery methods on the safety profile of rhBMP-2 in ACFs (Table 3). As already discussed, higher dose and placing BMP sponge outside the cage were probably

responsible for the greater incidence of adverse events in the case series presented by Schildts et al.¹⁰. Apparently, Buttermann³ used a smaller dose of BMP as compared to Boakye et al.² (0.9 vs 1.05 mg); however, the incidence of complications was

Table 3. Review of studies using rhBMP-2 for anterior cervical fusions

Authors (year)	No. of patients rhBMP-2/control (Total)	rhBMP-2 dose mg/level	Steroid peri/post operative	Spacer	rhBMP-2 Placement technique	Fusion rates % (rhBMP-2/control)	Functional outcomes	Complications rhBMP-2/control (p-value)	Readmissions/prolonged stay for neck swelling and/dysphagia
Baskin et al; 2003	18/15 (33)	0.6	NR	CORNERSTONE-SR™ Allografting	"inside"	100/100	Superior improvement in neck disability and arm pain in rhBMP-2 group	No adverse events	None
Lanman et al; 2004	20/0 (20)	NR ⁸	NR	CORNERSTONE-HSR (bioabsorbable)	"inside", thrombin glue separating infuse from spinal canal	100	Improvement from baseline scores in physical functioning, mental health, and bodily pain	Severe dysphagia-1 immediate postoperatively	None
Boakye et al; 2005	24/0 (24)	Initially 2.1, 1.05 in recent cases	10 mg dexamethasone ³ at the start of procedure	PEEK ¹	"inside"	100	Good 21 (95%) Fair 1 (5%)	Transient RLN ⁴ palsy-1, Transient C-5 palsy-1, CSF leak-1, Transient dysphagia-2	None
Shields et al; 2006	151/0	2.1	NR	PLDLLA ² Bioabsorbable cage (Hydrosorb)	"inside"+ "outside"	NR	NR	Complications rate 35 (23.2%) Hematoma=15 (9.9%) Others=25 (13.3%)	Readmission=8 (5.3%) Prolonged stay=5 (3.3%)
Smucker et al; 2006	69/165	Not Standardized	NR	Allograft or PEEK	"inside"+ "outside"	NR	NR	Cervical swelling, 19 (27.5%) vs 6 (3.6%) (<0.001)	Readmission=5 vs 0 Prolonged stay =9 vs 5
Vaidya et al; 2007	22/24	1	NR	Allograft or PEEK	Not specified	100/96	Improvement in arm pain, neck pain and Oswestry score in both groups	Dysphagia 85% vs 56%	LOS ⁷ =2.95 vs 2.3 days
Butterman; 2008	30/36	0.9	IV dexamethasone 8 mg/4 mg	Allograft or Autograft	Mainly "inside", small portion in posterior interbody space	96.6/94.4	Similar outcomes on the basis of VAS ⁵ , Oswestry Index, pain medication use, neurological recovery	Neck swelling=50% vs 14% Pseudoarthrosis=1 vs 2 Autograft donor site complications=2	Readmission=3 vs 1
Tumilan et al; 2008	200/0	2.1 (n=24); 1.05 (n=93); 0.7 (n=83)	IV dexamethasone 10 mg at start of procedure	PEEK	"inside"	100%	Good/excellent=85%, Fair=12.4%, Poor=2%	Dysphagia=14 (7%)	Readmission for evacuation of hematoma/seroma=4 (2%)
Stachniak et al; 2011	30/0	0.6	none intra-operative/ oral dexamethasone in taper doses postop	PEEK	"inside"	100%	Improvement in neck disability scores, neck pain and arm pain	Choking on food=19% drinking=4.8%, Food sticking=47.6%	None
Lu et al; 2013	100/50	2.1 (n=10); 1.05 (n=48); 0.7 (n=42)	IV 10 mg dexamethasone prior to incision	PEEK/Allograft	"inside"	100%/84%	Improvement of Nurick's grade in both groups; pseudoarthrosis 0% vs 16% (p=0.046)	Overall complications 13%/8% (p<0.005); Dysphagia 40%/44% (p>0.05)	Readmissions 8/0; Surgical evacuation of hematoma=5, Medical management of dysphagia=3
Our study	197	0.7	IV dexamethasone 8 mg at start of procedure/ 4 mg postop orally in taper dose	PEEK (191); PEEK Prevail (6)	"inside"	98.9%	Pseudoarthrosis=2	Dysphagia=13.2% Neck swelling=8.7% Dysphagia in DBM ⁶ non-DBM 9.8%/16.8% (p=0.145)	Readmission in 2 patients for the vs medical treatment of dysphagia

¹PEEK, polyetheretherketone; ²PLDLLA, poly-L-lactide-co-d, L-lactide; ³dexamethasone; ⁴RLN, recurrent laryngeal nerve; ⁵VAS, visual analogue scale; ⁶DBM, demineralized bone matrix; ⁷LOS, length of stay; ⁸NR, not recorded.

lower in the later study. Placement of INFUSE both within and outside the cage may be a possible explanation for higher incidence of adverse events observed by Buttermann. Usage of rhBMP-2 in ACFs has been described as a safe technique by several authors^{1,12,13}. It is also evident from the review of these studies that the authors either used low-dose BMP or placed it exclusively inside the cage or both (Table 3). On the basis of our findings, it appears that low dose BMP placed only inside the cage has a lower complication rate than previously reported higher doses (Table 3). Unlike higher readmission and reexploration rate in these reports, we had only 2 readmissions with BMP related complication and none of them required any surgical intervention. However, the risk of complications associated with the use of low-dose BMP seems to be greater than risk without its use. In a recent report from our institution, we documented relatively a lower risk of morbidity in a large group of patients who underwent ACDF without BMP (overall 8.4%, dysphagia 3.3%, neck hematoma 0.1%, and recurrent laryngeal nerve palsy 0.1%)⁸.

There are other factors, which may also influence the risk of complications in ACFs using BMP. Tumilian et al.¹³ stated that irrigation should be avoided after the placement of BMP to minimize any displacement of the protein into surrounding structures that can lead to inflammatory reactions in the adjacent tissues or cause heterotopic bone formation. This is something that is practiced at our institution as well. Perioperative steroid administration is also found to reduce the complaints of dysphagia and neck swelling³. Unless contraindicated, we also gave steroid in all patients and as discussed earlier. This may be responsible for spontaneous resolution of the symptoms in some patients. The authors in the past used several different designs of cages. The impact of type of spacer on the safety profile of BMP in ACFs is unknown.

Evaluation of outcomes in a retrospective manner is a major limitation of our study. The amount of rhBMP-2 in INFUSE sponge cannot be accurately measured and it is also difficult to determine that how precisely 1/3rd portion was separated from the remaining sponge. The impact of selection bias related to the surgeon's choice of using DBM in approximately half of the cases also cannot be denied. We also believe that the cost-effectiveness of rhBMP-2 and DBM should also be evaluated, which is another limitation of the present study.

CONCLUSION

The use of low-dose rhBMP-2 in anterior cervical fusion is not without risk. However, in comparison to previous reports with high dose BMP placed both inside and outside the cage, a low-dose of BMP placed exclusively within the spacer is asso-

ciated with lower incidence and severity of complications. Placing DBM putty around the BMP sponge does not seem to affect the safety profile of BMP in ACFs.

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