

# Bone Morphogenetic Protein in Scaphoid Nonunion: A Systematic Review

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## Abstract

**Background** Scaphoid nonunion can lead to carpal collapse and osteoarthritis, a painfully debilitating problem. Bone morphogenetic protein (BMP) has been successfully implemented to augment bone healing in other circumstances, but its use in scaphoid nonunion has yielded conflicting results.

**Case Description** The purpose of this study is to assess the outcomes and complications of scaphoid nonunion treated surgically with BMP.

**Literature Review** A literature review of all available journal articles citing the use of BMP in scaphoid nonunion surgery from 2002 to 2019 was conducted. We included studies that used BMP as an adjunct to surgical treatment for scaphoid nonunions in both the primary and revision settings with computed tomography determination of union. Demographic information, dose of BMP, tobacco use, outcomes, and complications were recorded. A total of 21 cases were included from four different studies meeting inclusion criteria.

**Clinical Relevance** The union rates were 90.5% overall, 100% for primary surgeries, and 77.8% for revision surgeries. Five patients (24%) experienced 11 complications, including four cases (19%) of heterotrophic ossification. Use of BMP in scaphoid nonunion surgery resulted in a 90.5% overall union rate but was also associated with complications such as heterotopic ossification. All included studies used BMP to augment bone graft, screw or wire fixation, or a combination of methods. The efficacy of BMP in scaphoid nonunion is unclear, and a sufficiently powered, randomized controlled trial is needed to determine optimal fixation methods, dosing, and morbidity of the use of BMP.

**Level of Evidence** This is a Level IC, therapeutic interventional study.

## Keywords

- ▶ scaphoid
- ▶ scaphoid fracture
- ▶ bone morphogenetic protein
- ▶ scaphoid fixation
- ▶ scaphoid nonunion

The scaphoid is the most commonly fractured carpal bone.<sup>1</sup> Scaphoid nonunion rates have remained at approximately 10% over the last two decades with certain factors predisposing to higher nonunion rates, including proximal pole fractures, displaced fractures, unstable fractures with deformity, and

increased time to treatment.<sup>2–4</sup> Persistent scaphoid nonunion can progress to carpal bone collapse and radiocarpal arthritis.

There are many forms of scaphoid nonunion surgery, including screw fixation, with<sup>5</sup> and without<sup>6</sup> vascular pedicle, and free vascularized bone transfer.<sup>7,8</sup> The gold standard for

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treatment of scaphoid waist nonunion is open reduction and internal fixation with bone graft.<sup>3,6,9</sup> Autologous bone grafting from the iliac crest (ICBG) and distal radius have comparable healing rates with both osteoconductive and osteoinductive properties but are associated with donor site morbidity, including chronic pain, hematoma formation, fracture, and infection.<sup>10-12</sup> Donor site morbidity and technical difficulty for free vascularized flaps are also concerns with medial femoral condyle (MFC)<sup>8</sup> and medial femoral trochlea (MFT)<sup>7</sup> grafting. A recent case series<sup>13</sup> and systematic review<sup>14</sup> have demonstrated improved efficacy from earlier studies<sup>5</sup>; however, the importance of vascularity remains uncertain in scaphoid nonunion surgery.<sup>6</sup>

It is possible that bone morphogenetic protein (BMP) may facilitate healing in these difficult fractures. BMPs, members of the TGF- $\beta$  family, were first discovered in 1965, and over 20 different types have been identified and implicated in bone formation and fracture healing.<sup>15,16</sup>

The BMPs used most often in orthopedic surgeries are BMP 2, 4, 6, 7, and 9.<sup>16</sup> No BMP is currently approved by the Food and Drug Administration (FDA) in hand surgery, and rhBMP-2 (recombinant human) is the only BMP that is FDA approved for lumbar interbody fusions and augmenting tibial fracture intramedullary nailing.<sup>17-19</sup> However, BMP use has increased steadily since its FDA approval in 2002, with over 340,000 BMP uses from 2002 to 2007, of which 85% were off-label uses for other orthopedic fractures.<sup>17</sup> Despite its use in the surgical setting, BMP augmentation for scaphoid nonunion surgery has not been well studied. The use of BMP in scaphoid nonunion surgery has been reported in small case series in either primary or revision settings with variable union and complication rates.<sup>20-25</sup> The purpose of this systematic review is to analyze the outcomes and complications of BMP use in scaphoid nonunion surgery.

## Materials and Methods

Following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, we performed a literature review of scaphoid nonunion surgery with the use of BMP, analyzing union and complication rates.<sup>26</sup>

A systematic search of the English literature was performed for all articles published on the treatment of scaphoid nonunions with BMP using the PubMed, Medline, EMBASE, and Cochrane databases between the years 2002 and 2019. Search terms included, BMP, scaphoid non-unions, osteogenic protein, distal radius bone graft (DRBG), and iliac crest bone graft (ICBG).

The inclusion criteria were papers that reviewed the outcomes and complications of patients with scaphoid nonunion treated with BMP, with or without autograft or allograft, and followed patients until evidence of union by computed tomography (CT). Studies were excluded if fixation was augmented with other materials other than autograft or allograft bone and BMP.

The primary outcome measure was union rate. The secondary outcome measure was complication rate. Complications included persistent nonunion, heterotopic ossification (HO),

reoperation, chronic pain, decreased wrist range of motion (< 40/40 degrees flexion/extension), and infection. Persistent nonunion was described as absence of union at 12 months following surgery with BMP. HO was described as periarticular ossification beyond the scaphoid nonunion following fixation augmented with BMP. Indication for use of BMP in primary and revision settings and amount of BMP used were independent variables. Primary surgeries were defined as procedures performed on scaphoid nonunions following a period of failed nonoperative treatment. Revision surgeries were defined as procedures performed on scaphoid nonunions that had previously undergone surgical fixation.

## Data Analysis

Demographic data, primary outcome measures, and secondary outcome measures from comparable studies were pooled for all patients receiving BMP in the treatment of scaphoid nonunions. Demographic variables of patient age, tobacco use, primary versus revision setting, scaphoid fracture location, initial delay from injury to surgery, amount and type of BMP used, fixation technique, duration of postoperative immobilization, and clinical follow-up were recorded. Heterogeneity in demographic and surgical variables among the included studies were assessed using Cochran's Q and I<sup>2</sup> statistics.<sup>27,28</sup> Complications and reoperations were similarly recorded.

## Results

The literature search resulted in six potentially eligible studies, while four met inclusion and exclusion criteria. One paper by Kujala et al was excluded because it used sea coral as an osteoconductive scaffold bridge for BMP.<sup>20</sup> One article by Rice and Lubahn described BMP use in nonunions in the hand and wrist, including seven patients with scaphoid nonunion, resulting in radiographic union in five patients and nonunion in two tobacco users seven months postoperatively without any other complications reported; however, all of these cases were excluded for lack of CT determination of union.<sup>25</sup> One case from Ablove et al that resulted in radiographic union without any reported complications was excluded from their series of four patients for lack of CT determination of union.<sup>23</sup> Two papers were level IV retrospective studies,<sup>23,24</sup> one was a level V case report,<sup>21</sup> and the remaining one was a level I randomized controlled trial.<sup>22</sup> (► **Table 1**) All patients had radiographic or CT evidence of nonunion with median delay from injury to surgery and BMP of 14.5 (range 9-55) months reported for 86% (18/21) of patients. None of the studies received external funding.

Cochran's Q and I<sup>2</sup> statistics demonstrated considerable heterogeneity among the demographic and surgical variables of patient age, tobacco use, primary versus revision setting, scaphoid fracture location, initial delay from injury to surgery, amount and type of BMP used, fixation technique, duration of postoperative immobilization, and clinical follow-up (I<sup>2</sup> > 95%). Publication bias was not directly assessed by funnel plots and Egger tests as control groups were not reported in 75% (3/4) of included studies. However, the I<sup>2</sup> statistic for study size, fracture location, age, tobacco use,

**Table 1** Studies

Author (year) Design	Study Size (n) Scaphoid NU Fracture location	Mean Age (years, range) Tobacco (%), n	Injury to Surgery with BMP (mo, method, n)	Follow-up (range, mo)	Amount and type of BMP (mg)	Bone graft (n)	Surgical fixation (n) Immobilization	Time to union (months, range)	Rate of union (%), n	Rate of complications (%), n
Jones <sup>21</sup> CR	1 Primary 1 PP	16 (NA) NR	14 XR, CT 1/1	72 (NA)	50 Human BMP	No graft (1)	K-wire (1) 12 weeks	3	100	0
Bilic <sup>22</sup> PRCT	6 Primary 1 PP 4 Waist 1 DP	22 (18-27) 50 (3/6)	14 (9-19) XR, CT 6/6	24 (NA)	None	Auto ICBG (6)	None (17) +28 weeks	2.25 (2-4)	100	0
	6 Primary 1 PP 3 Waist 2 DP	23 (18-28) 50 (3/6)	15 (10-20), XR, CT 6/6		3.5 rhBMP-7 (OP-1, Osigraft)	Auto ICBG (6)		1.5 (1-2)	100	0
	5 Primary 1 PP 3 Waist 1 DP	19 (15-23) 40 (2/5)	13 (9-17), XR, CT 5/5		3.5 rhBMP-7 (OP-1, Osigraft)	Allo ICBG (5)		2.5 (2-3)	100	0
Ablow <sup>23</sup> RCS	3 Revision 1 PP 2 Waist	NR NR	NR XR 3/3	3 (2-4.5)	0.53 rhBMP-2	No graft (3)	Screw exchange, HCS (3) 4 weeks	2.0 (1.5-2.4)	100	0
Brannan <sup>24</sup> RCS	6 Revision 2 PP 4 Waist	22 (16-29) 0 (0/6)	23 (10-55), XR 6/6, CT 5/6	8 (3-12)	2.1 rhBMP-2 (INFUSE)	Auto ICBG (3) Auto DR (1) Allo (2)	Screw exchange, HCS (6) until union or persistent NU, 24 ± 12 weeks	6.0 (3-12)	66.7 (4/6) Persistent NU in 1 waist, 1 proximal pole	83.3 (5/6) HO (4/6) Persistent NU (2/6) Reoperation (3/6) ↓ ROM (1/6)
For BMP cases: weighted mean ± SD median (range)	21 Patients 12 Primary 9 Revision 6 PP 12 Waist 3 DP	21.3 ± 4.6 (15-29) 39 ± 5.4 (5/17)	14.5 (9-55) 18 patients XR 21/21 CT 20/21	24 (2-72)	3.5 (0.53-50)	None (4/21) Auto ICBG (9/21) Auto DR (1/21) Allo (7/21)	None (11/21) K-wire (1/21) HCS (9/21) 12 ± 3 weeks	2.5 (1.5-12) XR 21/21 CT 20/21 MRI 1/21	90.5 ± 10 (19/21) (67-100) 100% (12/12) Primary 77.8% (7/9) revision	23.8 ± 4.9 (0-83) 5/21 patients

Abbreviations: allo, allogenic bone graft; auto, autologous bone graft; BMP, bone morphogenetic protein; CR, case report; CT, computed tomography; DP, distal pole; DR, distal radius; HCS, headless compression screw; HO, heterotopic ossification; ICBG, iliac crest bone graft; INFUSE (Medtronic, Minneapolis, MN); Osigraft (Stryker Biotech, Hopkinton, MA); mo, month; NA, not applicable; NR, not reported; NU, nonunion; PP, proximal pole; PRCT, prospective randomized controlled trial; RCS, retrospective case series; rh, recombinant human; SD, standard deviation; XR, plain radiograph. Considerable heterogeneity among demographic and surgical variables,  $Q = 6$ ,  $I^2 = 83\%$ .

**Table 2** Outcome by indication

Indication	Outcome		
Frequency	Union	Nonunion	Total
<b>Primary surgery</b>	12 (100%)	0	12
Distal	3	0	3
Waist	6	0	6
Proximal pole	3	0	3
<b>Revision surgery</b>	7 (77.8%)	2 (22.2%)	9
Distal	0	0	0
Waist	6	1	7
Proximal Pole	2	1	3
<b>Total</b>	19 (90.5%)	2 (9.5%)	21

delay from injury to surgery, primary versus revision surgery, use of bone graft, and surgical fixation demonstrated considerable heterogeneity ( $I^2 > 83\%$ ). Outcome variables of union rate by CT, time to union, and complications were consistently reported among the studies (► **Table 1**).

A total of 21 patients with an average age of 21.3 (range 15–29) years were treated with BMP for scaphoid nonunions in both primary and revision surgeries with a median follow-up of 24 months (range 2 months–6 years, ► **Table 1**). Median amount of BMP used was 3.5 (range 0.53–50) mg with three different BMP types. Overall ANOVA of demographic variables demonstrated homogeneity among the studies, excluding the case report by Jones et al<sup>21</sup> ( $p = 0.43$ , all pairwise  $p > 0.08$ ).

Overall union rate was 90.5% (19/21 patients, range 67–100%) with a median CT-determined time to union of 2.5 (range 1.5–12) months. The rates of union with BMP in primary versus revision surgery were 100% (12/12) and 88% (7/9), respectively (► **Table 2**). The two nonunions were revision surgeries (1 waist, 1 proximal pole).<sup>24</sup>

Five out of twenty-one patients (23.8%) had complications (► **Table 3**). The total number of procedural complications was 11 for 29 surgeries (52.4%) in 21 patients. The complication rates were persistent nonunions at 2/21 (9.5%),<sup>24</sup> HO at 4/21 (19%),<sup>24</sup> reoperation at 3/21 (14.3%),<sup>24</sup> and reduced range of motion at 1/29 (4.8%).<sup>24</sup>

## Discussion

Persistent scaphoid nonunions may result in carpal collapse and radiocarpal osteoarthritis, which can be debilitating and difficult to treat.<sup>29–31</sup> The common treatment options prior to advanced wrist arthritis yield reasonable outcomes with a certain degree of morbidity. The purpose is to determine the benefit of BMP in surgical fixation of scaphoid nonunions. We found that BMP had a union rate of 90.5% without the use of vascularized bone graft; however, BMP efficacy is unclear, and the HO incidence warrants additional investigation with controlled trials to determine optimal BMP use and postoperative immobilization duration.

**Table 3** Complications

Patients	21	Frequency (%)
<b>Surgeries</b>	<b>21</b>	
Total patients with complications	5	23.8
Total procedural complications	11	52.4
Persistent nonunion	2	9.5 1 Waist (revision) 1 Proximal pole (revision) – Both underwent midcarpal arthrodesis
HO	4	19.0 3 Waist (revision) 1 Proximal pole (revision)
Reoperation	3	14.3 2 Proximal pole (revision) –HO excision with capsulectomy –Midcarpal fusion 1 Waist (revision) – Midcarpal fusion
Decreased ROM	1	4.8 1 Proximal pole (revision) –Associated with HO and reoperation
Chronic pain	0	0
Infection	0	0

Abbreviations: HO, heterotopic ossification; ROM, range of motion.

## Limitations

The primary limitations are the poor methodologic qualities of the included studies. All studies used BMP to augment bone graft, screw or wire fixation, or a combination of methods, confounding the interpreted efficacy of BMP in scaphoid nonunion surgery. Although we enumerate all complications reported, there is an inherent risk in retrospective studies of underreporting complications, which may have decreased pooled incidence. All complications were attributed to one study of revision cases,<sup>24</sup> which may suggest publication and outcome reporting bias among the other studies. Further, there was considerable heterogeneity within the demographic and surgical variables, which was attributed to the variable fixation methods and use of bone grafting in the absence of standardized controls.

## Union Rate

This review demonstrated a union rate of 90.5% (range 67–100, 19/21 patients). Pinder et al performed a meta-analysis in 2015 on union and complication rates based on graft type and fixation method (screws, K-wires, no fixation) from 48 publications involving 1,602 patients with scaphoid nonunions from 1999 to 2014.<sup>3</sup> Overall union rate was 90% with CT and MRI in 18/48 studies (93%, 95% CI, 86–98). Union rate with nonvascular grafts was 88% (95% CI 84–92), which was comparable to vascularized at 92% (95% CI, 85–96). Treatment with BMP was not included in their meta-analysis, and the results of the present study suggest a similar union rate.

In this study, union with BMP and different types of bone grafts, or lack thereof, were reported for all 21 patients. The rates were 100% (5/5) for no graft with screws, 100% (9/9) for autologous ICBG with screws (3) and without fixation (6), 0% (0/1) for autologous distal radius with screw, and 86% (6/7) for allograft with screw (2, one persistent nonunion) and without (5). One theoretical use for BMP as an osteoinductive agent is to augment scaphoid nonunion surgery with allograft to limit donor site morbidity; however, there remain few reports in the literature of this use.<sup>3,32</sup>

### Complication Rate

Our literature review demonstrated a patient complication rate of 23.8% (range 0–83, 5/21 patients with 11 total complications). All complications occurred in the revision setting and were comparatively higher than those observed in large reviews. Pinder et al found that complications other than persistent nonunion were inconsistently reported.<sup>3</sup> The complication rates for fixation method was 7% for K-wires (434 patients, most common, HO, 3%) and 5% for screw fixation (645 patients, most common, hardware migration, 3%). Comparatively, HO was observed in four cases (19%) and hardware migration was not observed; however, three patients (14%) underwent a reoperation, including two midcarpal arthrodeses for persistent nonunion and HO excision with capsulectomy. A retrospective review of 1,670 cases of DRBG harvesting reported a 4% complication rate at 4.5 years.<sup>12</sup> Bone graft failure requiring a reoperation of harvesting ICBG was the most common complication (2.3%), followed by DeQuervain's tenosynovitis (1.3%), local soft-tissue infection (0.2%), and fracture through donor site (0.1%). Pinder et al reported complication incidence at ICBG harvest site of 40% (most common, donor site pain/scar sensitivity/lateral femoral cutaneous nerve injury sequelae 42%, iliac crest hyperostosis 28%, hematoma 13%, and infection 4.3%).<sup>3</sup> Reoperation rates were rarely discussed, and the authors concluded with guidelines for consistent reporting to optimize future comparison.

In this analysis, all four cases with HO were observed in a single study and all four patients had scaphoid union.<sup>24</sup> The one instance of a coincident complication was decreased wrist range of motion that required HO excision and capsulectomy. The authors attributed the high incidence of HO to the use of rhBMP-2, revision setting, and prolonged immobilization until determination of radiographic nonunion (3–5 months). The two cases of persistent nonunion in the study by Brannan et al later underwent scaphoid excision and midcarpal arthrodesis.<sup>24</sup> The authors concluded that the risk of motion-limiting HO and reoperation limits the off-label use of rhBMP-2 in their practice to complex cases of scaphoid nonunion in young patients.<sup>24</sup> There were no postsurgical infections reported in any of the studies. This is consistent with previous studies of BMP use in other locations.<sup>19</sup>

The largest study in this review was a randomized controlled trial and reported no complications in the 11 primary cases treated with BMP with either autologous or allogenic bone grafts.<sup>22</sup> Bilic et al reported on a third group of six patients treated with autologous ICBG without BMP who all went on to

scaphoid union at an average of 9 weeks. This time contrasted with the radiographic union at 4 weeks for the patients treated with autologous ICBG and BMP and 8 weeks for patients treated with allogenic ICBG and BMP, leading the authors to conclude that BMP accelerates time to union with autologous bone grafting and is a viable option for mitigating donor site morbidity with the use of allogenic bone grafting. However, the absence of an additional control group treated with BMP alone and without bone graft was not included and limits the interpreted efficacy of BMP when all patients in the study treated with either allograft or allogenic bone graft went on to union.

BMP use for scaphoid nonunion surgery is not currently FDA approved and must be performed with caution. While there may be a role for BMP use in scaphoid nonunion surgery, there is a paucity evidence to suggest that BMP alone promotes scaphoid union. A sufficiently powered, randomized controlled trial with sham BMP preparations is needed to determine the efficacy, dosing, and morbidity of the use of BMP.

### Note

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Defense Health Agency, Department of Defense, or the US Government.

### Ethical Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation at the respective institutions of the cited articles and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the cited studies. This article does not contain any studies with animal subjects.

### Funding

None.

### Conflict of Interest

None declared.

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