

Public awareness of the bone morphogenic protein controversy: Evidence from news publications

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Abstract

Background: Use of recombinant human bone morphogenic protein-2 (rhBMP-2) in spinal fusion has seen a tremendous increase. Public awareness of rhBMP-2 and its complications has not been assessed. The authors studied published news media articles to analyze information provided to the public on this bone graft substitute.

Methods: We utilized the academic database, LexisNexis, to locate newspaper articles published between January 2001 and July 2013. All articles were coded by a coder and reviewed by the principal investigator.

Results: The search identified 87 national and 99 local newspaper articles. Complications mentioned in national newspapers included cancer (24%), retrograde ejaculation (24%), and abnormal bone growth (14%). Local newspapers cited cancer (14%), inflammation (14%), and retrograde ejaculation (9.2%) most frequently. Fifty national (59%) and 35 local (54%) articles had no mention of complications. Sources of evidence cited by articles were (in order of frequency): Governmental agencies, medical research or published studies, healthcare personnel or patients, and companies or corporations.

Conclusions: Only a small percentage of newspaper articles presented potential complications. Despite lack of clear scientific causal relationship between rhBMP-2 and cancer, this risk was disproportionately reported. Additionally, many did not cite scientific sources. Lack of reliable information available to the public reiterates the role of physicians in discussing risks and benefits BMP use in spinal surgery, assuring that patients are making informed decisions. Future news media articles should present risks in an impartial and evidence-based manner. Collaboration between advocacy groups, medical institutions, and media outlets would be beneficial in achieving this goal.

Key Words: Bone morphogenic protein, BMP, news media, public, rhBMP-2, spine fusion surgery

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INTRODUCTION

Bone morphogenic proteins (BMPs) were discovered almost 50 years ago by Marshall R. Urist.^[27,29] Since then, multiple isoforms of BMP have been identified.^[29] Recombinant human bone morphogenic protein-2 (rhBMP-2), the active ingredient in the commercially available Infuse[®] and Amplify[®] (Medtronic, Inc., Minneapolis, MN), was introduced in 2002. This innovative synthetic bone protein is naturally occurring in humans and is not unlike insulin that is essential for life and administered to maintain health. It provided an alternative substitute to traditional bone grafting techniques involving harvesting of autogenous iliac crest bone graft (ICBG) in spinal fusion surgical cases. The disadvantages of ICBG harvesting techniques have been reported to not only increase surgical operative time, estimated blood loss, and rates of infection, but also have been linked to significant and chronic postoperative clinical pain and high rates of complications.^[4] The efficacy and even superiority of rhBMP-2 over autogenous ICBG have been reported in a variety of spinal fusion techniques including anterior interbody lumbar fusion (ALIF), posterior lumbar interbody fusion (PLIF), posterolateral lumbar fusion (PLF), and anterior cervical discectomy and fusion (ACDF).^[4]

In 2002, the Food and Drug Administration (FDA) approved the use of rhBMP-2 products for single-level ALIF spinal fusion. Soon after its introduction, it was being utilized by surgeons off-label for other spinal fusion operations.^[2] Usage of rhBMP-2 (instead of the conventional ICBG) increased in the United States from 0.7% of all fusions in 2002 to 25% in 2006.^[2] A year later, >50% of ALIF, 43% of PLIF, and 30% of PLF procedures were reported to have utilized BMP.^[21] Concurrently, industry-sponsored trials of BMP continued to support the increased use of the recombinant protein in spinal fusion procedures. However, beginning in 2006 there was a series of studies published that reported complications associated with the substance.^[4] Since then, numerous publications have been released highlighting its potential adverse events.^[10] Figure 1 highlights the increase in literary publications concerning the use of rhBMP-2 in the spine.

Today, medical products, procedures, and medications are often advertised on the internet, television and in printed media. Public response to this marketing system has shaped the future of numerous pharmaceutical companies and their products. This paper examines BMP, a bone growth adjuvant increasingly used in on-label spinal operations as well as off-label operations by spine surgeons. The federal government has questioned its complications and safety profile.^[1] Knowing that news coverage of medical risks and complications

are sometimes subjective, misleading and, at times, biased,^[19,20,24] our objective was to describe and assess what information was provided to the public about this bone graft substitute and its complications.

METHODS

We utilized the guided news search function in LexisNexis, an academic database that locates news articles in all major newspapers and news magazines in the United States. On June 30, 2013, we searched for articles with the terms “bone morphogenic protein,” “Infuse[®],” and “Medtronic.” All articles were coded by a coder (EW) and reviewed by a principal investigator (DD). The coding structure included the identification of: (i) headline topic (legal, medical, financial, no topic specified); (ii) year of publication; (iii) complication mentioned (sterility, cancer; infection, etc.); (iv) area where Infuse[®] was used (lumbar, cervical spine); (v) topic of the article, if complication was not reported (FDA approval, sales reports); (vi) type of circulation (national versus local). Each of the above characteristics was noted, and the frequency with which each item appeared in the pool of articles was recorded.

RESULTS

The database search yielded a total of 186 articles from U.S. newspapers published from the time period between January 2001 and June 2013. Eighty-seven were national newspaper articles and 99 were local newspaper articles. There were 9 duplicate national articles and 11 duplicate local articles; no article was coded twice. Headline topics were medical or product-related (35%), financial (investing and stocks) (28%), and legal (lawsuits and bribery charges) (26%). Eleven percent had no particular headline. Figure 2 displays the number of articles published each year.

Initial articles containing reports on BMP were published in 2001, coinciding with the release of the bone substitute. The frequency of articles then steadily decreased until 2005-2006, when negative reports and complications with BMP began to be increasingly reported [Figure 2]. Of the total coded articles, 52 (60%) national articles and 69 (70%) local articles contained no mention of complications associated with BMP. Most of these were prior to 2008 and covered one of these three categories: Sales reports and FDA approval of BMP (65%), conflict of interest concerning its use (30%), and studies critical of its effectiveness (5%). All of the articles (100%) published after 2008 had mention of one complication or more. The vast majority of articles did not mention what anatomic area of the spine was being investigated. The lumbar and cervical spines were most commonly identified in 32% and 26% of articles, respectively.

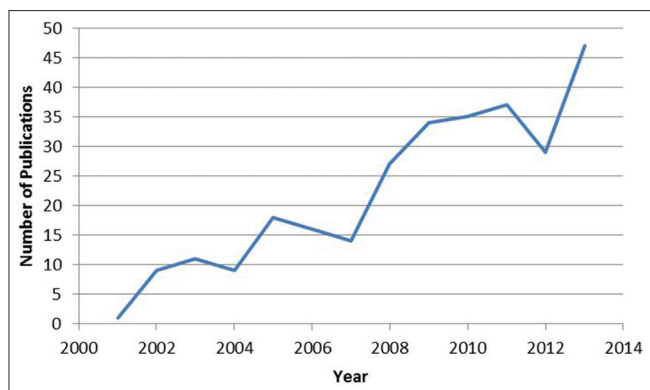


Figure 1: Number of literary publications concerning rhBMP-2 applications in the spine from January 2001 to June 2013

National newspapers

There were a total of 87 articles from national newspapers: 42 from the *Star Tribune*, 33 from *New York Times*, and 12 from the *Wall Street Journal*. A few of these were feature articles (13), many were short, concise pieces (43), and others had an actual extensive description of the topic of BMP (31). Fifty articles had BMP as their main focus, while the other 37 discussed it as part of another main medical topic. Most articles from national newspapers were published in 2008 or after, and almost all articles communicating complications were published post-2008. Opinions expressed in national publications on major complications included mention of cancer (24%), retrograde ejaculation (RE) (24%), and abnormal bone growth (14%). Table 1 displays the other associated complications including infection (8.2%), inflammation (5.8%), airway problems (5.8%), bladder dysfunction (3.5%), and pain (3.5%). Sources of evidence cited or quoted by articles were the local or federal governmental agencies (33), medical researchers or published medical studies (23), healthcare personnel (5), patients (5), and companies or corporations (2). Table 2 lists the percentage of articles citing medical research or publications of evidence with regard to the specific complications.

Local newspapers

There were a total of 99 articles from local newspapers, most commonly from the *St. Paul Pioneer Press* (51), *Investor's Business Daily* (11), and *Finance and Commerce* (5). Most articles were brief and short news items (57), 29 were features, and only 13 provided an extensive description of the BMP topic. Additionally, the majority (67) discussed BMP as part of articles on various medical issues, while only 32 had BMP as their central focus. Unlike national newspapers, local newspaper articles began to surface earlier in 2006 with reports of Medtronic bribing physicians to fabricate studies and under-report its risks. The first articles on complications were in 2008. Local newspapers and news magazines that reported complications cited cancer (14%), inflammation (14%),

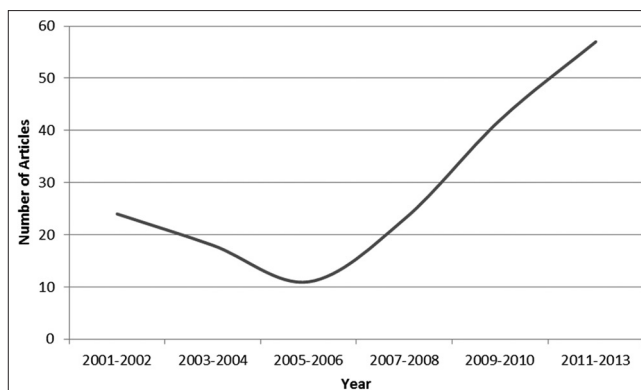


Figure 2: Number of newspaper and news magazine publications concerning BMP from January 2001 to June 2013. Note the significant increase beginning in 2005, a few years following reported evidence of complications concerning the drug

Table 1: Complications mentioned in major national U.S. newspapers describing the use of BMP in spinal fusion procedures

Complication mentioned	Frequency (%) ^a
Cancer	20 (24)
Retrograde ejaculation	20 (24)
Excessive bone growth	12 (14)
Infection	7 (8.2)
Inflammation	5 (5.8)
Airway	5 (5.8)
Pain	3 (3.5)
Bladder dysfunction	3 (3.5)
Bone loss	0 (0.0)
No complications mentioned	50 (59)

^aValues and percentages reflect the frequency in which complications were mentioned in articles after 2006, when increasing scientific publications and federal agencies began reporting such complications. BMP: Bone morphogenic protein

Table 2: Frequency of articles in national newspapers citing medical research or publications as evidence in regard to complications of BMP use in spinal fusion surgery

Complication mentioned	Frequency (%)
Cancer	14 (70)
Retrograde ejaculation	12 (60)
Excessive bone growth	6 (50)
Infection	4 (57)
Inflammation	3 (60)
Airway	1 (20)
Pain	2 (67)
Bone loss	0 (0.0)
Bladder dysfunction	2 (67)

BMP: Bone morphogenic protein

and RE (9.2%) most commonly. Table 3 presents these and other associated complications, which include excessive bone growth (7.7%), pain (7.7%), airway problems (6.2%), infection (6.2%), and bone loss (4.6%). Most newspapers cited either governmental (20) or

research (17) sources in their articles, with a few citing companies and businesses (6) and patients and healthcare personnel (6). Table 4 summarizes the sources of evidence with regard to the specific complications.

DISCUSSION

Public perception of medical drugs in general is largely influenced by news media publications and reports. The importance of reporting medical news accurately and scientifically is paramount to the public having an educated view on medical drugs and devices. In our current report, we identified notable trends among the news publications with regard to rhBMP-2. In our study, we found that from 2001 to 2005, news publications highlighted the release of BMP and its subsequent FDA approval with over half of these articles not mentioning adverse complications. After 2005, scientific reports of possible adverse events announced by the FDA and other independent researchers were cited by newspapers and by 2008, we found that the over-representation of complications from rhBMP-2 was significantly increased

and seen in 100% of national and local news media. Additionally, descriptions of previously unrecognized complications were also increased in their presentations to the public.^[23]

RhBMP-2 has only been approved by the FDA for use in anterior lumbar spine fusion procedures using a very specific interbody spacer. News articles most often cited the lumbar spine (32%) as the area where BMP was used but other articles reported its off-label use in the cervical spine. Although it is at the physician's discretion to use a given drug for indications not approved by the FDA, it was reported that spine surgeons had allegedly used BMP in an off-label manner as a result of financial reimbursement by manufacturing companies.^[28] Additionally, our search found news articles that reported life-threatening complications with the use of BMP in the cervical spine such as inflammation with concomitant airway compromise and death even though this was reported as scientific case reports and rare events. The formation of a negative public opinion toward rhBMP-2 certainly could have been impacted by these findings. An investigation was initiated by federal prosecutors into allegations that the manufacturer, Medtronic, had omitted safety concerns associated with Infuse[®] and had paid millions to researchers and physicians to assert its safety.^[26] On May 16, 2012, the Star Tribune reported that the federal investigation had been closed.^[28]

In 2011, amid the controversy of the effectiveness of BMP, Medtronic initiated and contracted with the Yale Open Data Access (YODA) group, and provided funds for an independent analysis of data published by Medtronic and its researchers.^[20] YODA selected two independent research teams, Oregon Health Sciences University (OHSU) and York University in the United Kingdom, to analyze the data and report their findings.^[12,22] While the OHSU group reported no significant difference in the fusion rate using rhBMP-2 compared with ICBG, the York group found modest clinical benefits with improvement in fusion rates with BMP. Both studies detailed an increase in the rate of all complications; however, they only reported a statistically significant increase in cancer rates when they compared rhBMP-2 with ICBG. Additionally, they both argued that reports of rhBMP-2 provided by the manufacturer inadequately presented adverse events and appeared to contain serious selective reporting.^[12,22]

Abnormal and unwanted bone growth

It has been suggested that BMPs may be toxic to neural tissue and may incite a vigorous inflammatory response in some patients.^[13] After BMP was implanted, some patients reported increased discomfort and pain leading to a concerning rise in incidence of reoperation. A recent study by Crandall *et al.* reported postoperative nerve damage and cage migration as sources of pain in

Table 3: Complications mentioned in local U.S. newspapers describing the use of BMP in spinal fusion procedures

Complication mentioned	Frequency (%) ^a
Cancer	9 (14)
Inflammation	9 (14)
Retrograde ejaculation	6 (9.2)
Pain	5 (7.7)
Excessive bone growth	5 (7.7)
Infection	4 (6.2)
Airway	4 (6.2)
Bone Loss	3 (4.6)
Bladder dysfunction	0 (0.0)
No complications mentioned	35 (54)

^aValues and percentages reflect the frequency in which complications were mentioned in articles after 2006, when increasing scientific publications and federal agencies began reporting such complications. BMP: Bone morphogenic protein

Table 4: Frequency of articles in local US newspapers citing medical research or publications as evidence in regard to complications of BMP use in spinal fusion surgery

Complication mentioned	Frequency (%)
Cancer	7 (78)
Retrograde ejaculation	4 (67)
Excessive bone growth	2 (40)
Infection	3 (75)
Inflammation	1 (11)
Airway	0 (0)
Pain	1 (20)
Bone loss	1 (33)
Bladder dysfunction	0 (0.0)

BMP: Bone morphogenic protein

patients.^[7] Additionally, they found that complications such as seroma and osteolysis occurred more often at higher doses.^[7] Fu *et al.* noted that BMPs may cause wound complications and bone formation in abnormal sites.^[12] In the cervical spine, it was noted that abnormal bone growth can be excessive, blocking the patient airway and causing difficulty swallowing and speaking.^[12] These complications of excessive bone formation were the third most frequently mentioned complications in national publications (14%) and fourth in local newspapers (5%).

Sexual and urological complications

RE was a prevalent complication reported with the use of BMP bone graft. RE is a condition in men where the internal vesical sphincter muscle at the base of the bladder fails to contract during ejaculation.^[25] While in reproductive young males RE could lead to sterility and the need for artificial insemination procedures, the female equivalent to this disorder has not been clinically described. RE was only noted when BMP was implanted in the lumbar spine in ALIF procedures, presumably due to its proximity to the reproductive system and bladder. According to a published report by Lubelski *et al.*, ALIF procedures already poses a high risk of numerous other urological complications, which are further exacerbated by both the inflammatory response potentially associated with rhBMP-2.^[15] In their study of two-level ALIF spinal fusion procedures in the lumbar spine region, Carragee *et al.* reported that the experimental group who had fusions with BMP-2 had 7.2% incidence of RE while it was only reported in 0.6% of patients in the control group.^[5] Although RE could be a problematic complication for young men of reproductive age having spinal fusion with BMP in the lumbar spine, our analysis found that this risk was mentioned in 24% of national newspapers and the third most commonly mentioned in local newspaper articles at 14%.

Risk for cancer

Our analysis found that the risk of cancer was commonly mentioned in 24% of major newspapers (1st highest, tied with RE) and 14% (1st highest, tied with inflammation) of local newspaper articles. Not all of the articles listed recognized research publications as cited evidence (<78%). The issue of cancer risk is an especially important one and multiple studies have reported conflicting evidence for this controversial risk.

Carragee *et al.* demonstrated that patients who were treated with rhBMP-2 were 4-5 times more likely to develop a new malignancy.^[4,11] The study also reported that BMP may fuel existing cancers and its use is only suggested in cases where ICBG is more problematic, especially in older patients.^[3] Other studies reported substantial evidence that the risk of cancer is dose-dependent, with higher doses of BMP increasing the

risk of new malignancies.^[6,11] Specifically, Caragee *et al.* noted that BMP stimulates the invasiveness of breast and pancreatic cancer cells and the mesenchymal transition of epithelial cells in lung cancer.^[3]

Two recent population-based studies, however, presented the issue of cancer and BMP in a different light. Lad *et al.*^[14] evaluated the association using a national database in which two groups, a BMP-treated group and a nontreated group, were propensity matched and compared. The propensity matched cohorts consisted of 2349 patients in each group with no significant differences in age, sex, type of insurance, or comorbidities. The authors found *no significant difference* between the association of BMP and the diagnosis of any sort of cancer (9.4% vs. 7.9%; $P = 0.08$). When further stratified by cancer type, only benign neoplasms were found to have an association with BMP (6.3% vs. 4.9%; $P = 0.04$). These included benign tumors of the nervous system and other unspecified sites. It was concluded that the use of BMP, although it may not increase overall cancer risk, may carry a significant increase in benign tumors. The study also pointed out that a higher dose of BMP was used in the above-mentioned Carragee *et al.* study. Another recent study pointed out a lack of correlation between cancer risk and even with high dose BMP used for spinal fusion.^[17]

Cooper *et al.*^[8] published the largest national study on the use of BMP in lumbar fusion surgery with a median follow-up of more than 4 years. Their study of almost 150,000 patients involved 15.1% receiving BMP with their fusion surgery. As a whole, an association between the osteoinductive adjuvant and the incidence of cancer was not present (hazard ratio: 0.98, 95% confidence interval [CI]: 0.95-1.02). Also, there was no difference between the two groups for each of the many individual cancer types considered, including bone and brain cancers.

Although *in vivo* and *in vitro* studies have shown evidence that BMP can cause neoplastic progression, there is no clear biological basis for how its administration can influence cancer risk.^[14] Moreover, others have described its antineoplastic properties such as impedance of cellular growth and proliferation.^[8] In fact, a recent animal study demonstrated that local administration of rhBMP-2 to breast cancer within the spine did not induce tumor growth but actually diminished its progression and delayed the onset of paresis.^[16]

Significance of our analysis for physicians

Evidence from contradictory studies suggests that cancer risk with BMP use may have been exaggerated in newspaper and news magazine articles. Lack of reliable information has not been made to the public and may, in fact, have created unnecessary patient anxiety. Since the risk of cancer is the most common complication publicized by the news media, surgeons utilizing BMP

must be prepared to: (i) explain the controversial nature of the cancer risk claim, (ii) provide patients with as much verbal and/or written information as is necessary to answer their questions, (iii) ensure full patient awareness of all potential benefits and risks, (iv) counsel patients, (v) assist patients in making an informed decision about whether to include or not include BMP in an upcoming surgery, and (vi) support the patient's choice.

It might be prudent to involve medical advocacy groups or medical institutions with media outlets to issue more frequent public statements regarding new medical research findings. These articles could present and discuss risks and complications in a more impartial and evidence-based manner than those authored by newspaper and news magazine reporters. These articles would then add to the print media and internet searches used by the public.

It is important that there be transparency in the dissemination of medical information. The harms and risks associated with BMP and all medications, products and procedures need to be presented without bias and without the potential impact of a conflict of interest. Only with reliable information and all the pertinent facts can a patient intelligently participate in decision-making and make informed choices.

Limitations in our study

The LexisNexis database does not represent all printed material and the search may miss articles on the topic. As such, findings may represent a skewed view of the topic. Besides printed sources like newspapers, patients may get their information online. The internet is commonly used by the public for personal research about a diagnosis, available treatments, risks, and complications. Articles that have been published in newspapers and news magazines may be referenced and read (or re-read) during this search. Although scientific articles (research studies, clinical trials, case reports, etc.) may have been published in professional medical journals, these articles may not be as readily available or as easily understood by the public. Therefore, it is important for physicians to inform their patients of the most recent medical research and to explain any relevant evidence that will help them make an informed choice.

CONCLUSION

Our analysis of published national and local newspaper and magazine articles on rhBMP-2 indicated that only a small percentage of printed media presented accurate and responsible information on the numerous potential complications. The risk for cancer was disproportionately reported and of specific concern because only a small fraction of articles cited scientific publications. Based

on our study, the lack of reliable information publically available makes it even more important for physicians to discuss both the risks and benefits of using BMP in spinal surgery. More news media articles are needed that present and discuss risks and complications in an impartial and evidence-based manner; advocacy groups and medical institutions with media outlets may be able to help facilitate this goal.

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