Selective Serotonin Reuptake Inhibitor and the Risk of Postsurgical Bleeding: A literature Review

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ABSTRACT Serotonin (5-hydroxytryptamin, 5-HT) is a vital monoamine neurotransmitter that modulates various physiological processes. Selective serotonin reuptake inhibitors (SSRIs) are commonly used for the management of depressive disorders. Prolonged administration of SSRIs may lead to reduced platelet aggregability due to the depletion of serotonin stores within platelets. However, the association between chronic SSRI use and the risk of postoperative bleeding remains a topic of debate, with no standardized guidelines for managing this risk in the field of plastic surgery. This literature review and case report highlights the importance of considering chronic SSRI use as a potential risk factor for postoperative bleeding in plastic surgery patients. Standardized guidelines for handling postoperative bleeding risk in patients using SSRIs are crucial for ensuring optimal surgical outcomes and patient safety.

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KEY WORDS: breast surgery, hematoma, plastic surgery, postoperative bleeding, selective serotonin reuptake inhibitors (SSRIs)

Serotonin (5-hydroxytryptamin, 5-HT) is a vital monoamine neurotransmitter that modulates various physiological processes, including mood, sleep, digestion, and blood clotting. Selective serotonin reuptake inhibitors (SSRIs) are commonly used for the management of depressive disorders. However, the association between chronic SSRI use and the risk of postoperative bleeding remains a topic of debate, with no standardized guidelines for managing this risk in the field of plastic surgery.

THE ASSOCIATION BETWEEN CHRONIC SELECTIVE SEROTONIN REUPTAKE INHIBITOR USE AND THE RISK OF POSTOPERATIVE BLEEDING REMAINS A TOPIC OF DEBATE WITH NO STANDARDIZED GUIDELINES

This literature review and case report highlights the importance of considering chronic SSRI use as a potential risk factor for postoperative bleeding in plastic surgery patients. While the underlying mechanisms warrant further investigation, plastic surgeons should exercise caution and awareness when managing patients on SSRIs. Standardized guidelines for handling postoperative bleeding risk in this population are crucial for ensuring optimal surgical outcomes and patient safety.

BACKGROUND

SSRIs are commonly used as antidepressants. Their use over the last two decades in the United States has experienced a notable surge in usage. According to data from the National Center for Health Statistics (NCHS), the prevalence of SSRI use among adults in the United States almost doubled, rising from 6.8% in 1999–2000 to 13.1% in 2011–2014 [1].

A study published in 2020 reported that the number of SSRI prescriptions in the United States increased from 131 million in 2005 to 214 million in 2019. In addition, the study revealed an increase in the percentage of patients receiving SSRIs as part of their visit, climbing from 6.6% in 2005 to 12.9% in 2019 [2].

Serotonin functions as a monoamine neurotransmitter with multiple roles in the human body. It influences mood, sleep, digestion, nausea, wound healing, bone health, blood clotting, and sexual desire [3].

One of serotonin's important functions is the induction of contraction in vascular smooth muscle cells, as observed in numerous in vitro studies on blood vessels. It is primarily transported by platelets and released on activation, resulting in the constriction of injured blood vessels and promoting platelet aggregation to minimize blood loss. Given this effect, serotonin receptor antagonists have been investigated for their potential anti-ischemic efficacy in atherothrombotic disease [4-6].

SSRIs exert inhibitory effects on both the 5-HTT transporters and 5-HT receptors found on platelets. Prolonged administration of SSRIs may lead to reduced platelet aggregability due to the depletion of serotonin stores within platelets. This condition may cause SSRI-induced reductions in platelet count and occasional occurrences of thrombocytopenia [4,5,7].

The SSRI, serotonin and platelets relationship is explained as follows: SSRIs block the reuptake of serotonin in the brain pre-synaptic terminals and therefore increase the amount and availability of serotonin in the synaptic cleft. This condition occurs by blocking serotonin reuptake transporter (SERT). SERT transports serotonin back into the brain nerve terminal, removing it from the synaptic cleft [5]. Platelets also express the serotonin transporter. Therefore, when SSRIs are used, they result in decreased storage of serotonin in platelet dense granules. Platelet serotonin depletion leads to decreased platelet aggregation amplification and can potentially lead to increased bleeding in patients taking SSRIs.

Several studies have demonstrated a correlation between the utilization of SSRIs and an elevated risk of perioperative bleeding across a spectrum of surgical contexts. This association has been observed not only in general surgical scenarios [8,9], but also in specific procedures such as aesthetic breast surgery [10], oncologic breast surgery [11], and closed rhinoplasty [12]. Conversely, a 2018 study demonstrated that the use of psychiatric medications, including SSRIs, does not predict an elevated risk of intraoperative surgical bleeding in facial cosmetic surgeries [13].

WHILE NOT DIRECTLY PROVEN, CURRENT SELECTIVE SEROTONIN REUPTAKE INHIBITOR USE MAY BE ASSOCIATED WITH AN INCREASED RISK OF RE-OPERATION DUE TO BLEEDING AFTER BREAST CANCER SURGERY

We present a case of postoperative bleeding in a patient who underwent bilateral mastectomy and immediate reconstruction with breast implants while using SSRIs. Our goal is to emphasize the association between SSRIs and perioperative bleeding and to raise awareness in the medical community and the need for further research on this subject.

PATIENT DESCRIPTION

A 60-year-old female with a medical history of hypercholesterolemia and hypertension, managed routinely with ACE inhibitors, statins, escitalopram (an SSRI), and multivitamin pills, presented with bilateral breast lumps that were diagnosed as bilateral invasive ductal carcinoma. The patient had a history of several surgical procedures at different ages, including tracheostomy, sympathectomy, cesarean section, and abdominoplasty at the age of 38 years, with no documentation of post-surgical complications. In addition, she had a history of heavy smoking in the past. There was no family history of coagulative disorders. Notably, 6 months prior to the breast cancer diagnosis, she began taking SSRI pills, prescribed by her family doctor, to manage a depressive disorder following a divorce process.

Based on the patient's preferences, physical examination, and body structure, she was considered eligible for bilateral skin sparing mastectomy with immediate breast reconstruction with breast implants.

During admission one day prior to surgery, the patient's blood tests and vital signs were found to be within the normal range. The surgery proceeded without documented intraoperative complications.

However, approximately 3 hours post-surgery, a hematoma was observed to be expanding on her right breast, prompting her re-admittance to the operation room for exploration. During the surgical exploration, a pulsatile artery arising from the lower medial quadrant of the right chest was identified as the source of bleeding. This finding led to hypovolemic shock, accompanied by metabolic acidosis and a decrease in hemoglobin levels. The patient's blood pressure during and following surgery was in the normal range, thus it was speculated that a clotting disorder might explain this significant postoperative bleeding.

A few hours after the revision, another hematoma was detected on her left breast during a physical examination. Subsequently, a second surgical exploration procedure was conducted, during which a significant quantity of blood clots and oozing were found both outside and inside the implant pocket as well as in the ipsilateral axillary area. Yet, coagulation function tests yielded results within the normal range.

COMMENT

Several studies have demonstrated a correlation between the utilization of SSRIs and an elevated risk of perioperative bleeding across a spectrum of surgical contexts. This association has been observed not only in general surgical scenarios [8,9], but also in specific procedures such as aesthetic breast surgery [10], oncologic breast surgery [11], and closed rhinoplasty [12]. Conversely, Harvey

and colleagues [13] demonstrated that the use of psychiatric medications, including SSRIs, does not predict an elevated risk of intraoperative surgical bleeding in facial cosmetic surgeries.

The correlation between SSRIs and postoperative bleeding was highlighted in the context of post-closed rhinoplasty bleeding [12]. Constantian [12] described two patterns of excessive intraoperative bleeding: constant slow bleeding starting at the first injection or normal hemostasis in the first 3 hours followed by multifocal bleeding. The second pattern was thought to occur due to previous chronic SSRI administration. Although it is theoretically ideal to stop antidepressants for 2 weeks preoperatively, it is impractical. The author recommended ordering a urinalysis during the preoperative meeting to prepare the patient for surgery. This proactive measure helps to rule out microscopic hematuria, enabling the medical team to address the use of amicar (aminocaproic acid) safely during surgery if the need arises.

RAISING AWARENESS OF PREVENTABLE AND UNNECESSARY EVENTS AMONG PATIENTS WHO CAN SAFELY DISCONTINUE SELECTIVE SEROTONIN REUPTAKE INHIBITOR MEDICATION UNDER CAREFUL MONITORING IS ESSENTIAL

Various studies have reported the occurrence of postoperative bleeding in patients who are on chronic SSRI use. In one study, serotonergic antidepressant use was tentatively linked to an increased risk of intracranial hemorrhage [14], but further research is required to fully understand this association [14,15]. In addition, the impact of SSRI use in patients with atrial fibrillation was examined, revealing that it can be safely combined with anticoagulants. However, there was a suggestion of an elevated bleeding risk when SSRI was added to warfarin [16].

Basile et al. [10] focused on patients undergoing breast cosmetic plastic surgery procedures, aiming to investigate bleeding events requiring intervention as the primary endpoint. Their findings demonstrated a higher incidence of bleeding events among the SSRI-using group, irrespective of the type of procedure performed, body mass index, or age group. The study concluded that the utilization of SSRIs is linked to a fourfold increase in the risk of bleeding following breast cosmetic surgery, a conclusion that is supported by another study with similar results [11].

In our case, despite the identification of a pulsatile artery during the first revision, we were unable to find an explanation for the bleeding on the opposite side several hours later. Although the coagulation functions were within the normal range in several sequential blood exams, making the diagnosis of disseminated intravascular coagulation post-hypovolemic shock less likely, it cannot be entirely ruled out. Furthermore, the initial bleeding could also be partially attributed to the use of SSRIs. Clearly, there were other contributing factors to the events, and the cause of the hematomas on both sides may remain elusive. Nevertheless, the question persists whether these bleeding events would have occurred with the same severity if SSRIs had not been administered.

An abrupt discontinuation of the SSRI treatment due to bleeding might cause an SSRI discontinuation syndrome. It is usually mild, commences within 1 week of stopping treatment, and resolves spontaneously within 3 weeks. It consists of diverse physical and psychological symptoms, the most common being dizziness, nausea, lethargy, and headache. Discontinuation reactions are clinically relevant due to the associated morbidity, the potential for misdiagnosis, and inappropriate treatment. Stopping may impair future antidepressant compliance; therefore, it should be withdrawn gradually [17].

CONCLUSIONS

While not directly proven, current SSRI use may be associated with an increased risk of re-operation due to bleeding after breast cancer surgery. Specific protocols for managing SSRIs in the perioperative period are currently lacking, with only brief mentions in textbooks. Many unreported cases resulting in bleeding events could potentially be attributed to the use of SSRIs. Perhaps cautious cessation of these medications could be monitored for predicted side effects.

Given the absence of guidelines, it is important to raise awareness and to avoid preventable and unnecessary events among patients who can safely discontinue SSRI medication under careful monitoring. Such decisions should not be made without a comprehensive discussion of the risks and benefits.

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Capsule

Regulatory T cell and endothelial cell crosstalk

Regulatory T (Treg) cells have a central role in the maintenance of immune surveillance and tolerance. They can migrate from lymphoid organs to blood and then into tissues and egress from tissues into draining lymph nodes. Specialized endothelial cells of blood and lymphatic vessels are the key gatekeepers for these processes. Treg cells that transmigrate across single-cell layers of endothelial cells engage in bidirectional crosstalk with these cells and regulate vascular permeability by promoting structural modifications of blood and lymphatic endothelial cells. In turn, blood and lymphatic endothelial cells can modulate Treg cell recirculation and residency. **Piao** et al. discussed recent insights into the cellular and molecular mechanisms of the crosstalk between Treg cells and endothelial cells and explored potential therapeutic strategies to target these interactions in autoimmunity, transplantation and cancer.

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Capsule

Slowing binge drinking

Alcohol dependence affects the function of a brain region called the medial orbitofrontal cortex (mOFC), which is involved in higher-level cognitive functions such as the suppression of impulsive actions. However, the effects of alcohol on specific mOFC circuits are unclear. **Gimenez-Gomez** et al. used genetically modified mice to identify a group of neurons in the mOFC that showed an increase in activity when blood alcohol levels were high. Optogenetic stimulation of these neurons decreased alcohol intake, whereas ablating them increased alcohol consumption. This effect was mediated by projections to the mediodorsal thalamus. These findings suggest that this brain circuit protects against binge drinking and could represent a target for the treatment of alcohol addiction.

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