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The Effect of Smoking on Spinal Fusion

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Abstract

Background

Spinal fusion surgery is performed about half a million times per year in the United States and millions more worldwide. It is an effective method for reducing pain, increasing stability, and correcting deformity in patients with various spinal conditions. In addition to being a well-established risk factor for a variety of medical conditions, smoking has deleterious effects on the bone healing of spinal fusions. This review aims to specifically analyze the ways in which smoking affects the outcomes of spinal fusion and to explore ways in which these negative consequences can be avoided.

Purpose

This article provides a complete understanding of the ways smoking affects spinal fusion from a biochemical and clinical perspective. Recommendations are also provided for ways in which surgeons can limit patient exposure to the most serious negative outcomes associated with cigarette smoking.

Study Design/Setting

This study was a retrospective literature review done using the NCBI database. The research was compiled at NYU Hospital for Joint Diseases and the NYU Center for Musculoskeletal Care.

Methods

A comprehensive literature review was done spanning research on a variety of subjects related to smoking and spinal fusion surgery. The biochemistry of smoking and fusion healing were examined in great detail. In addition, both in vivo animal studies and human clinical studies were evaluated to explore fusion success related to the effects of smoking and its biochemical factors on spinal fusion surgery.

Results

Smoking significantly increases the risk of pseudoarthrosis for patients undergoing both lumbar and cervical fusions. In addition to nonunion, smoking also increases the risk of other perioperative complications such as infection, adjacent-segment pathology, and dysphagia. Treatment options are available that can be explored to reduce the risk of smoking-related morbidity, such as nicotine replacement therapy and use of bone morphogenetic proteins (BMPs).

Conclusions

It has been clearly demonstrated from both a biochemical and clinical perspective that smoking increases the rate of perioperative complications for patients undergoing spinal fusion surgery, particularly pseudoarthosis. It has also been shown that there are certain approaches that can reduce the risk of morbidity. The most important recommendation is smoking cessation for four weeks after surgery. In addition, patients may be treated with certain surgical techniques, including the use of BMPs, to reduce the risk of pseudoarthrosis. Lastly, nicotine replacement therapy is an area of continued interest in relation to spinal fusion outcomes and more research needs to be done to determine its efficacy moving forward.

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Introduction

Spinal arthrodesis (fusion) surgery is performed about half a million times per year in the United States and millions more worldwide.[1] It is an effective method for reducing pain, increasing stability, and correcting deformity in patients with conditions such as spondylolisthesis, spinal stenosis, tumors, vertebral fractures, scoliosis, kyphosis, and other degenerative disc diseases causing myelopathy and radiculopathy, among other symptoms.[2] There are a number of risk factors and co-morbidities that have the potential to negatively influence the outcome of the procedure. One of the most prevalent of these co-morbidities is cigarette smoking. In addition to being a well-established risk factor for a variety of medical conditions such as hypertension, coronary artery disease, cancer, and hyperlipidemia, smoking has deleterious effects on the spine and musculoskeletal system.[3] This article provides a comprehensive and updated review of how smoking affects spinal fusion surgery, including the effect on the rate of fusion success and associated complications, as well as recommendations on how to minimize or eliminate the negative effects of perioperative smoking. With a full understanding of the systemic and local effects of smoking and their influence on specific complications associated with spinal fusion surgery, surgeons can be better prepared to devise customized treatment plans for patients and explain to patients how smoking affects their surgical outcomes.

Smoking influences spinal fusion surgical outcomes in many ways. To fully appreciate these effects, it is first necessary to understand how smoking affects vertebral bone, the biology of how fusions heal, and how smoking affects this process at the level of gene expression. The molecular effects range from inflammatory mediators and other cytokines to osteoinductive proteins and extracellular matrix components. Smoking's effects on fusion rate are also wide-ranging and depend on many factors, including the type of arthrodesis procedure, spinal location and number of levels of the procedure, and type of graft used among other variables. Recommendations are made regarding the time frame of smoking cessation and other therapies that may improve outcomes in patients who continue to smoke.[4-12]

Biological Effects of Smoking

Vertebral Bone Damage Caused by Smoking

Smoking causes changes in vertebral bone that result in conditions requiring surgical intervention with spinal arthrodesis. Due to its osteoporotic effects, smoking causes increased vertebral and endplate porosity and decreased trabecular thickness.[13] Smoking increases cortisol, causes estrogen imbalance, kills osteoblasts, impedes calcitonin, decreases oxygen supply, and decreases calcium absorption.[14-27] By increasing the levels of cortisol in the body, smoking decreases bone formation by inhibiting periosteal cell proliferation.[28] Cortisol has also been shown to downregulate the synthesis of collagen. Inhibition of calcitonin is also a contributing factor to decreased bone formation. In addition, downregulation of estrogen is responsible for decreased bone density, especially in post-menopausal women. In these patients, levels of estrogen are low to begin with, and smoking decreases estrogen levels further. The cumulative effect of all of these changes is to increase bone resorption and decrease bone formation. From a clinical perspective, Ward et al. were able to show that smoking significantly increased the risk of a lumbar spinal fracture.[26] This correlation was demonstrated to an even greater degree than patients with hip or long bone fractures, suggesting that smoking may have a greater weakening effect on vertebral bone than other parts of the skeleton.

How Does a Spinal Fusion Heal?

To understand how smoking affects the process of bone healing in a spinal fusion, it is first crucial to understand how a healthy bone fusion heals. The mechanism by which a spinal arthrodesis occurs is very similar to the healing of long bone fractures via secondary bone healing except for the fact that a bone graft is used in spinal fusion. Bone healing occurs in three stages; the early inflammatory stage, the repair stage, and the late remodeling stage.[35] During the inflammatory stage, which encompasses the first week of bone healing, a hematoma develops with subsequent infiltration of fibroblasts and inflammatory cells such as macrophages, monocytes, lymphocytes, and polymorphonuclear cells.[29] The result is a formulation of granulation tissue, vascular ingrowth, and migration of mesenchymal cells. The repair stage is

the point at which fibroblasts lay down a stroma that supports vascular ingrowth. At this stage, smoking has a significant negative effect on angiogenesis.[36] The next four to six weeks of repair consist of development of a collagen matrix, formation of a soft callus, and eventual ossification of the callus to form a bridge of woven bone between the fracture fragments. The final stages of fracture healing occur over the following months to years. The remodeling stage is the final fine-tuning of the bone in which mechanical stress plays a major factor. Areas of weakness induce bone formation and areas of strength promote resorption.

The main difference between spinal fusion and healing of long bone fractures via secondary bone healing is the utilization of a bone graft or bone graft substitute for use as a structural support and/or scaffold in a spinal fusion; autograft bone, allograft bone, synthetic bone graft substitutes or extenders, and bone promoting molecules or cells (or various combinations of all of these options) can be utilized. When using a graft to facilitate the healing process, there are three properties to consider: osteogenesis, osteoinduction, and osteoconduction.[30]

Osteogenesis is the ability of a graft to produce new bone, which is dependent on the presence of live cells in the graft. These cells are either osteoprogenitor cells or inducible osteogenic precursor cells. They function in the early part of the healing process to unite graft with bone and must be protected during the procedure to ensure viability.[29]

Osteoconduction describes the ability of the graft to serve as a scaffold for bone healing. This permits angiogenesis and the infiltration of osteogenic precursor cells. Smoking has significant detrimental effects because it disrupts angiogenesis at this stage of healing.

Lastly, osteoinduction is the ability of graft material to induce stem cells to differentiate into mature bone cells.[29] At this point in the process, the presence of bone factors, demineralized bone matrix, and other local mediators are necessary to facilitate osteoinduction.[31] Smoking has negative effects at this stage due to its interference with signaling molecules involved with osteoprogenitor cell differentiation.

Smoking affects fusion healing mainly because of how it influences local vasculature and metabolic factors. These metabolic mediators are wide-ranging and include many growth factors released from platelets, macrophages, and fibroblasts.[29] They induce differentiation of mesenchymal-derived cells into bone cells and facilitate bone healing. The proteins that promote bone healing are bone morphogenic proteins (BMPs), insulin-like growth factors, transforming growth factors, platelet-derived growth factors, and fibroblast growth factor.[32] One of the most important classes of proteins involved in this process is BMPs, which are glycoproteins derived from bone matrix.[29] They help induce mesenchymal cells to differentiate into bone cells and can be significantly affected by smoking. Another local mediator affected by smoking is TGF-β. The main function of this protein in fusion healing is to facilitate angiogenesis.[34]

Molecular Effects of Smoking on Fusion Healing

For healing to progress naturally, the fusion site must have adequate blood supply, proper levels of gene expression, and mechanical stability. Smoking cigarettes during the period of healing negatively affects all three of these factors. For many years, the increased rates of nonunion in smokers were thought to result from calcitonin resistance, increased bone resorption, and interference with osteoblastic function.[37] While these metabolic changes certainly contribute to impaired fusion healing, there are a number of others molecular influences on the fusion process. Many of these are proteins and other cytokines and include BMPs 2, 4, and 6, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and type I and II collagen. Theiss et al. used a rabbit model to show how nicotine affected the rates of gene expression of all of the above cytokines throughout the fusion process.[37] In addition, they evaluated gene expression in two different zones of the fusion mass: the outer zone (adjacent to the transverse process) and the inner zone (in between the transverse processes). The differences in gene expression they discovered that were the biggest contributors to nonunion were found in the inner zone.

Two of the most significant gene products that nico-

tine reduces the production of are bFGF and VEGF. They are particularly important to angiogenesis within the fusion mass. VEGF is a mitogen for endothelial cells, acting to increase vascular permeability and improve tissue oxygenation and nutrient delivery.[37] bFGF is activated by the heparin sulfate-degrading enzymes and is an important protein in angiogenesis because it plays a role in the subendothelial extraceullar matrix of blood vessels. It was previously demonstrated that nicotine is a systemic vasoconstrictor and inhibitor of efficient nutrient supply, but it has now been shown to additionally restrict neovascularization within the fusion mass. Nicotine also reduces the expression of BMPs within the inner mass, particularly BMPs 2, 4, and 6. These proteins, which are members of the TGF-β super family, are well-known inductors of osteogenesis. They play a vital role in spinal fusion by activating pathways involved in osteoblast differentiation and formation of new bone within the fusion mass. Lastly, nicotine has been found to reduce the levels of both type I and II collagen within the fusion mass. This reduces the compressive and tensile strength of the fusion mass and increases the likelihood of a nonunion. The above cytokines are only a small window into the effects of nicotine on gene expression within the fusion mass. More work needs to be done to consider the effects of both nicotine and non-nicotine components of cigarette smoke on levels of various cytokines.

Clinical Outcomes

There are a variety of ways in which smoking affects clinical outcomes of spinal fusion surgery. These include differences in fusion/nonunion rates, infection rate, delayed wound healing, and pain relief. A number of studies have evaluated the efficacy of different surgical techniques, nicotine replacement therapies, osteoinductive therapies, and other factors affecting patient outcomes.

In Vivo Animal Studies and Lumbar Fusion

Wing et al. showed increased rates of non-union in a rabbit model with only nicotine as opposed to cigarette smoke. Fusion occurred in seven of 13 control rabbits, four of 13 rabbits that "quit" nicotine one week pre-operatively, and none of the 14 rabbits exposed to continuous nicotine.[40] This showed a statistically significant difference between the control and continuous nicotine and between the discontinued nicotine and continuous nicotine groups. Silcox et al. were able to demonstrate similar results in another animal model. In their study, 56% of control animals were judged to have solidly fused lumbar spines whereas there were no solid fusions in the nicotine group.[38] However, in contrast Daffner et al. showed in an animal model that a small (5.25 mg) dose of nicotine actually improved fusion rates compared to the control.[43] These findings suggest that effects of nicotine on fusion may be dose-dependent and that the negative of effects of smoking on nonunion may be attributable to other components of cigarette smoke. Lee et al. used a rabbit model to show that acute cigarette inhalation may delay but not prevent the spinal fusion process.[33]

Lumbar Fusion Outcomes in Smokers

One of the biggest complication concerns for smokers undergoing spinal fusion procedures is the development of a pseudoarthrosis or non-union. There have been a number of clinical studies that demonstrate negative fusion outcomes for smokers. Glassman et al, in a large series of patients who underwent single level posterior instrumented lumbar fusions, showed a significant difference in non-union rate between non smokers and those who continued to smoke after the surgery (14.2% vs. 26.5%).[38] Interestingly, patients who were previously smokers but quit after surgery for longer than six months had a nonunion rate of 17.1%. This suggests that smoking cessation post-operatively significantly improves fusion outcomes, but not quite to the level of nonsmokers. Andersen et al. showed similar results. Patients who smoked more than 10 cigarettes per day and underwent a fusion procedure at two or more levels increased the risk of nonunion (OR 2.01).[39] Hermann et al. showed that fusion success in nonsmokers is greater than smokers and that reoperation rates caused by pseudarthrosis were greater in smokers.[44] The nonunion results in smokers are not necessarily uniform across all lumbar fusion studies. Bydon et al. obtained results that were consistent with the above findings for pseudarthrosis after 2-level posterolateral fusions, but not necessarily on single-level PLF.[42] This demonstrates that the surgical technique could also play a role in the risk of non-union. Seicean et al.

produced similar findings in terms of the ambiguity of the effects of smoking. Their study determined that smoking was not associated with early (30 day) perioperative morbidity or mortality.[46] It should be noted that this is a database study and is limited to review of 30 day complication rates, therefore the difference in fusion rates are not captured and it does not include clinical outcome scores. Nevertheless, the effects of nicotine alone in the absence of cigarette smoke needs to be further explored.

Based on the wide base of clinical results and knowledge about the molecular effects of smoking on fusion healing, it is safe to conclude that smoking is associated with a higher rate of lumbar nonunion. However, more studies are needed to determine what contents of cigarette smoke produce negative outcomes as well as which types of fusion procedures (number of levels, technique) places smokers at highest risk for non-union. It is possible that the negative effects of smoking are not exclusively caused by nicotine and that there is a certain dose-dependence to fusion rates.

Cervical Fusion Outcomes in Smokers

The effects of smoking on the development of pseudoarthrosis in cervical fusion procedures are less clear than in the lumbar spine. For one level anterior cervical discectomy and fusion (ACDF), multiple studies have showed no difference in fusion rates between smokers and non-smokers. Samartzis et al in a series of 66 patients an overall 95.5% solid fusion rate, with smoking not a factor in fusion rate or clinical outcome.[47] Luszczyk et al, in a recent retrospective study showed fusion rates of 91.6% for non-smokers and 91.0% for smokers in patients undergoing ACDF.[50] For multilevel ACDF the fusion rates have been shown to be significantly lower in smokers by Hilibrand et al.[49] With respect to the fusion rates in smokers after anterior corpectomy, the results are mixed. In the series by Hilibrand et al, there was no difference in fusion rates of smokers who underwent corpectomy and strut grafting. However, in the study by Lau et al current smoking was found to be risk factor for pseudoarthrosis (OR 1.72, 95% CI: 1.13-2.63).[65] Lau et al also noted higher rates of perioperative complcations in smokers ($p<0.001$), with infection constituting 75% of these complications. In posterior cervical fusions, Eubanks et al, showed that smoking did not decrease fusion rates with use of lateral mass instrumentation and iliac crest autograft, though this may not apply to cases when only local autograft is used. While the fusion rates in one level anterior procedures may not be impacted by smoking, patients who currently smoke should be counseled about the possibility of a higher non union rate when undergoing multilevel anterior procedures (multiple ACDF or corpectomy). Additionally, it may be beneficial to use iliac crest autograft during posterior cervical fusion procedures.

Perioperative Complications in Smokers after Spinal Fusion

Infection risk has been shown to be elevated in smokers after undergoing many different types of surgery. Furthermore, Saeedinia et al. were able to show that smoking is an independent risk factor for surgical site infection specifically in spinal surgery. While nicotine does result in leukocytosis, it has a negative effect on the function of leukocytes. In long-term smokers, nicotine suppresses serum immunoglobulin levels and inhibits antibody production in response to antigens. Ultimately, this reduces oxygenation and aerobic metabolism, disturbs immune cell migration, and increases proteolytic enzymes.[46] Truntzer et al. helped elucidate this is a clinical setting by identifying a 2.2 times higher rate of infection in smokers after certain orthopedic operations.[52] In addition to surgical site infection, there is also evidence to demonstrate delayed wound healing in smokers. This is predominantly based off of the decreased tissue oxygenation due to sympathetic vasoconstriction from nicotine and increased carboxyhemoglobin concentrations. It is also thought that the constituents in smoke could directly affect the function of fibroblasts and immune cells important to healing.[53] Lau et al. demonstrated that smoking is independently associated with higher perioperative complications (especially infectious complications), longer lengths of stay, and higher rates of pseudarthrosis in patients undergoing anterior cervical corpectomy.[65] Lastly, wound healing is delayed by smoking-associated microvascular disease that interferes with angiogenesis.

Another major complication concern associated with spinal fusion is adjacent-segment pathology (ASP) in

the months to years following the operation. Lee et al. showed in cervical fusions that smoking significantly increased the risk of reoperation due to ASP by 1.9 times (95% CI, 1.2-3.).[54] This may be in part due to the increased disc degeneration and decreased vertebral bone strength caused by smoking at adjacent levels.

Lastly, Olssen et al. showed that smokers were at significantly increased risk for dyphagia and that it was more severe than non-smokers after undergoing ACDF (1.17 vs 0.54).[66]

When Should Patients Quit Smoking To Optimize Outcomes?

Physicians should always recommend full smoking cessation, however, if a patient is undergoing a spinal fusion, there should at least be specific a timeframe in which smoking should be stopped. While preoperative smoking a significant risk factor for surgery due to its degenerative effects on the vertebral column, it is not as well-documented a risk for nonunion as post-operative smoking. Pre-operative smoking cessation within four weeks of spinal fusion surgery should be recommended as a method to reduce comorbidities and improve overall patient health if possible. It may improve rates of complications after spinal fusion surgery, but the results are not as definitive as post-operative cessation.

Post-operative smoking cessation will have the greatest benefit in terms of improving fusion rates and decreasing perioperative complication rates. As previously discussed, smoking exerts some of its most detrimental effects on fusion healing during the period of angiogenesis. This is due to both nicotine-induced systemic vasoconstriction and smoking's downregulation of gene expression of proteins involved in capillary ingrowth. The most critical time for angiogenesis is the first three to four weeks after the operation, so smoking cessation should be highly recommended during this time. Smoking has also been shown to inhibit the differentiation of osteoblasts and decrease the production of new bone and collagen within the fusion mass. This process occurs over approximately the first six months, so smoking cessation is likely beneficial during this time as well. However, due to patient compliance it may be difficult to effectively accomplish this task. Carlson et al. recently showed that the rates of recidivism are significant in patients who initially opt to cease smoking post-operatively. The study found that there was a 60% recidivism rates at three months, 61% at six months, and 68% at one year.[56] Based on this, 60% of patients who quit smoking post-operatively ultimately wind up affecting their chances of a healed fusion by early return to smoking. For this reason, emphasizing compliance during at least the first four weeks post-operatively may be the best way to realistically improve outcomes.

Is There Anything That Can Be Done To Overcome The Effects Of Smoking?

In an ideal world, patients would be 100% compliant with perioperative instructions regarding smoking. However, smoking is addictive, and there is always a fraction of patients who will continue to smoke, even when undergoing a major operation. For this reason, there has been research into therapies that could potentially curb the negative effects of smoking on spinal fusion. Silcox et al. demonstrated in a rabbit model that the use of osteoinductive bone protein with autogenous bone can overcome the effect of nicotine on fusion healing. This therapy was more effective than using autogenous bone alone or the osteoinductive bone protein with allograft.[61]

Clinical studies have shown similar fusion outcome results. In a study specific to single-level instrumented posterolateral fusions in smokers, Glassman et al. showed that the use of rhBMP-2 may enhance fusion rates. At two years post-operation, solid fusion was demonstrated in 100% of the rhBMP-2 nonsmoker group and 95.2% of rhBMP-2 smokers. This is in stark contrast to a 94.1% nonsmoker fusion rate in the iliac crest bone graft (ICBG) group and only a 76.2% fusion rate in the ICBG smoker group.[59] Macki et al. conducted a similar experiment in which they were

able to correlate the use of rhBMP-2 with 73% lower odds of reoperation for pseudoarthrosis and/or instrumentation failure.[60] The use of osteoinductive proteins is a promising field in regards to improving the efficacy of spinal fusion in both smokers and nonsmokers, but therapy is constantly evolving. For example, osteogenic protein-1 (OP-1), also known as BMP-7, was used for many years and implanted with a collagen matrix to facilitate the formation of bony fusion masses.[58] However, this therapy is no longer used. More research needs to be done to evaluate clinical outcomes and determine which specific proteins are the most helpful.

Another method that has been hypothesized to reduce the detrimental effects of smoking is nicotine replacement therapy (NRT). This can be done by a variety of methods, including e-cigarettes, Chantix (Varenicline, a nicotinic receptor partial agonist), nicotine patches, and nicorette gum. The theory behind the use of these therapies is that many of the components of cigarette smoke are much more harmful than the nicotine component. With regards to spinal fusion and bone healing in general, there are many studies to support this claim. Gullihorn et al. studied the differential effects of nicotine and smoke condensate on bone metabolic activity. Their data suggest that nicotine may actually directly stimulate bone metabolic activity, while smoke condensate with equivalent levels of nicotine elicits an inhibitory effect.[62] Daffner et al. produced somewhat more ambiguous results in terms of nicotine verses cigarette smoke as the predictor of negative outcomes in spinal fusion. They determined that the effects of nicotine on spinal fusion are complex, may be dose-dependent, and may not always be detrimental, concluding that the effects of smoking on spinal fusion may be due to other components of cigarette smoke.[63] Another study by Daffner claimed to show that nicotine increased osteoblast activity of induced bone marrow stromal cells in a dose dependent manner.[64] These studies should be scrutinize further because of the long-held consensus about the negative effects of nicotine on both bone health and bone healing, but they potentially open the door to the idea that other components of cigarette smoke may be even more harmful to the fusion healing process than nicotine alone. At this point, there is not enough evidence to conclusively recommend NRT instead of smoking for patients undergoing spinal fusion surgery. However, with more research it may be determined that NRT has less detrimental effects than cigarette smoke when evaluating outcomes.

Conclusion

Cigarette smoking is particularly damaging to the musculoskeletal system and the vertebral column specifically. It is linked to lower fusion success and higher complication rates after lumbar fusion surgery, and cessation, at least postoperatively, should be strongly recommended, particularly in the vital first four weeks after surgery. Research is currently being conducted into therapies that can overcome the negative effects of smoking and into alternatives to smoking that may better allow for smokers to quit perioperatively.

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Disclosures & COI

The authors declare no relevant disclosures.

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