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Pediatric post-tonsillectomy hemorrhage in the setting of post-transplantation immunosuppression

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ABSTRACT

Introduction: Long-term immunosuppressants form an integral part of therapy for post-transplantation patients. Immunosuppressants may also have an anticoagulant effect, and little is known about their effects on bleeding risk after adenotonsillectomy. Our objective was to investigate whether there is an increased observed rate of post-tonsillectomy hemorrhage in a population of pediatric patients on long-term immunosuppressants after solid organ transplantation, compared to healthy controls.
Methods: This was a retrospective chart review of pediatric patients with a history of renal or heart transplant undergoing adenotonsillectomy at our institution between 2000 and 2014. All patients underwent tonsillectomy with monopolar electrocautery. Retrieved data included perioperative medications, occurrence of post-operative bleeding and associated treatment. For comparison, we obtained a population of age-matched controls with no history of immunosuppression who underwent the same procedure.
Results: A total of 34 patients meeting criteria were identified, of which 3 (8.82%) suffered a post-operative bleed. Forty-seven controls were obtained, with a total of 2 (4.26%) postoperative hemorrhages ($p = 0.65$). Two of the post-transplantation patients who bled postoperatively required cauterization in the operating room. None of the controls required surgical treatment. The incidences of postoperative bleeding requiring surgical treatment were 5.88% and 0%, respectively ($p = 0.17$).
Conclusion: We failed to demonstrate an increased risk of bleeding after undergoing adenotonsillectomy in our cohort of post-transplantation pediatric patients on chronic immunosuppression. Future research, likely requiring a multi-institutional effort, could stratify by immunosuppressive agent to elucidate bleeding risk with specific medications.

1. Introduction

Remarkable progress has been made in the world of organ transplantation in the last few decades. Around the time of the first transplants in the 1950's, relatively little was understood about immunology and no immunosuppressive drugs existed, obligating the use of transplantation between individuals with identical tissue types (i.e. identical twins) [1]. Since that time our understanding of the immune system has expanded the reaches of solid organ transplantation. Long-term immunosuppressants now form an integral part of therapy for post-transplantation patients. Immunosuppressants may also have an anticoagulant effect and other side effects that could impair wound healing and appropriate coagulation function (see Table 1). Little is known about their effects on post-surgical bleeding risk. We sought to investigate whether chronically immunosuppressed patients with a history of solid organ transplantation have an increased risk of bleeding after adenotonsillectomy.

2. Material and methods

We performed a retrospective chart review of pediatric patients with a history of renal or heart transplant undergoing tonsillectomy with or without adenoidectomy at our institution between July of

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Table 1
Immunosuppressant medications used in our cohort of patients: mechanism of action and side effects relevant to perioperative risk [1,6].

Medication class and subtypes	Mechanism of action	Side effects related to perioperative complications
Anti-proliferatives	Selectively inhibit the proliferation of T and B lymphocytes by interfering with purine nucleotide synthesis; inhibit antibody formation and cytotoxic T cell clonal expansion	Bone marrow suppression (anemia, thrombocytopenia), infections
Mycophenolate (Cellcept® or Myfortic®)		
Azathioprine (Azasan®, Imuran®)		Bleeding, bone marrow suppression (anemia, leukopenia, thrombocytopenia), increased incidence of malignancies, infections
Calcineurin Inhibitors	Inhibit T cell and cytokine activation and proliferation primarily by impairing the activation or induction of gene coding for interleukin(IL)-2, IL-4, tumor necrosis factor-a, and gamma interferon.	Infections, increased incidence of malignancies
Tacrolimus (Prograf®)		
Cyclosporine (Sandimmune®, Neoral®, Gengraf®)		Anorexia, infections
Mammalian Target of Rapamycin (mTOR) Inhibitors	Inhibit cytokine-dependent cellular proliferation and T lymphocyte activation; also inhibit antibody production	Anemia, thrombocytopenia, impaired wound healing, infections
Sirolimus (Rapamune®)		
Anti-inflammatory agents	Prevent transcription of interleukin-1 and tumor necrosis factor-a by antigen presenting cells, thus preventing major histocompatibility complex expression; this results in decreased antigenicity of transplanted tissue; also, anti-inflammatory effects result in decreased inflammatory reaction at transplant site	Bone marrow suppression (anemia, leukopenia, thrombocytopenia), easy bruising, delayed wound healing, increased incidence of malignancies, infections
Glucocorticoids (corticosteroids): prednisone or methylprednisolone		
Antiplatelet medications	Permanent inhibition of the cyclooxygenase activity of prostaglandin H synthase, affecting platelet aggregation	Affects platelet function
Acetylsalicylic acid (aspirin)		

2000 and November of 2014. For comparison, we obtained a population of age- and date-matched controls with no history of immunosuppression who underwent the same procedure. Two controls were obtained per each patient case. The controls were matched by age (±10 months in age) and by date (surgery performed within the same year). In order to make the group more homogeneous, only patients who had undergone tonsillectomy using an electrosurgical monopolar pencil cautery were included. This method is the most commonly used at our institution. All adenoidectomies were performed with suction monopolar electrocautery. Retrieved data included perioperative medications, occurrence of post-operative bleeding and associated treatment. Statistical analysis was performed with a two-tailed Fisher's exact test.

3. Results

A total of 41 patient cases and 82 controls were identified from a search through our electronic health record system in the specified dates. However, after applying exclusion criteria to both cases and controls (surgical technique), 34 cases and 47 controls remained. Post-transplantation cases were on immunosuppression regimens which consisted of a variety of combinations of the following medications: steroid (e.g. prednisone or methylprednisolone), tacrolimus (e.g. Prograf®), sirolimus (e.g. Rapamune®), mycophenolate (e.g. Cellcept® or Myfortic®), cyclosporine and azathioprine (see Table 2). Some patients were also on antiplatelet therapy with acetylsalicylic acid (e.g. aspirin), which is also included in Table 2.

See Table 3 for a comparison of clinical characteristics between the two groups, including indications for surgery, pathology results, and perioperative platelet count. For the 34 cases, although a complete coagulation profile was not consistently obtained all patients had a normal platelet count within the 2 months prior to surgery. None of the patients or controls had a positive family history for bleeding disorders. All patients had benign lymphoid hyperplasia on pathologic analysis, with two showing positivity for Epstein-Barr virus. No evidence of post-transplantation lymphoproliferative disease was found. The most common indication for surgery was obstructive sleep apnea. A total of 3 patients had an episode of post-surgical bleeding, consistent with an 8.82% bleed rate. One of these patients had minor bleeding noted by parents on post-operative day 8 and was observed at home, without any recurrence reported. The other two patients presented to the emergency room and required cauterization in the operating room. Therefore, the bleed rate requiring surgical control in these patients was 5.88%.

There was significant variability in the perioperative management of the patient's immunosuppressive regimen. Many of these patients were kept on the regimens throughout the operative and postoperative period, while others had the medications stopped and restarted a few days after surgery. See Table 4 for a description of the perioperative medication management and occurrence of hemorrhage for each post-transplant patient who had a post-operative bleed.

For the 47 controls, a total of 2 (4.26%) postoperative hemorrhages occurred. When compared to the cases, this incidence is not significantly different ($p = 0.65$). Neither of these two control patients with postoperative bleeding required surgical treatment. When comparing the incidences of postoperative bleeding requiring surgical treatment between the two groups, again the results was not significant: 5.88% and 0%, respectively ($p = 0.17$).

Table 2
Medication regimens for immunosuppressed patients.

Medication[a]	Tacrolimus	Sirolimus	Mycophenolate	Cyclosporine	Azathioprine	Steroid	Acetyl-salicylic acid
# patients on medication at time of T&A ($n = 34$)	31	9	22	2	5	10	4
# patients who were on this medication at time of T&A and/or postoperative bleed ($n = 3$)	2	2	3	0	0	1	1

[a] Of note, one of the patients who bled postoperatively was on fish oil at the time of the surgery and the postoperative bleed.