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Peri-operative Antithrombotic Therapy in Hair Transplantation

Kuniyoshi Yagyu, MD, FISHRS Tokyo, Japan nhttkyo11@kioicho.jp

Introduction

Patients under antithrombotic therapy sometimes visit our clinic for hair transplantation. Antithrombotic therapy is of critical importance to prevent serious cardiovascular events in patients with a mechanical heart valve, a coronary artery stent, or atrial fibrillation (Figure 1). Hair transplantation is considered safe surgery, therefore, peri-operative cardiovascular complications must be avoided.¹⁻⁶

Mechanical Heart Valve

Thrombus formation on the metal surface of the mechanical prosthetic heart valve results in malfunction and acute regurgitation of the valve with severe heart failure, which makes the patient critically ill. A thrombosed mechanical heart valve needs to be replaced with a new mechanical heart valve, and replacement surgery is a high-risk procedure.

Peri-operative control of antithrombotic therapy is of critical importance for prevention of thrombotic events and safe surgery in patients with a mechanical heart valve (Figure 2). According to the most recent guidelines, antithrombotic drugs should not be stopped and should be continued in a reduced dose before surgery.

Bridging Anticoagulation

The author doesn't stop warfarin before surgery in patients with a mechanical heart valve. Some cardiologists and other physicians may recommend stopping warfarin and antiplatelet drugs for one week before surgery. Because it is written in many books, sometimes cardiologists recommend bridging antithrombotic therapy using low molecular weight heparin.

This heparin-bridging regimen is one of incorrect information in modern medicine, and it should not be recommended. There is no evidence based on scientific data for heparin bridging. For more than 30 years, basic scientists

⇒ page 247

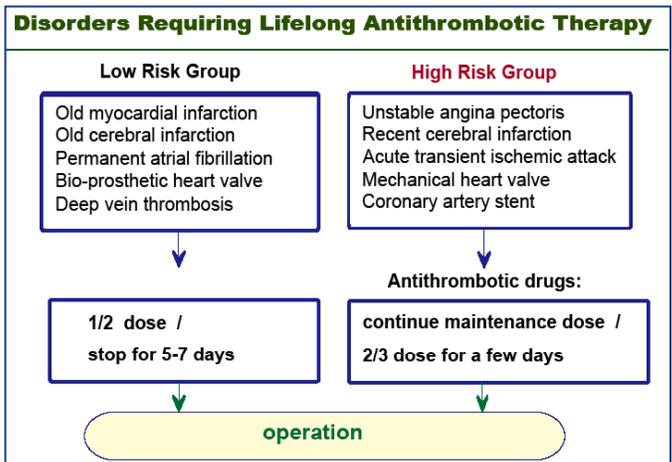


Figure 1. Disorders requiring lifelong antithrombotic therapy.

A note from Dr. True: One of the greatest strengths of our Society is the diversity of backgrounds of our membership. Because of our primary specialties, many of us bring unique expertise to our Society—neuro-surgery, urology, facial plastics, dermatology, cardiology, ENT, anesthesiology, etc. And when our members share insights from their background, it often enhances all of our practices. The lead article in this issue is a perfect example. Our immediate Past President, Dr. Kuniyoshi Yagyu, is a cardiologist by training. He has contributed many articles and presentations on the management of cardiology conditions during hair restoration surgery and in this issue he offers a very thorough and clearly written guide to help us provide correct peri-operative management of antithrombotics in hair transplantation.

I also would like to express Dr. Mario Marzola's and my gratitude on behalf of all the members to Dr. Yagyu for his outstanding leadership of our Society. We have been fortunate to have had the right leader at the right time to guide us through some difficult issues. We should hope that other societies and nations will be fortunate to have leaders of the same quality.

On page 252, we share an excerpt from Dr. Yagyu's opening remarks at the 24th ISHRS World Congress just concluded in Las Vegas.

**Las Vegas
World
Congress
Review
begins on
page 266!**



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President's Message

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THANK YOU, MARIO AND BOB!
Drs. Robert H. True & Mario Marzola
Forum Editors, 2014–2016

On behalf of the ISHRS Board of Governors and the membership, I wish to extend a heartfelt THANK YOU to outgoing editors, Drs. Mario Marzola and Bob True, who have published 18 thought-provoking and educationally rich issues for our membership over the past 3 years. This is their last issue, and it is more packed with hairy content than ever, showing their endless ability to stimulate members to contribute articles and continue the ongoing discussions, queries, comments, and opinions about our wonderful field.

In the same spirit, I am pleased to announce our two new editors, Drs. Andreas Finner and Brad Wolf. Drs. Finner and Wolf will begin with the January/February 2017 issue. Below are short biographies about each.

We welcome them to these positions!

Andreas Finner, MD

Dr. Andreas Finner is a German dermatologist who has specialized in hair disorders for more than 18 years. He wrote his doctoral thesis on light and electron microscopy of experimental hair damage and hair care products. He was trained at leading university hair clinics in Germany and completed a fellowship in hair at UBC Vancouver. During these years, he was involved in basic research projects, clinical trials, medical treatments and hair transplantation.

Since 2008, he has been practicing at his Trichomed Hair Clinic in Berlin combining medical therapies and hair transplantation. Dr. Finner has published on hair disorders, has given lectures on hair at conferences, and is a member of the European Expert Group for the establishment of the evidence-based S3 guideline for androgenetic alopecia. He is vice president of the German Society of Hair Surgeons. As co-editor, he aims to contribute to the great value of the *Forum* as an excellent medium for teaching, presenting research, and the exchange of ideas and techniques between members.



Bradley R. Wolf, MD, FISHRS

After two years of general surgery residency and 10 years of Emergency Medicine, Dr. Bradley Wolf has practiced hair restoration exclusively for over 26 years. He has been a member of the ISHRS since the first meeting in Dallas, Texas, in 1992 and became board certified by the ABHRS in its inaugural class in 1998. During the past 20 years, he has given over 50 lectures and participated in numerous workshops as well as live surgeries at hair restoration meetings. He has lectured on a wide variety of topics including the psychological aspects of hair loss, medico-legal issues, recipient site creation/placing, strip excision as well as all aspects of FUE surgery. As a columnist for the *Forum* for the past three years, he has written numerous articles covering a variety of topics and has developed a concise writing style. Dr. Wolf's clinical experience, broad knowledge of the topics, and writing experience have prepared him well to serve as co-editor of the *Forum*.



On a final note, I wish you—our membership—and your families a joyous holiday season as we approach the end of 2016. Our Society is stronger than ever, and we are fortunate to have an amazing membership with diverse backgrounds that brings creative, ingenious ideas all with the intent to continually improve the results for our patients. Here's to continued friendship, collegiality, education, and the ongoing pursuit to help our hair loss patients in 2017!♦

Co-editors' Messages

Mario Marzola, MBBS Adelaide, South Australia editors@ISHRS.org

This is the last issue of our beloved *Forum* magazine for your current co-editors, dear readers. Mixed emotions for me and I imagine the same for my friend Dr. Bob True. For three years we have brought together articles on all types of hair subjects—for beginners, for the experienced, for scientists—and from many countries. We reported on so many workshops and conferences bringing new developments and inventions. Sometimes the magazine came together easily, at other times it was a struggle, but always with the good humour of Bob True and our managing editor, Cheryl Duckler, it was much more fun than work. We particularly enjoyed receiving articles from new contributors, first-time publishers from all parts of the world; our thanks to all of you. This is a healthy sign.

The backbone of our *Forum* is our columnists on whom we rely to come up with something interesting, topical, or controversial for just about every edition: Drs. Russell Knudsen (Controversies), Bradley Wolf (Cyberspace Chat), Marco Barusco (Complications), Jerry Cooley (Hair Sciences), Sara Wasserbauer (Hair's the Question), Timothy Carman (How I Do It), Henrique Radwanski (Meetings and Studies), and Nicole Rogers and Jeffrey Donovan (Review of Literature). We thank you for all your efforts over the past three years and apologise for any badgering you may have received when it was close to copy deadlines. You have all been wonderful to work with.

How good is our Society? I am continually amazed by the restless inventiveness of our members, always searching for better outcomes for our patients. It is as if the status quo is not good enough, so we must keep searching. We feed on each other's thoughts and ideas and come back with our own. We all want to contribute.

We have critical mass in our Society now, so there's no stopping us. Sooner or later we will understand our mysterious hair follicles, know their secrets and know how to keep them happy and growing at their best. No more miniaturizing from there on!

Nurturing all this in the background is a very professional and able ISHRS Head Office lead by our esteemed Victoria Ceh. She has surrounded herself with like-minded people who serve and stay for so long that it appears to be a family, the same faces year after year. Thank you all for your care, your help, and your encouragement.

To Drs. Bradley Wolf and Andreas Finner, our new co-editors, congratulations and best wishes. In the tradition of all past editors, Dr. True and I stand ready to help at any time should the need arise.

I want to thank my first family for allowing me to spend some Sunday hours at the office in the last three years and the ISHRS, my second family, for this opportunity to serve. ♦



Robert H. True, MD, MPH, FISHRS New York, New York, USA editors@ISHRS.org

Throughout the history from hair restoration surgery, there have been several times that things have gone awry. Complications and unaesthetic results have frequently occurred. Sometimes this is because a technique, that is inherently flawed, has been popularized among practitioners. Sometimes the underlying cause is not the technique itself but the overly aggressive use of the technique that has led to problems.

An example of an inherently flawed technique was the "Laser Hair Transplant" of the early 1990s. The laser was promoted as being a more sophisticated way to make recipient sites, and this concept was attractive to consumers because lasers were associated with advanced technology. However, the technique was a disaster. The laser sites were dry and sealed and the grafts didn't survive. Cases of extremely poor growth became rampant and the technique was abandoned within a short period of time.

Another example of an inherently flawed technique was the "multibladed scalpel" for donor harvesting. It was appealing because it was an efficient way to create narrow donor strips to be divided into micro and mini grafts. But the transection rate was so high that it was referred to as "follicular holocaust." For a period of a few years, many patients lost a lot of their potential donor hair due to the technique. Thankfully, this was replaced by single blade donor strip harvesting.

An example of a surgical technique that was not intrinsically flawed but created many problems for patients because of flawed application was the scalp reduction. The intent of the procedure was to reduce the size of the balding scalp so that grafts could be concentrated in a smaller area and produce denser coverage. Unfortunately, too many practitioners turned scalp reduction into "scalp

elimination"; that is, rather than using it to reduce the bald scalp they aggressively and repeatedly used it to attempt to eliminate the bald scalp. One or two well-performed scalp reductions would accomplish reduced bald scalp with virtually no problems. But performing three, four, five scalp reductions or trying to take too much in a single procedure would cause deforming scars and slot deformations and scalps so attenuated that they would not support grafts—often disfiguring patients. Overly aggressive use was the flaw. Scalp lifts were a very aggressive form of scalp reduction and the undermining below the nuchal ridge led to some horrific complications of scalp necrosis and permanent sensory loss. Another example of the negative consequences of overly aggressive use of a technique was TPO flaps. Properly done they did produce results that were more aesthetic than standard punch grafts, but when surgeons tried to take too much in a single procedure disfiguring necrosis occurred in both the donor and recipient areas. One could argue that there was an inherent flaw with TPO flaps as well in that they produced unnatural hair direction.

With single-blade donor strip harvesting, I don't think problems have arisen because of any intrinsic flaw but rather because of unskilled and overly aggressive application that has led to the unsightly donor scars that have become a maligned aspect of the technique.

And now we come to FUE. During the Las Vegas meeting in the Q&A part of a session on FUE, our esteemed colleague Dr.

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OUR APOLOGIES: As co-editors of the ISHRS *Forum* magazine, we, Drs. True and Marzola, wish to apologize unreservedly to Ms. Busra Eryigit, International Sales and Marketing Manager, and to all at Ertip Medical and any punch manufacturer referenced for any offense that may have been taken from comments published in the recent July/August 2016 issue. The views expressed there are not the views of the editors, the magazine, nor of the ISHRS. Dr. Marzola uses Ertip punches and has been a satisfied customer of Ertip Medical for 4 years.

INTERNATIONAL SOCIETY OF HAIR RESTORATION SURGERY

Vision: To establish the ISHRS as a leading unbiased authority in medical and surgical hair restoration.

Mission: To achieve excellence in medical and surgical outcomes by promoting member education, international collegiality, research, ethics, and public awareness.

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Editorial Guidelines for Submission and Acceptance of Articles for the Forum Publication

- Articles should be written with the intent of sharing scientific information with the purpose of progressing the art and science of hair restoration and benefiting patient outcomes.
- If results are presented, the medical regimen or surgical techniques that were used to obtain the results should be disclosed in detail.
- Articles submitted with the sole purpose of promotion or marketing will not be accepted.
- Authors should acknowledge all funding sources that supported their work as well as any relevant corporate affiliation.
- Trademarked names should not be used to refer to devices or techniques, when possible.
- Although we encourage submission of articles that may only contain the author's opinion for the purpose of stimulating thought, the editors may present such articles to colleagues who are experts in the particular area in question, for the purpose of obtaining rebuttal opinions to be published alongside the original article. Occasionally, a manuscript might be sent to an external reviewer, who will judge the manuscript in a blinded fashion to make recommendations about its acceptance, further revision, or rejection.
- Once the manuscript is accepted, it will be published as soon as possible, depending on space availability.
- All manuscripts should be submitted to forumeditors@ishrs.org.
- A completed Author Authorization and Release form—sent as a Word document (not a fax)—must accompany your submission. The form can be obtained in the Members Only section of the Society website at www.ishrs.org.
- All photos and figures referred to in your article should be sent as *separate* attachments in JPEG or TIFF format. Be sure to attach your files to the email. Do NOT embed your files in the email or in the document itself (other than to show placement within the article).
- Images should be sized no larger than 6 inches in width and should be named using the author's last name and figure number (e.g., TrueFigure1).
- Please include a contact email address to be published with your article.

Submission deadlines:

December 5 for January/February 2017 issue

January 5 for March/April 2017 issue

February 5 for May/June 2017 issue

*Please note new submission address:

forumeditors@ishrs.org



Red Flags—Misleading & Inappropriate Messaging

The International Society of Hair Restoration Surgery (ISHRS) is serious about protecting the public. The ISHRS has published guidelines for its membership about *Misleading and Inappropriate Messaging* on physicians' websites and marketing materials.

The ISHRS encourages its members to only include website and marketing messaging to the public that will augment their understanding and knowledge of the causes and scientifically proven therapies for hair loss.

Guidelines have been established to help members avoid what can be universally considered as misleading or unacceptable messages.

The following are considered misleading or inappropriate.

Please note that 1a has recently been added.

We encourage ISHRS members to review their websites and marketing materials to **ensure that these infractions are not included**. Members of the public who are seeking professional services from a hair restoration surgeon should consider these terms as “red flags.” If they are used in a doctor’s marketing material or website, the consumer should beware.

False Statements and Copyright Infringement

1. Including inaccurate credentials, e.g., claiming ABHRS (American Board of Hair Restoration Surgery) Diplomate status or FISHRS (Fellow of the International Society of Hair Restoration Surgery) status when the individual has not earned these designations, or claiming inaccurate expertise in hair restoration surgery
 - a. **Members should not mislead the public with regard to their qualifications. Reference to Board Certification should be specific to the certification that has been achieved. Those who have passed the American or International Board of Hair Restoration Surgery examination have agreed to refer to themselves as “Diplomates” of the ABHRS or IBHRS and to not refer to themselves as Board Certified in Hair Restoration.**

2. Using other physicians' before & after photos as their own
3. Violating copyright of others with photos or text
4. Using ISHRS Members Only logo inappropriately, e.g., when they are not a full Member
5. Using Fellows Only logo inappropriately, e.g., when they are not designated as a Fellow status of the ISHRS
6. Using the ISHRS logo. Note: Nobody except the ISHRS is allowed to use the official ISHRS logo.

Inappropriate Use of Staff

7. Evidence of unlicensed, non-physicians performing surgical procedures

Inappropriate, Misleading, Inaccurate Terminology

8. “Scarless surgery”
9. “No incision”
10. “No touch”
11. “No cutting”
12. “Cloning”
13. “Hair multiplication”
14. “Non-invasive”
15. “Eliminates the need for additional procedures”



True Co-editor Message from page 243

Walter Unger offered a comment addressing concerns about donor utilization with FUE (pronounced “eff-you-ee”). In his comment, Dr. Unger indicated that while he had serious reservations about the technique, he was also appreciative of it. But it was curious in his remarks he referred to FUE as fu-ee (pronounced “phooey”). Phooey has a meaning in English of expressing disdain or disbelief. At the time, I was curious as to his usage, but as I have thought about it, I have begun to wonder if the unusual pronunciation was not intentional and meant to express a belief that FUE is an intrinsically flawed technique. Maybe this was not the intent, but it raised the question for me. I do know that there are some among our membership who do consider FUE to be an inherently flawed technique citing the hair transection rate and the false promise of being able to shave the head without harvesting being visible. While I understand these points, I would strongly argue that FUE is not “phooey,” and that the problems associated with the technique that we are seeing manifested currently are not a consequence of inherent flaws but rather of misapplication, and particularly

because of overly aggressive application of the technique. This is most evident in the performance of FUE mega sessions of 4,000 or more grafts from the scalp in a single surgery. This can only be done if the density of harvests is too high, there is a disregard for transection, and areas outside of the safe zone are harvested to the same extent as within the safe zone. We are unfortunately seeing patients (many of whom are young) who have their donor zone depleted in a single surgery while at the same time having little growth to show for the surgery, and who certainly cannot hide the donor depletion without wearing their hair long. FUE is still referred to as a “new” technique, but it has been around for 15 years. It has evolved and improved substantially during this time, and I believe right now we will see the technique becoming even better because of recent innovations. FUE does not belong in the same company as laser hair transplants and the multi-bladed knife. But in order for it to not become associated with more harm than good, it must be applied thoughtfully, conservatively, and honestly while avoiding overly aggressive use. ♦

Notes from the Editor Emeritus

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Coincidental Epigenetics or Post-Finasteride Syndrome (PFS)?

The 2016 ISHRS World Congress in Las Vegas featured Dr. Alan Jacobs as guest speaker. Dr. Jacobs is a Neuroendocrinologist in private practice after a stint as Assistant Professor of Neurology at SUNY/Downstate Medical Center. In 2003, he opened his clinical practice in Behavioral Neurology, Memory Disorders and Neuroendocrinology in Manhattan. He has seen over 500 cases of persistent sexual, emotional, and cognitive impairment, some of which he directly attributes to finasteride use. It is from this extensive experience and knowledge that he presented a talk titled "Post-Finasteride Syndrome and the Neuroendocrine System."

By definition, Dr. Jacobs believes PFS is a side effect of the drug finasteride, and it is primarily a sexual impairment phenomenon. Many cases have accompanying depression and cognitive impairment occurring simultaneously. In some cases, it is not reversible and can persist long term after discontinuing the medication. Dr. Jacobs recalled his first case involving a hedge fund manager who reported experiencing a "brain fog" and sexual dysfunction very similar to drinking 3-4 glasses of wine. This brain fog had persisted for 1.5 months. The patient had been on finasteride for 10 years. He stopped the finasteride and noticed his brain fog and sexual dysfunction improved. He went back on finasteride and all of his symptoms recurred. The patient's DHT and A-DIOL glucuronide were very low. Following discontinuation of finasteride, his A-DIOL glucuronide normalized. Dr. Jacobs stated he became involved with studying this syndrome after this case and reports there may be common neuroendocrine findings in other cases. A low FH and LFH, low bioavailable testosterone, and finally the biotestosterone/estradiol testosterone is altered. He gave a lengthy expose on testosterone biotransformation and noted that testosterone itself can be reduced by 5 α -reductase to 5 α -dihydrotestosterone (Figure 1). It can also be reduced by 5 β -reductase to 5 β -dihydrotestosterone and a third pathway involves reduction by aromatase 17 β -estradiol. The mechanisms of production of PFS is theory, but it appears the testicular function in these individuals is normal. He also stated the pituitary gonadotrophs function is normal in the cases he studied. The hypothalamic GnRH cells may be the area of dysfunction. This would involve the limbic HPG axis. The GnRH is released at various times in life by stimulation of various neuropeptides, one of which is a hypothalamic neuropeptide kisspeptin. Kisspeptin is a potent stimulus for GnRH secretion. Dr. Jacobs believes this may later be found to play some sort of role in PFS (Table 1).

Several other potential processes were discussed, including the phenomenon of epigenetics. Specifically, there have been cases of persistent sexual dysfunction after discontinuation of SSR reuptake inhibitors that may be linked to epigenetic mechanisms. A similar occurrence has been reported with isotretinoin. Concerning genetics and finasteride, reference was given to an article that demonstrated the smaller the CAG-repeat number, the larger the improvement with finasteride. CAG counts are important in the axon 1 region of the androgen receptor gene. The CAG-repeat length of axon 1 of the androgen receptor has shown causal interactions with depression, personality traits, body composition, sex hormone levels, libido, and other findings, so it would follow that certain individuals are predisposed to react differently to finasteride depending on their genetic makeup.

A recent article posted in the Journal of Clinical Endocrinology and Metabolism showed no differences in the sequences of AR, SRD5A1 and SRD5A2 genes among symptomatic finasteride users versus asymptomatic users. Dr. Jacobs was critical of the methodology used in the genetic testing of this particular study. He reported that although the study mentioned above was sponsored by The Post Finasteride Syndrome Foundation, and was largely negative, it didn't rule out an epigenetic effect. He believes the same epigenetic effects from various drugs could cause similar symptomatology, specifically among users of antidepressants, isotretinoin, and 5 α -reductase inhibitors.

Dr. Jacobs's discussion was well received by the Society, but key questions remain. Audience members voiced their concerns. Chiefly,

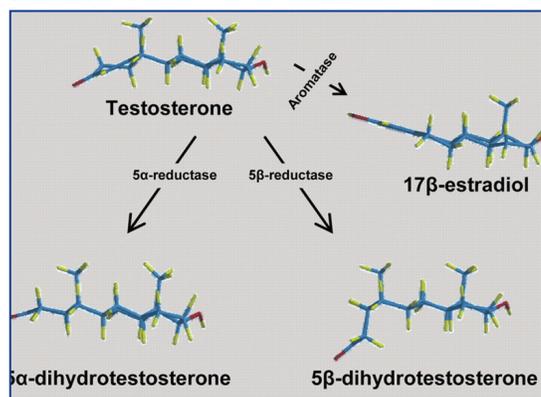


Figure 1. Testosterone biotransformation (Credit: Alan Jacobs, MD. "Post-Finasteride Syndrome and the Neuroendocrine System." Presented at the ISHRS 24th World Congress, Las Vegas, Nevada, USA. September 2016.)

Mechanisms of PFS

1. Testicular functioning is normal.
2. The pituitary gonadotrophs function normally.
3. The hypothalamic GnRH cells may be the area of dysfunction.
4. The temporal lobe limbic structures often inhibit hypothalamic GnRH function.

Table 1. Mechanisms of PFS (Credit: Alan Jacobs, MD. "Post-Finasteride Syndrome and the Neuroendocrine System." Presented at the ISHRS 24th World Congress, Las Vegas, Nevada, USA. September 2016.)

PFS was not reported in the literature for the first 10 years the drug was on the market. Hair transplant surgeons are responsible for prescribing a large amount of this medication yet there was no mention on PFS for the first 10 years of the drug release. Why all the sudden reports? Could this drug really be responsible for the PFS or could it simply be coincidental epigenetics? In other words, would these men have suffered the same syndrome whether or not they were on drug? Does epigenetics explain this occurrence after SSRIs, 5ARs, and isotretinoin? My own take-home lesson from his talk was if a young man has any history of depression, mood swings, or sexual dysfunction, then do not prescribe finasteride for him. He may just have the wrong set of genes. The finasteride syndrome findings should still be studied along with the concept of a coincidental epigenetic phenomenon. ♦

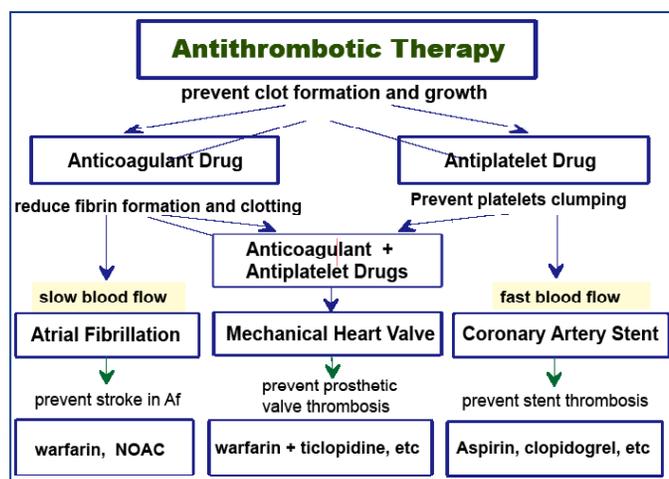
Antithrombotic Therapy *from front page*

Figure 2. Antithrombotic therapy in patients with cardiovascular diseases.

have pointed out that heparin doesn't prevent platelet activation and coagulation cascade. Heparin doesn't stop the thrombotic process, even though heparin seems to prevent blood clot formation. A few years ago the American Heart Association and the American College of Cardiology Foundation (AHA/ACCF) published a guideline stating that the societies don't recommend the heparin bridging regimen anymore.^{1,3-5} Several studies show that heparin doesn't prevent arterial thromboembolic events whereas heparin increases the risk of major bleeding.^{2,6} There are many physicians and cardiologists who don't know the new guideline and still recommend heparin bridging for patients under antithrombotic therapy.

Safe Guide on Peri-operative Control of Warfarin

Warfarin (Coumadin) is slow-acting and has a long half-life. The half-life of warfarin is about 36 hours in the blood. The anticoagulant effect of warfarin appears in 12-24 hours and lasts for 48-72 hours. In the clinical experience, warfarin remains effective for 3-4 days after it is stopped, and it takes 4-5 days for warfarin to reach the therapeutic effect after it is restarted. The anticoagulant activity of warfarin is closely monitored by the prothrombin time/international normalized ratio (PT/INR) to ensure that an adequate and safe dose is taken.⁷ The targeted PT/INR level tends to be 2.0-3.0 in most conditions as maintenance anticoagulant therapy for the prevention of thrombosis in patients with mechanical heart valves.

If the PT/INR is 2.0-3.0, the patient has a risk of bleeding but there is little risk of thrombosis.⁸ This strict anticoagulation is applied to patients with a mechanical heart valve or atrial fibrillation. A PT/INR of 0.8-1.2 is normal coagulability, and there is little risk of bleeding but there is a risk of thrombosis. If the PT/INR is around 1.5-1.6, there is little risk of bleeding or thrombosis. This means low-intensity anticoagulation can be applied for less than one week to a patient with a mechanical heart valve and paroxysmal atrial fibrillation (Figure 3).

Interruption of anticoagulation before surgery can be problematic. If warfarin is stopped for longer than 4-5 days pre-operatively, the PT/INR will return to normal (<1.2) on the day of the procedure, and the patient will remain unprotected for about 3-4 days post-operatively. The period off warfarin can be shortened by restarting warfarin in the maintenance dose one day before the procedure with the expectation that coagulability will become nearly normal on the day of the procedure and warfarin will become effective again soon after the surgery.

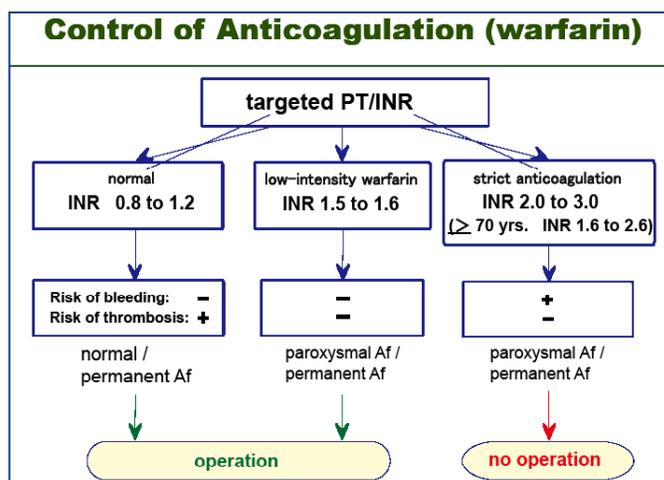


Figure 3. Control of warfarin and PT/INR before surgery.

If warfarin is stopped, there is a risk of thrombosis in patients with a mechanical heart valve. Therefore, the dose of warfarin should be reduced gradually 5-6 days before surgery. The final dose of warfarin can be reduced to two-thirds to three-fourths of the maintenance dose for 2-3 days before surgery to allow the PT/INR to fall to around 1.5-1.6 on the day of the surgery. If the PT/INR is around 1.5 on the day of the procedure, warfarin will not cause hemorrhagic tendency or thrombus formation. This low-intensity warfarin doesn't interfere with surgical procedures including abdominal surgery, orthopedic surgery, cardiac surgery, and tooth extraction. Hair transplantation can be performed without any difficulty. Further reduction of the dose of warfarin is dangerous and not necessary. Warfarin should be restarted in the maintenance dose soon after the surgery. Warfarin should not be stopped before hair transplantation in patients at high risk of thrombosis (Figure 1).

Safe Period with Low-Intensity Warfarin

At the outpatient clinic, the result of PT/INR varies often according to a patient's dietary habits. If the patient takes antiplatelet drugs, the patient is safe even if the PT/INR is kept around 1.4-1.6 for several weeks or one month. If the patient takes no antiplatelet drugs, the period of PT/INR of 1.5-1.6 should be kept short and the period off warfarin should be less than a few days.

Aortic Valve vs. Mitral Valve

As for the difference in the location of the mechanical heart valve, a prosthetic heart valve at the aortic position has less possibility to form thrombus than one at the mitral position because of high blood velocity and high driving pressure to open and close the valve. Patients after aortic valve replacement have less possibility of thrombosed valve than those after mitral valve replacement, even when they are kept under insufficient antithrombotic therapy for a few months.

Prosthetic heart valves at the tricuspid and pulmonary positions are more likely to form thrombus because of slow blood flow and low driving pressure to open and close the valve. This is the reason why mechanical heart valves are not used at the tricuspid and pulmonary position.

In addition, there is an increased risk of thrombosis of a mechanical heart valve if the patient receives poor control of antithrombotic therapy for several months.

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Antiplatelet Drugs

Patients with a mechanical heart valve need a combination of anticoagulant and antiplatelet drugs to prevent clot formation and growth.⁸ Dipyridamole and ticlopidine are usually used as antiplatelet drugs for mechanical heart valves. Dipyridamole has a moderate antiplatelet effect. Ticlopidine is a relatively strong antiplatelet drug.

About 30-40 years ago, only an anticoagulant without antiplatelet drugs was prescribed for patients after valve replacement, and thrombosed mechanical heart valve was not rare in those days.

Antiplatelet drugs should only be stopped for a short period in patients with a mechanical heart valve. The length of time without antiplatelet drugs is determined by the half-life and irreversibility of the drug.⁸ The half-life of dipyridamole is short and the effect is reversible, and dipyridamole can be stopped only 1-2 days before surgery. If the antiplatelet drug has a long half-life and irreversible effect, it needs to be stopped 3-7 days before surgery. Ticlopidine can be stopped 5-7 days before surgery, but not longer than one week. It is also important to restart the antiplatelet drugs in the maintenance dose on the first day following the surgery.

Aspirin is a weak antiplatelet drug, and aspirin is not enough for antithrombotic therapy in patients with a mechanical heart valve. Usually, aspirin is not used as an antiplatelet drug in patients with a mechanical heart valve. If a patient does take aspirin as an antiplatelet drug, aspirin can be continued for surgery. Low-dose aspirin doesn't cause hemorrhagic tendency during the surgery.

Patients with a Mechanical Heart Valve

Over 30 years of practice, this author has treated hundreds of patients with mechanical heart valves in an outpatient clinic. Patients with a mechanical prosthetic valve need lifelong antithrombotic therapy using a combination of warfarin and antiplatelet drugs.⁸ As these patients aged, some needed various kinds of operations including major surgery such as cholecystectomy for gallstones, colectomy for colon cancer, knee joint replacement, another heart valve replacement, coronary artery bypass graft surgery, etc. Patients sometimes also needed minor surgery such as tooth extraction, cataract operation, skin cancer removal, and empyema operation in the nasal cavity. All the patients went through these procedures safely without a thrombotic event when managed as outlined above.

As for the duration of hair transplantation, there is enough time to operate on the patient as usual. It is not necessary to hurry to finish the operation. If the drugs are controlled properly before surgery, patients remain safe for several days with a reduced dose of antithrombotic drugs.

Coronary Artery Stent

Stent thrombosis is a serious complication.^{9,10} Thrombus in the coronary stent occludes the lumen of the stent, which results in acute myocardial infarction. Stent thrombosis is a life-threatening complication with a high mortality rate of 20%. Antiplatelet drugs are necessary to prevent thrombus formation in coronary artery stents. Patients with coronary artery stents need long-term antiplatelet therapy (Figure 2).

Drug eluting stents are usually selected for percutaneous coronary intervention. Antithrombotic therapy for patients with drug eluting stents is as follows (Figure 4). Patients within one year after the coronary intervention using drug eluting stents need a combination of two antiplatelet drugs. This dual antiplatelet therapy (DAPT) means the combination of aspirin 81mg per day (ranging 75-100mg) and another stronger antiplatelet drug such as a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor).

Aspirin is always continued in patients with coronary artery disease regardless of the duration of DAPT.

DAPT

DAPT is used to reduce the risks of future heart attack and coronary stent thrombosis, which means occlusion of a stent by a blood clot. In general, DAPT cannot be stopped for one year. Hair transplantation should be postponed until one year after the stenting treatment.

In patients from one to two years after stenting treatment using drug eluting stents, hair transplantation is possible. Patients usually need both aspirin and clopidogrel in this period. Clopidogrel can be stopped for 5 days as long as aspirin is continued, and safe hair transplantation is possible as usual in these patients (Figure 4). If you want to stop both drugs, you can stop them for only 3 days before surgery but not longer. After hair transplantation, however, both drugs should be restarted.

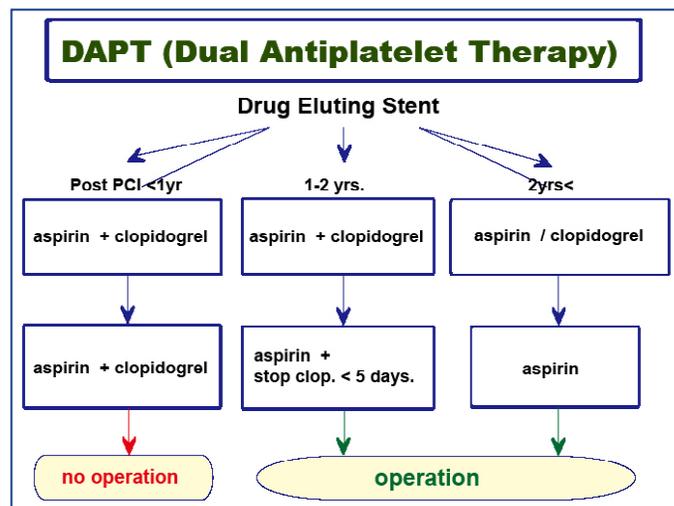


Figure 4. Control of dual antiplatelet therapy in patients with coronary artery stents.

In patients more than two years after stent implantation using a drug eluting stent, one antiplatelet drug is used in the long term. If the patient takes clopidogrel, it can be changed to aspirin for one week before surgery, and then the clopidogrel can be restarted after the hair transplantation. If the patient takes aspirin as an antiplatelet drug, it can be continued before surgery (Figure 4). Safe hair transplantation is possible as usual with a maintenance dose of aspirin. Even FUE is possible in patients with low-dose aspirin because low-dose aspirin doesn't cause hemorrhagic tendency during surgery. Aspirin should be stopped for no more than 3-5 days.

This year, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) released updated guidelines for dual antiplatelet therapy in patients with a coronary artery stent.¹¹ The new guidelines are based on the findings of recent studies in patients with a new type of stents that lowers the risk of clotting complication better than the older types of coronary stents. The updated recommendations on duration of DAPT compiled six previously published guidelines, which were published by the ACCF/AHA from 2011 to 2014. The new guidelines recommend a shorter duration of DAPT (short DAPT) in patients with a low risk of stent thrombosis and a high risk of bleeding. The guidelines also recommend a longer period of DAPT (long DAPT) in patients with a high risk of stent thrombosis and a low risk of bleeding. In general, DAPT for 6-12 months is a Class I recommendation, and DAPT for more than 12 months is a Class IIb recommendation. These recommendations apply to

a new generation of coronary stents with less possibility of stent thrombosis and to patients without oral anticoagulant therapy.

Maintenance drugs should be checked in patients with a coronary artery stent. If the patient needs antiplatelet drugs as maintenance therapy, it is important to talk to the patient's physician about these drugs. If the cardiologist doesn't mind stopping the antiplatelet drugs for several days, antiplatelet drugs can be stopped before surgery and restarted after the surgery. If the cardiologist doesn't allow the antiplatelet drugs to be stopped, the drugs should be continued before the procedure. Hair transplantation is an operation with low risk of bleeding. Safe operation is possible even in patients using low-dose antiplatelet drugs.

Risk of Cardiovascular Event

It is important to compare the risk of bleeding and the risk of thrombosis in cardiovascular patients (Figures 1 and 5). Patients with a coronary artery stent and unstable angina pectoris belong to a high-risk group. In these patients, thrombosis may cause serious cardiovascular events and acute myocardial infarction. Antithrombotic drugs should be continued in the maintenance dose or they can be reduced to two-thirds dose for only a few days before the hair transplantation. If antithrombotic drugs are stopped before surgery, the patient will be put at risk for thrombosis with high mortality.

If a patient needs clopidogrel as anti-thrombotic therapy, there are two possibilities. First, ask the cardiologist if clopidogrel can be switched to low-dose aspirin for one week. If the cardiologist agrees with low-dose aspirin, it can be continued and a safe hair transplantation without difficulty in hemostasis can be performed. Second, if the cardiologist doesn't agree with aspirin, ask if the dose of clopidogrel can be reduced to one-half to two-thirds of the maintenance dose. If the dose of clopidogrel can be reduced before surgery, the hair transplantation can be performed without major difficulty. If the cardiologist doesn't agree with dose reduction of clopidogrel, the hair transplantation should be performed carefully, or the operation postponed for one year. After one year, the cardiologist will probably agree with dose reduction or change of the drug.

Atrial Fibrillation

Loss of wall contraction and stasis of blood flow tend to cause thrombus formation in the left atrial appendage in patients with atrial fibrillation.¹²⁻¹⁷ Thrombus in the left atrial appendage is usually large in size, and thromboembolism of the clot occludes the large artery in the cranium. Symptoms of large vessel embolic ischemic stroke include hemiplegia, speech disturbance, etc.

An anticoagulant drug prevents clot formation in the left atrium (Figures 1-3). Warfarin is used to prevent ischemic stroke in patients with atrial fibrillation. Targeted maintenance anticoagulation of warfarin is usually a PT/INR of 1.6-2.6 in patients with atrial fibrillation.

Patients with paroxysmal atrial fibrillation have a high risk of thrombosis if warfarin is discontinued; rather, warfarin should be reduced to two-thirds of the maintenance dose for 4-5 days in advance of surgery to allow the PT/INR to fall to near normal (1.4-1.6) (Figure 3). The maintenance dose of warfarin should be resumed post-operatively.

Patients with permanent atrial fibrillation have a low risk of thrombosis, and warfarin can be stopped or reduced to half of the maintenance dose for 5-7 days before surgery to allow the PT/INR to fall to normal or near normal (1.0-1.5). The maintenance dose of warfarin should be restarted after surgery.

If the PT/INR is around 1.5-1.6, there is little risk of bleeding or thrombosis. This means low-intensity anticoagulation can be safely prescribed for less than one week for patients with paroxysmal or permanent atrial fibrillation.

NOAC

Recently, several new anticoagulants (novel oral anticoagulants [NOAC]) have become commercially available. They are direct thrombin inhibitors. Their bioavailability is not affected by foods, and similar effective results are expected without blood tests. The half-life of dabigatran is 12-14 hours, the half-life of apixaban is 9-14 hours, rivaroxaban 7-11 hours, and edoxaban 9-11 hours. Dabigatran is a direct thrombin inhibitor. Apixaban, rivaroxaban, and edoxaban are selective direct inhibitors of clotting factor Xa. The dosage of NOAC is reduced to two-thirds or one-half per day to avoid bleeding complication in patients over 70-80 years of age or in patients with moderately impaired renal function. If NOAC is stopped for 24 hours before surgery, coagulability will return to nearly normal on the day of the procedure. Major surgery is possible if NOAC is stopped for 2 days before surgery.

NOAC is usually recommended as antithrombotic therapy in patients with atrial fibrillation. NOAC reduces the risks of stroke, systemic thromboembolism, and major bleeding in comparison with warfarin. However, if a major bleeding complication happens, the patient's condition may become serious and sometimes be fatal. There are several recent reports on fatal intracranial bleeding in elderly patients under antithrombotic therapy using NOAC. There is no laboratory measure for the effect of NOAC, or to determine when NOAC is overdosed. Currently, there is also no drug to counteract the effect of NOAC when the patient has bleeding complications. Therefore, NOAC should be used carefully and only by experienced cardiologists.

Risk of Bleeding vs. Risk of Thrombosis

It is important to compare the risk of bleeding and the risk of thrombotic events in patients under antithrombotic therapy (Figure 5). Diseases that require lifelong antithrombotic therapy are classified into either 1) a low-risk group or 2) a high-risk group (Figure 1).

Disorders in the high-risk group include unstable angina pectoris, recent cerebral infarction, paroxysmal atrial fibrillation, and patients with mechanical prosthetic heart valve and coronary artery stents. Thrombosis may cause serious cardiovascular events in these patients, and antithrombotic drugs should not be stopped before hair transplantation.

Disorders in the low-risk group include old myocardial infarction, old cerebral infarction, permanent atrial fibrillation, bioprosthetic heart valve, deep vein thrombosis, and pulmonary embolism. Thrombosis does not directly cause serious cardiovascular events in these patients, and antithrombotic drugs can be stopped only for a short period before surgery.

Antithrombotic Therapy

Antithrombotic therapy consists of anticoagulant and antiplatelet drugs (Figure 2). Anticoagulant drugs reduce fibrin formation

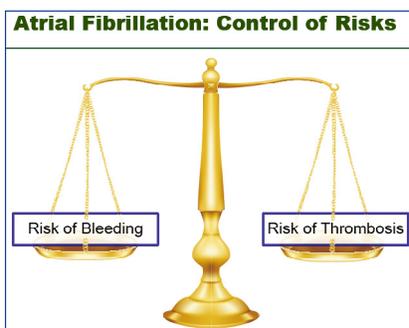


Figure 5. Risk of bleeding vs. risk of thrombosis.

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and slow down clotting. Antiplatelet drugs prevent platelets aggregation. A combination of anticoagulant and antiplatelet drugs is important to prevent clot formation and growth.

An anticoagulant drug prevents thrombus formation in slow blood flow, where an antiplatelet drug has little effect. An anticoagulant is effective to prevent thrombus formation in the left atrial appendage in atrial fibrillation, deep vein thrombosis, venous thromboembolism, etc.

An antiplatelet drug prevents thrombus in the arterial circulation with fast blood flow, where an anticoagulant is not effective. Antiplatelet drugs prevent thrombosis in the coronary artery stent, and in many cerebrovascular and cardiovascular diseases.

Patients with a mechanical heart valve need both anticoagulant and antiplatelet drugs to prevent thrombosis. Only an anticoagulant drug or only an antiplatelet drug is not enough to prevent thrombosis on the mechanical heart valve.

Other Issues in Cardiovascular Patients

There are other considerations for safe surgery in elderly patients and patients with cardiovascular diseases.

Beta Blocker

Patients with cardiovascular diseases sometimes need a beta blocker as one of maintenance drugs for the treatment of hypertension, heart failure, and tachyarrhythmia.^{18,19} Usually, a beta-1 selective blocker such as bisoprolol, atenolol, or metoprolol is used (Table 1). A beta blocker works effectively to control hypertension and tachyarrhythmia including paroxysmal atrial fibrillation. If a patient takes a beta blocker for cardiovascular diseases, it is not a good idea to stop the beta blocker before hair transplantation. If a beta blocker is stopped before surgery, there is the possibility that the patient will have uncontrollable hypertension or dangerous tachyarrhythmia during surgery.

There is a guideline on peri-operative usage of beta blockers published by the American Heart Association/American College of Cardiology Foundation (AHA/ACCF) that recommends continuation of a beta blocker before non-cardiac vascular surgery. If the patient needs a beta blocker for the treatment of tachyarrhythmia, hypertension, and other cardiovascular diseases, a maintenance dose of beta blocker should not be stopped before surgery. Peri-operative beta blockade in cardiovascular patients is a Class I indication on the level of evidence B or C in the ACCF/AHA guidelines. Safe operation is possible as usual even when

a small dose of epinephrine is added in the tumescent solution. A beta-1 selective blocker reduces peri-operative mortality and non-fatal heart attacks in patients undergoing non-cardiac vascular surgery. A beta blocker should be continued before hair transplantation in patients with cardiovascular diseases.

Epinephrine

This author usually dilutes epinephrine in the concentration of 1:500,000 to 1:1,000,000 in the tumescence. The concentration is enough for vasoconstriction and hemostasis. The author prefers intradermal injection of tumescent solution all around the recipient area and the donor area. Most of the blood flow comes through the dermal layer, and there is little blood supply from the subcutaneous adipose tissue. This author usually has difficulty finding slits in the recipient area, because only a little bleeding can be seen during surgery. Over the past 10 years, this author has never used “super juice” with high epinephrine concentration during surgery.

Hair transplant surgeons are sometimes afraid of bleeding from slits, and they want to stop antiplatelet drugs and anticoagulants before surgery. However, bleeding from slits and antithrombotic drugs are different issues. Bleeding from slits can be reduced by intradermal injection of tumescent solution containing a small dose of epinephrine all around the recipient area. If bleeding from a slit is caused by injury of an intradermal vessel, an additional intradermal injection of tumescent solution at the site of bleeding can be given. Increased tissue pressure minimizes bleeding from the slit; gauze can be used to compress the slit for a few minutes while making slits in other places in the recipient area. Subcutaneous injection of super juice has little effect on bleeding from slits.

Others

In at-risk patients, electrocardiogram, blood pressure, heart rate, and peripheral oxygen saturation (SpO₂) should be monitored throughout surgery.

This author always uses nitroglycerin (NTG) tape in patients with ischemic heart disease or patients older than 60 years of age. A half size of 5mg NTG tape is put on the anterior chest wall of the patient 15-20 minutes before surgery. It will keep a stable subtherapeutic concentration of NTG in the blood during surgery, which will make the operation safer. When the tape is removed, the effect of NTG will disappear. Usage of a small dose of NTG has no side effect.

Sedative drugs will be helpful to reduce anxiety and sympathetic nerve activity in patients with ischemic heart disease and tachyarrhythmia. Painkillers also can be helpful during operation. The author prefers fentanyl tape to reduce pain during and after surgery. A half size of 1mg fentanyl tape works satisfactorily.

Nasal oxygen 1.5-2L/min should be prepared to avoid hypoxemia during surgery. It is safer to keep SpO₂ of 96-98% or greater during surgery.

An intravenous cannula should be inserted before surgery in cardiovascular patients And an anesthesiologist should be there to help during the surgery. In addition, 500-1,500cc Lactated Ringer’s solution should be prepared for volume replacement in case of hypotension and hypovolemia. Drinking isotonic sports drinks is also useful as volume replacement before surgery.

Hypotension should be avoided during surgery in patients with ischemic heart disease.²⁰ If the systolic arterial pressure drops to less than 90mmHg during surgery, the patient’s lower legs should be raised and the patient should be put in Trendelenburg position. If the systolic arterial pressure drops below 80mmHg, the patient

Beta Blocker				
		ISA	MSA	agents
I	Non-selective	+	+	alprenolol, penbutolol, oxprenolol, penbutolol
		+	-	pindolol, carteolol
		-	+	propranolol, bufetolol
		-	-	timolol, nadolol, nipradilol, tilisolol
II	β1-selective	+	+	acebutolol
		+	-	celiprolol
		-	-	metoprolol, atenolol, bisoprolol, betaxolol
III	α-blocking	+	+	labetalol
		-	+	carvedilol
		-	-	arotinolol, amosulalol

ISA: Intrinsic Sympathomimetic Activity, MSA; Membrane Stabilizing Activity

Table 1. Beta Blocker

with ischemic heart disease will be at risk of cardiac arrest and should be given transfusion and vasopressor. The author gives the patient rapid transfusion of 1,000-1,500cc Lactated Ringer's solution and an intravenous injection of ephedrine. Ephedrine is effective to treat low arterial pressure during surgery. Intravenous injection of 4-6mg ephedrine can be repeated every several minutes up to 2-3 times. After an injection of a total of 12-16mg ephedrine, the systolic arterial pressure should become greater than 90-100mmHg again, and the operation can be restarted. Ephedrine is a safe and effective vasopressor to treat low systolic arterial pressure during surgery.

Conclusion

Over a 10-year period, the author has performed 48 hair transplantation surgeries in 26 male patients with cardiovascular and cerebrovascular diseases. Patients needed maintenance antithrombotic therapy in 26 operations. They included ischemic heart disease in 11, ischemic cerebral disease in 8, atrial fibrillation in 4, prosthetic heart valve in 2, and pulmonary embolism in 1. All these patients underwent safe surgery without complications. The author always continued beta blocker, anticoagulant, and antiplatelet drugs before surgery, which made the hair transplantation safer.

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