Intra-abdominal Adhesion Prevention: Are We Getting Any Closer?

James M. Becker, MD, and Arthur F. Stucchi, PhD

We are pleased to comment on this timely article by Fevang et al[1] that highlights a problem that has plagued abdominal surgeons since the earliest reports of abdominal surgery: intra-abdominal adhesions. Unfortunately, in this day and age when surgical sophistication and new operating room (OR) technology are nearly outpacing our ability to stay current, our age-old nemesis, the intra-abdominal adhesion, remains a significant, long-term, and recurrent postoperative problem.

Many studies, including by our own group,[2] have reported that up to 94% of patients develop primary abdominal adhesions following laparotomy.[3] Abdominal adhesions, whether caused by peritoneal trauma, radiation, infection, or are congenital, are associated with a range of complications including difficult and dangerous reoperation, infertility, and chronic abdominal and pelvic pain; however, the most serious and life threatening sequela is adhesive small bowel obstruction (ASBO). Despite the retrospective study by Beck et al[4] showing that bowel obstruction, adhesiolysis for obstruction, and additional abdominal operations occurred more often after abdominal surgery than was previously published, we lacked an accurate account of the recurrence rate following these procedures until the present report. Fevang et al[1] showed that nearly 30% of the patients who underwent lysis of adhesions (LOS) for ASBO required yet another operation to lyse recurrent adhesions. This is a troubling statistic because it not only brings added risk to the patient, but also further economic burden to an already overwhelmed health care system. These data also suggest that surgery to lyse adhesions is nearly as adhesiogenic as the original operation. Although two-thirds of the initial ASBO incidences occurred within the first 5 years, the fact that nearly one-quarter of the ASBO complications occurred more than 10 years after the initial surgery, and considerable risk was present 20 years even after an ASBO episode, clearly places adhesions in the long-term complication category.

Interestingly, we have known about adhesions for at least 1500 years now, when pleural adhesions were described in the Babylonian Talmud in 440 A.D.[5] Some accounts suggest that ancient Egyptians, known for their detailed descriptions of human anatomy, described pelvic adhesions even centuries before. Although adhesions caused by peritonitis have been recognized since the early 1700s, it was not until the widespread use of anesthesia in the mid-1800s that more invasive abdominal procedures became more prevalent and the extent of the problems caused by intra-abdominal adhesions was realized. By the 1880s, the first published reports describing the use of adjuvants for adhesion prevention began to appear in the surgical literature. What followed over the next 100 years or so was a plethora of scientific reports and anecdotal accounts that described

From the Department of Surgery, Boston University Medical Center, Boston, Massachusetts.
Reprints: James M. Becker, MD, James Utley Professor of Surgery, Chairman, Department of Surgery, Boston University Medical Center, One Boston Medical Center Place, Boston, MA 02118. E-mail: James.Becker@bmc.org.

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the use of everything from amniotic fluid, bovine cecum, gold-beater's skin, shark peritoneum, fish bladder, vitreous of calf's eyes, various gums, lubricants, fluids, gels, polymers, physical barriers, and a host of mechanical separation methods to prevent adhesions. Unfortunately, the results of most of these studies were equivocal, with no more than a small percentage of success. The point that we are attempting to make by detailing these important historical events is to emphasize that we have known about adhesions for a very long time, yet the strides we are making in our understanding of the basic physiology of adhesion formation are seriously lagging. The present communication[1] makes it painfully clear that we must understand the outcomes of our unsuccessful attempts to gain a better understanding of the pathophysiology of adhesiogenesis. A quick glance at recent issues of the major surgical journals and even a MEDLINE search of the past few years show only a few basic science papers addressing the molecular mechanisms underlying de novo adhesion formation. Current treatment of adhesions is primarily focused on prevention through meticulous surgical technique in concert with the use of protective physical barriers or gels.

By far, the most common cause of primary and recurrent intra-abdominal adhesions is prior laparotomy, a point that is clearly demonstrated in the present communication, in which 83% of the patients requiring surgery for ASBO had at least 1 prior surgery.[1] Prior laparotomy implies that peritoneal trauma is undoubtedly the initiating event. However, adhesion formation is a complex interaction of cellular components involved in inflammation and tissue repair. Although the interrelationships and identity of all the factors involved in adhesion formation have yet to be defined, the key pathogenic elements of adhesion formation have been fairly well understood for more than half a century. These include serosal and subserosal trauma accompanied by an inflammatory cell infiltrate, fibrinous exudation, formation of filmy, fibrinous adhesions between serosal surfaces, and, unless resolved, progression to fibrous adhesions. Interestingly, as noted, this depth of understanding dates back over 6 decades,[6] at which time adhesion prevention was focused on the removal or dissolution of fibrin deposits in the peritoneum. Basically, this remains our level of understanding today. We now know from our own research efforts in animal models[7] and in humans[8] that the peritoneal fibrinolytic capacity is acutely compromised within hours of surgical trauma, thus preventing the resolution of newly forming fibrinous adhesions. Work in our own laboratory has also identified the proinflammatory peptide, substance P, in mediating a reduction in tissue plasminogen activator levels within hours of surgery,[9] although the molecular mechanism(s) of this pathology have yet to be determined.

Interestingly, it was recently shown[10] that adhesions, in addition to being highly vascularized, are also innervated with substance P-containing sensory neurons, suggesting that adhesions themselves are capable of generating pain stimuli and perhaps finally suggesting a mechanism to explain the pain associated with adhesions. Pain following abdominal surgery has always been a difficult issue for surgeons to contend with, but as pointed out in the paper by Fevang et al,[1] ASBO may just be the "tip of the iceberg" for these patients. Even though 40% of patients experienced abdominal pain after surgery, Fevang et al feel this estimate is too low, suggesting that this patient group is not only at high risk for recurrent ASBO, but also suffers from more abdominal pain than the background population. This is troubling and further evidence for an increased effort into a better understanding of adhesion formation.

Since the earliest days of abdominal surgery, surgeons have encountered intra-abdominal adhesions and have learned over the years to recognize and deal with their complications, including ASBO. Yet, despite our best efforts in practicing the surgical principals of adhesion prevention—gentle handling of tissues, meticulous control of bleeding, avoidance of foreign materials, excision of necrotic tissue; minimization of ischemia and desiccation; and prevention of infection—adhesions continue to occur with high incidence, especially for certain types of abdominal surgery. Colorectal surgery has a particularly bad reputation for subsequent ASBO. At the larger centers that perform proctocolectomy with ileal pouch-anal anastomosis, such as the Cleveland Clinic and the Mayo Clinic, the reported incidence of ASBO was 25% of 1500 patients and 15% of 1193 patients, respectively. In both cases, approximately one-third required reoperation, confirming the high risk for ASBO after colorectal procedures. In our own series of nearly 700 such operations, the incidence of ASBO is approximately 17% with 6% requiring surgical intervention. What the present study by Fevang et al highlights, and something that needs to be followed more closely, is the nearly one-third recurrence rate after the initial operation for ASBO. The fact that ASBO can manifest 20 or more years after an abdominal procedure makes it a particularly difficult complication to contend with and to follow.

Clearly, in addition to the apparent perioperative morbidity and mortality associated with multiple operations for recurrent ASBO, the problem is also financially noteworthy. Increased operating times coupled with longer hospital stays for ASBO and other adhesion-related problems account for rapidly escalating healthcare costs. When Ray et al[11] assessed the financial impact of adhesiolysis on health care costs in 1994, they estimated an annual price tag of $1.3 billion in the U.S. alone. Data from the Health Care Financing Administration showed that Medicare paid more than $3.2 billion for adhesion-related complications in 1996.

An interesting point raised by the Ray et al[11] study was that the increased use of laparoscopy for abdominal procedures between 1988 and 1994 did not appear to be associated

with a concomitant reduction in the hospitalization rate for ASBO, suggesting that although minimally invasive techniques may offer advantages such as decreased morbidity, whether such procedures actually reduce adhesion formation remains unclear at this time. Laparoscopic adhesiolysis for ASBO has also come to the forefront[12] and obviously offers similar advantages over laparotomy. However, there are no long-term results, and thus, the question concerning decreased recurrence after laparoscopy compared with laparotomy requires further investigation.

Abdominal adhesions are truly the nemesis of the abdominal surgeon and troublesome from many aspects. Adhesive small bowel obstruction, inadvertent enterotomy at reoperation, prolonged operative times, increased clinical workload, and high financial costs are important adhesion-related problems that need to be addressed. Based on the high rates of recurrence and the longevity of the risk demonstrated in this paper, we, as surgeons, must attempt to reduce the burden of adhesive disease. Significant advances have been made in the business of adhesion prevention, such as the multicentered, double-blinded, prospective, randomized clinical trial preformed at 11 centers, including Boston University Medical Center, that showed that the bioresorbable physical barrier Seprafilm® (Genzyme Corporation, Cambridge, MA) was efficacious in reducing adhesions to the site of application.[2] Despite this significant advance in adhesion reduction, it is unclear whether physical barriers can provide protection in areas other than the site of application. Our own studies have shown that adhesions can readily form at uninjured peritoneal sites distant from the midline incision and that a midline laparotomy initiates a generalized peritoneal inflammatory response.[13] Hence, a single preventative measure, such as a physical barrier alone applied to 1 area, may not completely eliminate adhesion formation.

Although this paper by Fevang et al[1] is somewhat reiterative in what we already knew about adhesions, it brings to bear some significant issues regarding long term risk and the potential for a lifetime of chronic pain. It also brings to light the enormity of the problems and challenges that lie ahead. We are making progress, but far too slowly. We are just beginning to understand the intricate role of the mesothelium in the early formation of adhesions and how mesothelial cells regulate the peritoneal fibrinolytic environment. More basic research into the mechanisms of adhesiogenesis is truly needed so we can identify new opportunities for therapeutic intervention. Cures for some of the most devastating diseases and pharmacologic control of conditions such as hypertension and hypercholesterolemia were not discovered until we had a clear understanding of the underlying metabolic defects. It has taken us more than a century to get where we are today in adhesion prevention: a 94% occurrence rate and a 30% recurrence rate. Let us strive to make the accomplishments of the next decade more fruitful.

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