Review / Derleme

Topical hemostatic agents in otolaryngologic surgery

Kulak burun boğaz ve baş boyun cerrahisinde topikal hemostatik ajanlar

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Topical hemostatic agents are largely used to reduce blood loss during otolaryngologic surgery. These agents play an important role in both keeping the patient's hemodynamic equilibrium and allowing for a better view of the surgical field. These agents can be classified based on their mechanism of action, and include physical or mechanical agents. Most complications of topical hemostatic agents are sustained because of the antigenic reaction of those products. This paper reviews traditional and newer topical hemostatic agents with regard to their chemical properties, their mechanisms of action, and the benefits and complications of topical agents.

Key Words: Bleeding; local hemostasis; otolaryngologic surgery.

Topikal hemostatik ajanlar kulak burun boğaz ve baş boyun cerrahisinde kan kaybını azaltmak için yaygın olarak kullanılmaktadır. Bu ajanlar hem hastanın hemodinamisinin bozulmasını engeller hem de daha iyi cerrahi görüş alanı sağlar. Bu ajanlar etki mekanizmalarına göre fiziksel ve kimyasal ajanlar olarak sınıflanabilir. Topikal hemostatik ajanların en sık komplikasyonlarının bu ürünlerin antijenik reaksiyona neden olmalarından kaynaklandığı öne sürülmektedir. Bu yazıda geleneksel ve yeni topikal hemostatik ajanların kimyasal özellikleri, etki mekanizmaları, fayda ve yan etkileri derlenmiştir.

Anahtar Sözcükler: Kanama; lokal hemostaz; kulak burun boğaz ve baş boyun cerrahisi.

Effective hemostasis is an important requirement of otolaryngologic surgical procedures because unsuccessful hemostasis can result in persistent bleeding, increased operating time, delayed wound healing, and infection. Preoperative evaluation of the patient's medical conditions, which affects hemostasis, can help the otolaryngologist be prepared to effectively control operative haemorrhage.

There are various conventional haemostatic techniques such as direct pressure, electrocoagulation, and application of a tourniquet or suture ligation for controlling blood loss. However, these techniques can be labour-intensive and take a long time in the operation.[1] Hemostasis can also be achieved by the introduction of monopolar and bipolar electrocauterization, but these lead to areas of carbonisation and necrotic tissue, increasing the likelihood of infection and damaging wound edges. These may also cause delayed wound healing.[2] Conventional haemostatic methods are also less effective in preventing haemorrhage from complex injuries and in difficult to reach locations. Topical haemostatic agents may be helpful in such situations.

Topical haemostatic agents have various mechanisms of action. Some of them contribute to primary haemostasis, whereas others stimulate

Received / *Geliş tarihi:* January 19, 2010 Accepted / *Kabul tarihi:* January 29, 2010

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fibrin formation or inhibit fibrinolysis.[3] The ideal topical hemostatic agent should include high hemostatic action, minimal tissue reactivity, nonantigenicity, in vivo biodegradability, ease of sterilization, low cost, and suitability to specific needs.[4] Unfortunately, no hemostatic agent alone has all of these features.

A literature search for topical hemostatic agents in otolaryngology revealed only a few randomized clinical trials. This article reviews the scientific basis behind each hemostatic agent clinically used in otolaryngologic surgical procedures and reports detailed information for their administration.

MATERIALS AND METHODS

An English literature search to identify all relevant studies related to topical haemostatic agents and otolaryngologic surgery was carried out using the MEDLINE, PubMed, and Cochrane electronic databases. All manuscripts were carefully evaluated, and any relevant references were also obtained and reviewed.

Historical background

Hemostasis is naturally achieved by vasal contraction, platelets, blood flow and activation of the coagulation factors. Natural hemostasis may be augmented through thermal, mechanical, and chemical means.[5,6] Mechanical hemostasis is principally ligature.

The use of caustic agents for chemical hemostasis dates back to Hippocrates, whereas the use of thermal energy to obtain hemostasis dates to ancient Egypt.[7] The history of modern chemical hemostatics began at the end of the 18th century with introduction of gelatin by Carnot. A few years later, Horsley developed a mixture of beeswax with salicylic acid and almond oil.[8]

In 1909, Bergel suggested that fibrin could be a hemostatic agent. The use of fibrin has been limited by concerns about viral transmission.[9,10]

Oxidized cellulose (OC) was introduced in 1942, while oxidized regenerated cellulose (ORC), manufactured from wood pulp, was developed in 1960. Gelatin foam was introduced in 1945 and microfibrillar collagen (MC) from purified bovine corium was developed in 1970 by Hait.[8,9,11]

Bone wax

Bone wax is commonly used to control bleeding during mastoid surgery by physically plugging osseous channels which contain the mastoid emissary veins.[12] It has physical (tamponade) rather than chemical hemostatic actions. First used in surgery by Parker in 1892, it is used today for hemostasis from bony surfaces.[13] This compound is composed essentially of white beeswax (88%) and isopropyl palmitate (12%), with or without pure paraffin wax; the wax may also contain almond oils and sterilized salicylic acid.[14] Bone wax is applied with a MacDonald's spatula, melted into bone, or applied through a warmed syringe.[15] Its advantages include its relatively inert properties, ready availability, ease in preparation, and immediate hemostatic action.[16] The material is also relatively inexpensive. Complications of bone wax use may include foreign body granulomatous reactions, sigmoid sinus thrombosis, wound infection, and even foreign body venous embolization.[12]

Silver nitrate

A topical application of silver nitrate is a readily available haemostatic agent. It is an inexpensive method for the hemostasis of epistaxis from the anterior septum. The two concentrations commercially available for use by otolaryngologists are the 75% and 95% silver nitrate concentrations.[17] The silver nitrate applicator is applied to the area of bleeding, creating a thin eschar. The black tissue discoloration is temporary and shed with the eschar several days later. Hemostasis is achieved by the behavior of free silver ions. They bind to tissue proteins, causing precipitants that obstruct small bleeding vessels. Silver nitrate also precipitates bacterial proteins, decreasing the risk of Gram-positive and Gram-negative organisms.[18]

Complications of nasal cautery, although infrequent, are occasionally reported. These complications, which include septal perforation and crusting, mucocutaneous reaction and tattooing of the septal mucosa, are more commonly seen in patients undergoing repeated or bilateral cautery.[17,19,20] In the event of over-application, the effect of silver nitrate can be neutralized with saline solution that precipitates the silver.[21]

In a recent publication assessing its efficacy, silver nitrate cauterization was described as 93% having total or near-total control of epistaxis, whereas a septal perforation rate was reported almost 7%.[22]

Cocaine

Cocaine is a medical agent isolated from the leaves of the coca shrub called Erythroxylon coca.

It is mainly renowned for its quick-onset topical anesthetic and potent vasoconstrictive properties. Cocaine was introduced for endonasal surgical procedures by Hajek[23] and Halle[24] at the turn of this century. It is still widely used for intranasal otolaryngologic procedures.[25] Solutions from 2% to 10% are most commonly available. Epinephrine is added to cocaine to delay systemic absorption and to improve haemostasis. Some publications suggest powdered cocaine, cocaine gel, or cocaine flakes that can be applied as pledgets or cotton-tipped applicators for intranasal use.[26,27] The maximally safe dose of topical intranasal cocaine is generally recommend as 200 mg or 2 mg/kg, but adverse effects have been reported from doses as low as 10 mg.[28] Cocaine provides local vasoconstriction through inhibition of noradrenaline reuptake, which may lead to tachycardia, hypertension, systemic vasoconstriction, mydriasis and diaphoresis.[29] Long et al.[25] have reported cardiac arrhythmias, chest pain, myocardial infarction, syncope, central nervous system stimulation, stroke, and death. Systemic epinephrine enhances the adverse effects. Patients must be monitored with a pulse oximeter or cardiac monitor or both. Since there is addictive potential for cocaine's categorization as a controlled substance, protective storage is required.

Gelatin-based haemostats

Gelatin-based haemostats have been used in surgical procedures since 1945 and have been marketed by their present seller since 1952.[30] Their mode of action is still unclear, but it appears to involve physical properties by surface effect. They are commercially available as sponge, powder, paste and viscous gel (FloSeal Matrix). These hemostatic agents are commonly combined with a procoagulant substance, often thrombin, in order to enhance the effectiveness. FloSeal Matrix is applied in a number of ear, nose and throat interventions that are mostly used by otolaryngologists.[31] These agents are typically metabolized and resorbed by proteinases within six to eight weeks.[21]

Gelatin sponge or Gelfoam®, which is commercially known as Surgifoam®, has been used as a scaffolding substance to support tympanic membrane grafts and the ossicular chain rather than hemostatic actions in middle ear surgery.[32]

FloSeal (Baxter Healthcare Corp., Deerfield, IL, USA) is a bovine collagen-derived gelatin matrix that is combined with bovine thrombin at the time of use. It is applied as a high-viscosity gel for hemostasis and has been clinically proven to control bleeding ranging from capillary oozing to arterial spurting.[33]

FloSeal is easily extruded from a syringe applied to the operative site. FloSeal gel corresponds with irregular bleeding surfaces and wet tissue due to its hydrophilic features. FloSeal Matrix has both mechanical and pharmacological effects. The gelatin granules swell by 10-20% when in contact with blood or body fluids and it also provides some tamponade of injured vessels. In addition, the thrombin converts the patient's native fibrinogen to fibrin. The fibrin clot that is formed incorporates the FloSeal particles, resulting in a FloSeal-fibrin matrix composite clot that seals the bleeding site. Because of these hemostatic advantages, FloSeal has been advocated to control intraoperative bleeding in transphenoidal pituitary,[34] epistaxis,[35] adenotonsillectomy[36,37] and endoscopic sinus surgery.[31,38]

A recent study showed that FloSeal is safe and efficacious, and decreases postoperative morbidity compared to electrocautery hemostasis in children undergoing adenotonsillectomy.[37]

For anterior epistaxis and after functional endoscopic sinus surgery, FloSeal has been found to be more effective, rapid, safe, easier to apply than nasal packing, with good patient satisfaction.[35,38]

FloSeal reduced crusting from persistent oozing and mucosal irritation compared to controls,[39] but one study reported that its use increases postoperative granulation tissue and adhesions.[38]

Although FloSeal is an expensive hemostatic agent, its cost effectiveness was established by reducing the length of operation time.[36]

FloSeal has been reported to possibly predispose to future anaphylaxis as a result of formation of antibodies to bovine thrombin or factor Va.[40]

Collagen-based haemostats

Microfibrillar collagen (MC) was developed in 1970.[11] Collagen-based hemostatic agents are derived from bovine, porcine or equine origin, and also exist in different forms such as sheets, powder, or sponges. It is marketed under the brand names Avitene (Davol, Cranston, RI), Instat (Ethicon), Helistat and Helitene (Integra

LifeSciences, Plainsboro, NJ), and Collastat and Collatene (Xemax, Napa, CA).[41]

Microfibrillar collagen has not been evaluated in clinical trials in otolaryngologic surgery. Only two publications were found in the literature. Microfibrillar collagen powder (Avitene) is mostly used by otolaryngologists as an hemostatic agent.[42] Uses of Avitene in otorhinolaryngologic surgery have been described in tonsillar bleeding[42] and epistaxis.[43] Microfibrillar collagen sponge (Instat) is also used to support tympanic membrane grafts.[44]

The Microfibrillar collagen acts as a framework that aggregates platelets, which in turn act on platelet aggregation and activates the Hageman factor (F XII). The helical structure, and large surface area provided by MC are important to the haemostasis achieved.[1] These agents are commonly combined with a procoagulant substance, often thrombin, in order to enhance their effect. Advantages of collagen fleece are fast induction of hemostasis, low tissue reaction, and fast resorption. Avitene is used by applying the powder with dry instruments to the bleeding site. Pressure with gloved fingers should never be placed during application, as the MFC would adhere to the glove more than to the hemorrhage site. Microfibrillar collagen is fully absorbed within three months.[45]

Adverse effects of the collagen-based agents are infrequent, and rarely serious. Adverse events with collagen agents including adhesions, foreign body reactions, or allergic reactions have been reported. Serious adverse events have been reported most often with Avitene.[46]

Cellulose-based haemostats

Oxidized cellulose has been developed in 1942, while oxidized regenerated cellulose (ORC) was not introduced until 1960. Oxidized regenerated cellulose is a chemically altered form of cellulose. Oxidized regenerated cellulose is produced by the oxidation of cellulose with nitrogen tetroxide (N_2O_4).[47]

The mechanism of action for cellulose in hemostasis is unknown. The greatest use of this material has been for the control of oozing from broad surfaces. Oxidized regenerated cellulose presents multiple mechanisms of action, including blood absorption, surface interactions with proteins and platelets that provide a physical meshwork and activation of both the intrinsic and extrinsic pathways.[48] The low pH of these agents may contribute to haemostasis by causing small vessel vasoconstriction.

One major advantage of oxidized cellulose is its bacteriostatic properties against a wide range of gram-positive and gram-negative organisms.[49] The current theory for the bactericidal activity is that the acid hostile ambient decreases the amount of initial inoculum.[6] This beneficial effect is immediate, and is exerted by the low pH effect.[50] The absorption rate of ORC usually takes 14 days, whereas absorption of oxidized regenerated cellulose requires about 3-4 weeks.[10]

Oxidized regenerated cellulose is formed into mesh, gauze or woven strips, fibrillar tufts, and sponges. It is marketed as Oxycel (Becton Dickinson, Franklin Lakes, NJ) or as Surgicel (Ethicon). This agent is never used soaked in thrombin. Its power is maximal if applied dry. The most commonly used agent in this group is Surgicel (Ethicon), which has been used in otorhinolaryngologic surgery as a surgical barrier to prevent haemorrhage. Two forms are available, a tightly woven knitted patch (Nu-Knit) and a fibrillar form that can be used in thin layers. The fibrillar form also provides a favorable three-dimensional structure for a better clot organization.[50,51] It is supplied as a mesh which is placed over the operative site.

Fibrillar form is commonly used to control intraoperative bleeding during mastoid surgery,[52] whereas Surgicel Nu-Knit has been used to control postoperative bleeding in endonasal surgery.[53] A recent study showed surgicel Nu-Knit to be more effective to apply than merocel nasal packing, with good patient satisfaction.[54]

Karkos et al.[53] have reported that Surgicel Nu-Knit pack is dissolvable within five days, whereas other nasal packs require removal. Removable nasal packs have some postoperative complications such as scarring, middle turbinate lateralization and formation of adhesions. Though data on the use of cellulose packs is limited, Surgicel Nu-Knit does not appear to be associated with postoperative complications. However, more studies are required for this subject.

Despite its absorbable property, surgicel granulomas have been reported,[55] thus the agent should be removed (which is also recommended by the manufacturer), once haemostasis has been achieved.

In 1996, Wagner[6] presented an overall activity ranking of the materials used: microfibrillar collagen>gelatin>oxidized regenerated cellulose in vitro tests.

Cellulose agents are relatively inexpensive, easy to use, and easy to obtain.

Fibrin-based haemostats

Fibrin sealants have been used for local hemostasis in a wide range of surgical procedures since the beginning of the 20th century.[56,57] It was applied mainly for burns during the Second World War, and has been marketed for commercial use in the late 1970s. Fibrin sealant was introduced in otolaryngology mainly for larynx repair and in otologic surgery.[58-60] Initial preparations were composed of bovine and human products, creating the risk of transmitting bloodborne infectious agents. For this reason, the use of fibrin glue was abandoned in the early 1980s, and resumed in the late 1980s with the addition of viral inactivation steps during the manufacturing process.

Fibrin sealants can be obtained from a patient's own cryoprecipitate, from a homologous donor, or synthetically. They have both haemostatic and adhesive properties, and are comprised of a source of fibrinogen, which is combined with thrombin plus, possibly, factor XIII and/or an antifibrinolytic agent, such as bovine aprotinin or tranexamic acid, which stabilizes the clot.[51] Fibrin sealants reproduce the last phase of coagulation: the formation of a fibrin clot. A fibrin clot forms in approximately 30 seconds and is metabolized naturally within several days without causing inflammation or crusts. Fibrin sealants are used to facilitate hemostasis and reduce operative and postoperative bleeding and oozing during surgical procedures. The terms first and second generation refer to the presence or absence of animal products, present in first generation sealants and absent in second generation agents.

In the late 1980s, the use of fibrin sealant became established in otolaryngology mainly for tympanoplasty and tonsillectomy.[61-63] However, the use of fibrin sealant was not studied in rhinology except for neurosurgical problems such as management of cerebrospinal fluid rhinorrhea or endonasaltranssphenoidal pituitary surgery.[64,65]

A number of commercial products are also available as Tissucol™, Tisseel™, Beriplast™ and Quixil™. The second generation surgical fibrin sealant Quixil™ (Omrix Biopharmaceuticals, Brussels, Belgium) has most commonly been studied by otolaryngologists in epistaxis, adenotonsillectomy, and endoscopic sinus surgery. The studies presenting its successful use have been published in epistaxis[66,67] and endonasal surgery.[68,69] On the other hand, its use has also been reported for tonsillectomy patients.[70,71]

Fibrin sealant provides effective hemostasis and sealing with good systemic and local compatibility. Quixil, a new surgical sealant, is based on a concentrate of human clottable proteins and a highly purified native human thrombin. Quixil contains tranexamic acid instead of aprotinin as antifibrinolytic adjuvant. It also contains no fibrinogen. The amount of sealant required depends upon the area of tissue to be treated. In the case of endonasal operations, the amount is small. The glue is sprayed using compressed air onto the tissue in short bursts (0.1 to 0.2 mL) to produce a thin, even layer. If the hemostatic effect is not complete, a second layer is applied.

The complications of nasal packing are well known after endonasal surgery. The second generation surgical fibrin sealants have been found to be particularly helpful in eliminating the postoperative difficulties such as disturbance of breathing during sleep and even a decrease in nocturnal arterial PO_2, pain, infection, allergy, mucosal lesions including septal perforations, effects on Eustachian tube function, and rarely, toxic shock syndrome caused by nasal packing. For this reason, Quixil was recommended as an alternative to nasal packing in all kinds of endonasal operations.[66-69]

In a controlled study, Vaiman et al.[70] have reported that fibrin glue provides effective hemostasis, and decreases intraoperative blood loss. A comparison with electrocautery in 179 children undergoing adenotonsillectomy found fibrin glue to be more effective than electrocautery. However, contrary to the studies, some authors have reported no significant beneficial effect of fibrin glue for pain control, prevention of bleeding or facilitating of eating and thus did not recommend its routine use for tonsillectomy.[71,72]

During the 10 years that this fibrin glue has been in use, no cases of the above-mentioned infections have been reported with the use of commercial fibrin sealants.[73] The use of bovine thrombin

may pose a safety problem in the context of spongiform encephalitis. Adverse reactions associated with bovine thrombin include hypotension, anaphylaxis, and coagulopathy. Bovine thrombin has been reported to be potently immunogenic; however, the antibodies developed against thrombin presence does not cause clinical consequences in most patients.[74] Coagulopathy is likely to be related to cross-reactive antibodies developed against bovine products, particularly factor V.[75] However, no reported case of coagulopathy results in haemorrhage.[77]

As one of the antifibrinolytic constituents, tranexamic acid, may cause neurotoxic reactions, its use can not be recommended where the possibility of CNS contamination exists.[67]

Another disadvantage of fibrin sealants, particularly commercial products, is their high cost.

Bismuth subgallate

Bismuth subgallate (BSG) is a relatively insoluble, poorly absorbed heavy metal for use as a hemostatic agent. It is thought to accelerate the intrinsic clotting pathway through the activation of factor XII (Hageman factor).[77] Maniglia et al.[78] were the first to report the use of BSG in tonsillectomy. These authors found a very low rate of post-tonsillectomy hemorrhage. The deficiency of the study is that it had no control group. Follow-up controlled studies described achieving haemostasis or the reducing operating time in the BSG group.[79-81] Although comparable with control group in tonsillectomy, no superior haemostatic effect of BSG was found by some authors.[82,83] Application is easy: BSG paste is prepared by mixing 20 ml normal saline with BSG powder until a consistency like toothpaste is obtained. BSG paste is spread on the gauze swabs used to pack the tonsillar fossae. After 3-5 min, the swabs are removed.

The major drawback of using this BSG paste is the risk of foreign body response, and aspiration that may result in acute pneumonia.[84] Therefore, the recommendation of Murray et al.[85] is that it should be carefully used with a cuffed endotracheal tube for intubation. In addition, BSG paste has shown a tendency to smudge at the wound site.

In conclusion, the hemostatic effects of using BSG in tonsillectomy is controversial and needs to be demonstrated by further clinical studies.

The antifibrinolytics

The antifibrinolytic agents are commonly used, due to less adverse effects and more hemostatic effects. The hemostatic agents reversibly bind plasminogen, which significantly limits the ability of plasminogen to be activated to the plasmin of the clotting cascade and thus, accelerate coagulation. There have been several reports on the use of tranexamic acid and E-aminocaproic acid in otolaryngology.

Transexamic acid is a synthetic antifibrinolytic agent, which has 10 times the hemostatic effect of the same group agent epsilon (E) aminocaproic acid.[86]

Transexamic acid and E-aminocaproic acid have been studied by several otolaryngologists in tonsillectomy[87,88] and endoscopic sinus surgery.[89,90]

The local application of E-aminocaproic acid was first described by Overbosch and Hart[91] These authors studied the local application of EACA to reduce the incidence of haemorrhage following 508 tonsillectomies. However, contrary to the study, intravenous application of transexamic acid was successfully reported, whereas local application was not suggested in tonsillectomy by Falbe-Hansen et al.[87]

Thomas and Wormald[89] have reported a statistically significant reduction in the grade of bleeding when E-aminocaproic acid without methyl cellulose was used, compared to normal saline in a controlled animal study of endonasal operation.

Furthermore, no side effects were observed when E-aminocaproic acid was used topically. Transexamic acid may cause neurotoxic reactions.

Finally, the studies for using these antifibrinolytic agents by otolaryngology are insufficient and need to be substantiated by further controlled studies.

Platelet gels

Platelet gel is a fibrin tissue adhesive obtained from autologous platelet-rich plasma (PRP). The current centrifuge systems are used the PRP for separating from the other blood component. Platelet gel contains more than 300.000 to 350.000 platelets/μl. The mechanism of action for platelet gel is through the stimulation of skin fibroblasts

and by supplying multiple growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF) for the new synthesis of collagen.[92]

Platelet gel has many advantages, including comfort, hemostasis, and growth factors that may improve wound healing.

Although it seems an ideal surface packing material, it has received only a single study so far, and has not yet been accepted in rhinology.[93] In this study that received Merocel packing and PG packing were compared after endoscopic sinus surgery. The platelet gel was injected into each sinus cavity as a packing material after endoscopic sinus surgery. The study demonstrated no superior effect for postoperative epistaxis synechia formation or exuberant granulation tissue, whereas the quality of life scores did show statistically significant improvement over the control group.

The major disadvantage of this hemostat is its high cost and requirement of operator experience.

In conclusion, there have been many applications related to the use of topical hemostatic agents in otolaryngologic surgery. For now, the key question is which agent should be chosen for enhancing hemostasis. In surgery, severity, location and type of hemorrhageare important for the identification of the selected agent in enhancing hemostasis. Therefore, the most convenient product should be selected for each procedure. Many new agents are marketed each year. The biggest obstacle for the clinical studies on topical hemostatic agent use is the high cost and ethical issues.

A topical hemostatic agent must provide efficient and fast hemostasis, convenience of use, no adverse effects and low cost. Unfortunately there is no agent that meets all these criteria.

Most of these agents use the clotting mechanism of human beings. Intraoperative and postoperative unstoppable hemorrhages upset surgical comfort for tonsillectomy and rhinology and they pose risk to life. Predisposing features of patients such as hypertension and coagulopathy sometimes increase the hemorrhage frequency and amount. In this case, topical hemostats, which do not discomfort the patient, are also needed, apart from a thorough surgical operation and adequate hemostasis before bleeding reaches at a life-threatening level. Topical hemostats and hemostats such as spray, gel, etc, which do not require clotting of nasal passage are needed, as nasal packings cause discomfort to the patient and increase the risk of infection[66] in rhinology.

Among reported agents so far, Collagen based hemostatics, Fibrin sealants, Gelatin-based hemostats and cocaine offer efficient hemostasis yet cost much.

However, in some studies it was reported that the use of these agents decreases operation period and postoperative hospital stay and therefore decreases overall costs.[36]

There is a need for many comparative clinical trials to find out if they meet the identified criteria for both existing and developing agents.

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