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Clinical Implications of Postsurgical Adhesions and Fibrosis: The Role of Vitamin C in Prevention and Control

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ABSTRACT

Postsurgical adhesions are common complications of surgery that affect millions of postsurgical patients worldwide. These are abnormal fibrous bands that form between organs or between organs and the respective walls during the healing process post surgery. Patients undergoing all kinds of surgeries can develop postsurgical adhesions. Increased risk of morbidity (including longer operative hours, multiple readmissions, longer hospital stays, and increased healthcare expenses) and mortality are among the associated complications. Despite various interventions being implemented with varying levels of success, their application and effectiveness remain limited. Due to its ready availability, affordability, and lack of significant side effects or reported adverse drug reactions, vitamin C supplementation can be an effective approach for preventing and controlling postsurgical adhesions and fibrosis, given the growing evidence supporting its effectiveness as the postsurgical adhesions and fibrosis preventive and control agent.

1 | Introduction

Around 17 million (33%) deaths globally were attributed to conditions that required surgical intervention in 2010, far exceeding the combined deaths from HIV/AIDS, tuberculosis, and malaria [1]. Expanding basic surgical care in low- and middle-income countries could prevent 1.4 million deaths and 77.2 million DALYs each year [2].

Common, easily treated diseases can develop into diseases with high mortality rates in the absence of surgical intervention [2]. However, the diverse causes of conditions needing surgery are not well represented in current disease-focused epidemiological frameworks [2]. Most developing countries will experience an epidemiological shift over the next 20 years whereby non-communicable diseases or conditions will be more prevalent than communicable diseases as it was in the past [1]. Therefore, it is anticipated that there would be a significant increase in the need for equitable access to surgical treatments in these nations [1].

Surgical conditions has been found to contribute 28% to 32% of the total global disease burden, depending on the estimation approach and whether the burden is measured by deaths or DALYs [1].

Despite several benefits carried by surgical interventions, they are not without risks. Surgical intervention is associated with risks such as immediate complications like bleeding, anesthesia-related complications, and other late potential

complications such as infection. Complications risk increases with factors like age, obesity, smoking, and underlying medical conditions. One of the most common complications of surgery is the formation of postsurgical adhesions and fibrosis which have significant morbidity and mortality implications in clinical practice and quality of life.

This article highlights on the global burden, etiology, pathophysiology, clinical implications and interventions in place and gaps in prevention and control of postsurgical adhesions. Moreover, it explores the role of of vitamin C as a potential therapeutic approach towards postsurgical adhesions prevention and control.

2 | Postsurgical Adhesions

Postoperative adhesions are the common and serious complication affecting patients undergoing various types of surgeries [3]. These adhesions are pathological bonds that form between surfaces within body cavities, and can be classified as thin films of connective tissue to thick fibrous bridges that have blood supply and nerve innervation [3]. Adhesions are associated with serious complications, including higher risk of morbidity and mortality [3]. The financial burden of postsurgical adhesions is significant, given increased hospitalization, longer operative times, and longer length of hospital stay [3]. Peritoneal adhesions are common after abdominal surgery, but their severity and symptoms vary unpredictably [5]. They occur as a natural healing response to injury of the peritoneal surfaces during the procedure [4, 5]. Despite some benefits, adhesions can cause serious complications like bowel obstruction, infertility, pain, and challenges in future surgeries [3, 5].

3 | Postsurgical Adhesion Pathophysiology

The clear pathophysiology of postoperative adhesions development is uknown and their formation mechanisms are still unclear [6]. Peritoneal adhesions were first observed in 1836, and in 1849 and lymph vessel coagulation was proposed as a cause [6]. Their precise pathophysiology has until now eluded researchers. Despite numerous clinical and experimental studies, the pathogenesis of postsurgical adhesions is still debatable.

It has been shown that adhesion formation is a complex process of tissue repair, marked by specific cellular and immune reactions [7, 8]. Induction of an inflammatory response that produces cytokines and transforming growth factor (TGF), induction of tissue hypoxia which results in increased expression of vascular endothelial growth factor (VEGF), and inhibition of the fibrinolytic and extracellular matrix degradation systems are the three main processes involved in the formation of postsurgical adhesions [3, 9].

For example; normal peritoneal healing or adhesion formation depends on the equilibrium between fibrin deposition and breakdown [10]. Partially degraded fibrin can act as a framework for fibroblasts and capillaries to grow, leading to the formation of peritoneal adhesions [10]. Damage to the peritoneum, whether from surgery, infection, or irritation, sets off an inflammatory response that results in fibrin formation. This happens through the activation of the coagulation process, where fibrinogen is transformed into fibrin by thrombin [10]. Normally, the fibrinolytic system breaks down intra-abdominal fibrin deposits. However, after abdominal surgery, the balance shifts towards coagulation, leading to fibrin deposits that serve as a scaffold for fibrocollagenous tissue growth [10]. Extracellular matrix (ECM) is created and deposited as fibroblasts infiltrate the fibrin matrix, which is typically degraded by MMPs to ensure normal healing. However, if MMP activity is blocked, the fibrin matrix remains and allows fibroblasts to deposit collagen, resulting in peritoneal adhesions [10]. Angiogenic factors induce the growth of new blood vessels and the production of peritoneal adhesions as a result of this process [10, 11]. When the fibrinolytic system is activated, plasminogen is converted into plasmin, which efficiently breaks down fibrin [10]. Plasminogen activators, including tissue-type (tPA) and urokinase-type (uPA), are expressed in macrophages, mesothelial, and endothelial cells [10]. tPA, the main plasminogen activator, is a serine protease with high fibrin affinity. When it binds to a receptor on fibrin, it reveals a plasminogen-binding site, increasing plasminogen activation. However, without fibrin, tPA's ability to activate plasminogen is significantly reduced, leading to lower activation rates [10, 12]. Plasminogen activator inhibitors (PAI)-1 and 2 block plasminogen activation by forming inactive complexes [10]. PAI-1 is the most potent inhibitor of tPA and uPA, while PAI-2 has a reduced capacity and likely aids peritoneal tissue healing [10]. They are produced by endothelial, mesothelial, monocytes, macrophages, and fibroblasts [10]. Other inhibitors include protease nexin 1, PAI-3, and direct plasmin blockers such as α2-macroglobulin, α1-antitrypsin, and α2-antiplasmin [10]. However, the role of these inhibitors in peritoneal fibrinolysis remains unclear [10]. Adhesion formation depends on the balance of plasminogen activators and inhibitors. PAI-1 plays a key role, with patients having extensive adhesions showing high PAI levels in their peritoneal tissue and adhesions [13].

4 | Implications of Postoperative Adhesions in Clinical Practice

4.1 | Thoracic Adhesions

The incidence of adhesions following cardiothoracic surgeries is gaining more attention due to the rise in redo surgeries accounting for 6%–17% of coronary artery bypass and valve operations, leading to more adhesion-related complications [3]. During sternal re-entry, postoperative adhesions extend surgery time and increase the risk of injury to the heart, lungs, and major blood vessels [3]. Up to 33% of all pediatric and congenital heart surgeries are repeated operations, and patients with congenital cardiac disease are likely to need multiple redo cardiac operations throughout their lives [3]. Animal models have been used primarily to study the formation of pericardial postsurgical adhesions [3]. The pericardium should be closed following surgery because it protects the heart and major vessels during subsequent surgeries but this can be difficult due to the typical inflammation of the intra-thoracic structures [3]. Many surgeons leave the pericardium open because there is a

risk of the pericardium compressing the heart and any bypass grafts [3]. Right ventricular dysfunction, decreased coronary artery bypass graft patency, and life-threatening bleeding following redo sternotomy are all complications of intra-thoracic and cardiac adhesions which tremendously lengthen repeat cardiac operations [3].

4.2 | Pelvic and Abdominal Adhesions

Regardless of the procedure, it has been observed that 95% of all procedures result in the development of pathologic adhesions [3]. Additionally, in the decade following abdominal or pelvic surgery, 35% of patients were readmitted averagely twice for conditions associated to postsurgical adhesions [3]. Major complications include intestinal obstruction, perforation, increased surgical risk, hemorrhage, and longer surgical durations as a result from postsurgical adhesions [3]. The causes of adhesion formation are multifactorial, including peritoneal trauma during surgery, ischemia and reperfusion injury, bacterial contamination, foreign bodies, and inflammation [5]. Certain patient factors, such as age, obesity, and comorbidities, may also increase the risk of adhesion formation [5].

4.3 | Diagnosis, Prevention, and Control of Postsurgical Adhesions

Diagnosis of postsurgical adhesions can be challenging, as they may be asymptomatic or present with nonspecific symptoms depending on the site affected [5]. Patients may present with chronic abdominal pain, bowel obstruction, infertility, or difficulty during subsequent surgeries [5]. Imaging studies such as CT scans and MRIs may help to diagnose adhesions, but they are not always conclusive [5].

The development of safe and efficient therapeutic solutions that can be used to reduce postoperative adhesion formation is a clinical need that is not currently being met [3]. Currently, there are no effective therapies for postoperative adhesions and prevention strategies are the focus of research [3]. Several interventions are in place to manage postoperative adhesions, including nonsurgical and surgical approaches [3].

Surgical interventions include lysis of adhesions and adhesiolysis, which aim to remove or break up the adhesions [3]. There is also the use of adhesion barriers during surgery; pharmacological interventions such as anti-inflammatory drugs, and physical therapy [14]. Adhesion barriers have been shown to reduce the incidence and severity of postoperative adhesions, while anti-inflammatory drugs are effective in reducing inflammation and promoting healing [3,14]. Other therapies that have shown promise in managing postoperative adhesions include physical therapy, the use of radiofrequency ablation and laser therapy [14]. Recently, scientists have evaluated the possibility of gene therapy and nanoparticles application in the determination of having a precise medicine for the prevention of postsurgical adhesion formation, even though their clinical applications have been practically challenging [14].

The most researched vitamin for prevention and control of adhesions and fibrosis is vitamin E, whereby studies conducted in vitro have shown that vitamin E inhibits collagen synthesis and possesses antioxidant, anti-inflammatory, anticoagulant, and anti-fibroblastic properties [10]. Furthermore, it has been found to be successful in minimizing adhesion formation. But different literatures revealed that no human trials have suggested using vitamin E to prevent postoperative adhesions [10].

4.4 | Vitamin C and Postsurgical Adhesions Formation

Vitamin C is an essential nutrient that is required for the synthesis of collagen, a key component of connective tissue. Collagen is involved in wound healing and tissue repair, making Vitamin C important in the healing process. A deficiency in Vitamin C can lead to delayed wound healing and impaired collagen synthesis, resulting in poor scar formation [15].

Vitamin C has been shown to play a role in reducing oxidative stress and inflammation, which are important factors in the healing process [15]. It has been shown that, for allowing the positive signaling function of reactive oxygen species (ROS) required for cell survival, high dose vitamin C should be given immediately after the initial traumatic event when oxidative stress is highest [16]. Vitamin C also functions in enzyme activation, immune function, and oxidative stress reduction [16–18]. Patients undergoing uncomplicated surgical procedures may need more vitamin C than the recommended dose while those in surgical intensive care units may need much higher doses [19]. Continuous intravenous vitamin C at 500 mg/day reduced postoperative oxidative stress in gastrointestinal surgery, as shown by lower urine isoprostane levels [19].

Meanwhile, several methods have been put in place for postsurgical adhesions and fibrosis formation prevention and control. The potential use of Vitamin C in prevention and control of postsurgical adhesions and fibrosis cannot be underestimated. It is essential for connective tissue repair by serving as a cofactor for enzymes that stabilize collagen through hydroxylation of proline and lysine in procollagen [18]. It also acts as a powerful antioxidant, neutralizing reactive oxygen species (ROS) that contribute to cell death during the inflammatory phase of healing [18].

Vitamin C can help in the reduction of postsurgical adhesions and fibrosis formation by reducing oxidative stress and inflammation [18]. Moreover, it was found that high-dose Vitamin C supplementation ($\geq$ 500 mg/day) for a duration of at least 4 weeks was necessary to reduce the incidence and severity of postsurgical adhesions and fibrosis [18]. It does this by scavenging free radicals, reducing oxidative stress, and enhancing the immune system's response to injury [18]. Vitamin C has also been found to reduce local and systemic PAI-1, an inhibitor of fibrinolysis, when elevated, promotes fibrin deposition and is implicated in postsurgical adhesion formation [20, 21]. The inflammatory response following surgical trauma leads to increased PAI-1 levels, exacerbating adhesion risk [13]. Vitamin C may modulate PAI-1 expression and enhance

fibrinolysis, potentially reducing excessive fibrin accumulation and subsequent adhesion development [20, 21].

However, in addition to Vitamin C, several other methods have been put in place to prevent postsurgical adhesions. These methods include the use of physical barriers, such as adhesion barriers and tissue-separating agents, and pharmacological anti-adhesion agents in the market such as anti-inflammatory drugs, hormones, and fibrinolytic agents [18]. Other supplements and medications may also be used to prevent postsurgical adhesions and fibrosis. For example, omega-3 fatty acids have been shown to have anti-inflammatory effects and may help to reduce the risk of adhesion formation [22]. Anti-inflammatory medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) may also be used to reduce inflammation and prevent the formation of scar tissue [3, 14].

While these methods have been beneficial in the reduction of postsurgical adhesion formation, they also have some drawbacks; physical barriers can be expensive and may not be suitable for all types of surgery. Pharmacological agents, on the other hand, can have side effects and may not be suitable for all patients. In contrast, Vitamin C is readily available, inexpensive, and has no known significant side effects or reported adverse drug reactions. It can be easily administered orally or intravenously and is therefore suitable for a wide range of patients and surgeries.

5 | Conclusion and Recommendation

Following tissue damage and ischemia, postsurgical adhesions are fibrosis are mostly formed as a healing process. These subject patients to a number of serious complications with both clinical implications and quality of life concern.

Despite the availability of different interventions towards prevention and control of postsurgical adhesions and fibrosis, their effectiveness and application is limited. For example, there is a lack of consensus on the optimal timing for lysis of adhesions, as well as the best surgical technique to use.

While Vitamin C supplementation can be an effective method of preventing postsurgical adhesions and fibrosis, it should not be the only method used. Proper surgical techniques, appropriate wound care, and other measures such as physical therapy may also be necessary to prevent or treat these complications. A combination of available interventions may be considered when necessary, so as to achieve the best possible outcome. Further clinical studies are needed to establish the clinical effectiveness of vitamin C supplementation as a therapeutic approach towards prevention and control of postsurgical adhesions and fibrosis in terms of intervention timing and the administration approach.

Author Contributions

Jacob H Kitundu: conceptualization, writing – original draft, data curation. **Harold L Mashauri:** conceptualization, data curation, supervision, writing – review and editing, project administration.

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Ethical Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Jacob H. Kitundu affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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