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Review of Topical Thrombin Adhesive and Its Effect on Cutaneous Wound Healing

A Graduation Project Submitted to the Department Council of the Internal and Preventive Medicine-College of Veterinary Medicine/ University of Al-Qadisiyah in a partial fulfillment of the requirements for the Degree of Bachelor of Science in Veterinary Medicine and Surgery.

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

فَتَعَٰلَى ٱللَّهُ ٱلْمَلِكُ ٱلْحَقُّ ۗ وَلَا تَعْجَلْ بِٱلْقُرْءَانِ مِن قَبْلِ أَن يُقْضَىٰٓ إِلَيْكَ وَحْيُهُۥ ۖ وَقُل رَّبِّ زِدْنِى عِلْمًا ﴿١١٤﴾

صَدَقَ ٱللَّهُ ٱلْعَظِيمُ

من سورة طه

Dedication

To the source of my generosity, my great father.

To the source of kindness, the greater my mother.

To the lovely ……my brothers and sisters.

Certificate of Supervisor

I certify that the project entitled (Review of Topical Thrombin Adhesive and Its Effect on Cutaneous Wound Healing)was prepared by **Yaqin Abood Hamad** under my supervision at the College of Veterinary Medicine / University of Al-Qadisiyah.

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/ / 2021

Certificate of Department

We certify that Yaqin Abood Hamad has finished his Graduation Project entitled (Review of Topical Thrombin Adhesive and Its Effect on Cutaneous Wound Healing) and candidate it for debating.

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Contents

Chapter one

Introduction

1 .Introduction

In the prehistoric era, many natural sources, such as honey, were used as antibacterial medicines. In today's society, these traditional wound treatment treatments are still in use. In the 1960s and 1970s, polymeric dressings were launched in a variety of forms and were custom made. New discoveries are currently being made that include everything in a nutshell to support optimal wound healing.

From prehistoric times to the present, wound closure has evolved alongside humanity. Numerous treatments and advancements have occurred in the management and closure of wounds. It has always been difficult to close wounds in such a way that they leave an aesthetically pleasing scar. The ideal surgical wound would be as tough as normal tissue when closed. Douglas and Forester discovered that the maximal tissue strength that may be regained following wound closure is 80 percent even after a year of follow-up. (1).

Wound healing (WH) is a complex process that demands more skill, and it is the most prevalent ailment in veterinary medicine. It also necessitates a lot of new altered care searches. Rats were chosen as a model for this experiment because of their ease of handling and similarities to the healing process that occurs in human skin wound recovery.

The goal of this study was to look at the effects of topical thrombin adhesive and see how it affects cutaneous wound healing.

Chapter two

Review of Literatures

2 . Literatures Review

It is common knowledge that adhesives are favored over stitches. There is no discomfort, no need for surgical equipment, less time is required, and tissue regeneration time can be reduced when adhesives are used (Douglas,1969).

2-1: Wounds:

Damage to the integrity of biological tissue, such as skin, mucous membranes, and organ tissues, is defined as a wound. These can be caused by a variety of traumas, and it's vital to keep wounds clean and well treated to prevent infection and further injury. (Wilkins, 2013; Kujath, 2008) The CDC has produced categorization definitions consisting of four kinds of wound statuses to appropriately classify the cleanliness and state of wounds:

Clean wounds are classified as Class 1 wounds. They're not infectious, don't have any inflammation, and are mostly closed. If these wounds need to be drained, a closed draining procedure is required. These wounds also do not penetrate the respiratory, alimentary, vaginal, or urinary tracts.

Clean-contaminated wounds are classified as Class 2. There is no unusual pollution in these wounds. The respiratory, alimentary, vaginal, or urinary tracts are all affected by Class 2 wounds. These wounds, on the other hand, have infiltrated these tracts under regulated circumstances.

Contaminated wounds are classified as Class 3. Fresh, open wounds might occur as a result of an insult to sterile procedures or gastrointestinal system leaks into the wound. Incisions that result in acute or nonpurulent inflammation are also classified as class 3 wounds.

Dirty-infected wounds are classified as Class 4. These wounds are usually the result of traumatic wounds that were not appropriately cared for. Microorganisms present in perforated viscera or the operating field are the most prevalent cause of Class 4 wounds, which show devitalized tissue.

(Onyekwelu,2017).

The wound categorization scheme's fundamental flaw is that it has low inter-rater reliability among healthcare personnel (Wilkins ,2013, Onyekwelu,2017). Furthermore, in neonatal surgical wounds, this wound classification approach has been demonstrated to be ineffective. For this demography, a separate wound classification methodology may be required. Vu (2009).

According to a 2020 statistical study, abdominal wounds are more likely to be misclassified as clean wounds, causing the patient's recovery to be delayed.

Depending on the etiology of the muscle injury, such as traumatic causes from athletics or traumatic causes from war, the injury will respond differently. Alternatively, if there is a considerable loss of muscle volume, the metabolic environment will trigger anti-reparative molecular reactions (lower amount of IGF-1 and pro-fibrotic activity).

2-2: Wound healing process:

Cutaneous wound healing is a vital physiological process that involves the cooperation of a variety of cell strains and their products. Shaw (2009). Early in the inflammatory stage, attempts to restore the damage caused by local aggression begin. Finally, they result in repair, which is the replacement of specialized structures caused by collagen deposition, and regeneration, which is the process of cell proliferation and posterior differentiation by preexisting cells in the tissue and/or stem cells (Eming et al.,2007).

These methods are not mutually exclusive, which means that after a skin lesion, regeneration and repair can occur in the same tissue, depending on the cell strains affected by the injury. Following the commencement of the injury, tissue regeneration and healing ensue. Whether as a result of trauma or a specific clinical condition. All of the stimuli that disrupt the physical continuity of functioning tissues combine to form a single lesion. External or internal stressors, as well as physical, chemical, electromagnetic, or thermal stimulation, can produce lesions. Furthermore, the lesions may cause harm to individual organelles or entire cells. Shaw and Martin (2009) are two authors that have written about this topic.

Tissue repair is a straightforward linear process in which growth factors drive cell proliferation, resulting in the integration of dynamic changes involving soluble mediators, blood cells, extracellular matrix synthesis, and parenchymal cell proliferation. According to Mitchel et al., the skin healing process exemplifies the principles of tissue restoration for the vast majority of tissues. (2005, Cotran et al.) Inflammatory reaction, cell proliferation, and production of the extracellular matrix elements, as well as the post-healing period, known as remodeling, are the stages of cell and biochemical events in wound repair. (Nayak and colleagues, 2009). These stages do not exclude one another; rather, they overlap through time (Cotran et al.2005). The goal of this literature review is to emphasize the biological processes involved in wound healing, with a focus on the cells, growth factors, and cytokines involved in tissue repair.

INFLAMMATORY STAGE:

The lesioned blood vessels constrict and the released blood coagulates during a vascular inflammatory reaction, helping to maintain the integrity of the vessel. Coagulation is the aggregation of thrombocytes and platelets in a fibrin network, which is based on the activation and aggregation of these cells by particular stimuli (Martin,1997) In addition to reestablishing homeostasis and building a barrier against microbe invasion, the fibrin network arranges the essential temporary matrix for cell migration, restoring the skin's role as a protective barrier and maintaining skin integrity. Shaw (2009).

This also allows for cell migration into the lesion's microenvironment and fibroblast proliferation promotion. The influx of leukocytes in the wound area characterizes the inflammatory stage of cell response. This is a rapid response that correlates with the major indications of inflammation, which are edema and erythema at the site of the lesion. Cell response is often developed within the first 24 hours and can last up to two days. Mastocytes, gamma-delta cells, and Langerhans cells, which release chemokines and cytokines, may cause a rapid activation of immune cells in the tissue. The lesion causes tissue destruction by producing inflammation, which is a limited and protective tissue response. Inflammatory cells aid wound healing by contributing to the release of lysosomal enzymes and reactive oxygen species, as well as assisting in the removal of different cell debris. Medrado and colleagues (Medrado et al., 2003).

Buckley claims that during an acute inflammatory response, the interplay of leukocytes and stromal cells settles around the inflammatory focus (Buckley,2011). At the site of the lesion, neutrophils are known to express a huge number of pro-inflammatory cytokines as well as a substantial quantity of highly active antimicrobial compounds such as reactive oxygen species (ROS), cationic peptides, and proteases. The active recruitment of neutrophils in response to complement activation, platelet degranulation, and bacterial breakdown products continues the inflammatory response. Gurtner et al., 2008. Many inflammatory cytokines released by active platelets, endothelial cells, and pathogenic agent degradation products attract them. (2011) Nunes et al. In this way, neutrophils are the major activated and recruited cells that help clean up the tissue while also assisting in the killing of invading invaders. Shaw and Martin (2009) are two authors that have written about this topic. A large number of neutrophils transmigrate through the endothelial cells present in the blood capillary walls, which are triggered by pro-inflammatory cytokines such as IL-1, TNF-, and IFN- (interferon gamma) near the site of the lesion, only a few hours after the injury. Many different types of adhesion molecules are induced by these cytokines. Selectins and integrins are among the adhesion molecules that determine

Neutrophil diapedesis (CD11a/CD18 (LFA-1); CD11b/CD18 (MAC-1); CD11c/CD18 (gp150, 95); CD11d/CD18) (Eming et al.,2007). - which interact with those already present on endothelial cells' membrane surfaces. Many other elements of tissue repair are also influenced by referent cells, such as the resolution of fibrin and extracellular matrix coagulation, the induction of angiogenesis, and reepithelialization. Shaw (2009). The migration of monocytes from surrounding blood arteries, which also infiltrate the lesion area, is enhanced 48 hours after the development of the lesion, and they are differentiated into macrophages with the development of new genic expression profiles.

These cells, which are triggered by chemokine signaling, can serve as antigen-presenting cells and enhance neutrophil phagocytosis. As can be shown in extracellular matrix protein fragments, TGF-, and MCP-1, in addition to resident macrophages, the major population of macrophages in the lesion is recruited from the blood in response to chemotactic agents (protein 1 chemotactic for monocytes).(Thuraisingam *et al.*2010). Macrophages can be classed as classically activated (M1 pro-inflammatory) or alternatively activated (M2 anti-inflammatory and pro-angiogenic) based on genic expression profiles (Rodero and Khosrotehrani,2010).

Since animals with a depletion of macrophages have defects in wound repair, these cells play a key role in the transition of the Graph exsudative stage to the proliferative stage within the tissue repair process, these cells release growth factors such as PDGF and VEGF, which are commonly required for the triggering and propagation of new tissue in the lesioned area, conferring upon these cells a key role in the transition of the Graph exsudative stage to the (Singer and, Clark,1999). Macrophages are responsible for phagocytosis of muscle debris, as well as the creation and release of cytokines, pro-angiogenic, inflammatory, and fibrogenic substances, as well as the elimination of free radicals (Tidball,2005). Furthermore, macrophages recruit other inflammatory cells to the wound site by secreting chemotactic proteins. They also create prostaglandins, which are powerful vasodilators that modify micro-blood vessel permeability. Endothelial cells are activated when these elements come together (Li et al.2007). These cells also produce PDGF, TGF beta, FGF, and VEGF, according to Mendonça & Coutinho Netto, which are the primary cytokines capable of encouraging the production of granulation tissue (Mendonça et al.2009).

PROLIFERATIVE STAGE:

The proliferative stage's goal is to reduce the size of the lesioned tissue by contracting and fibroplasia, generating a viable epithelial barrier to activate keratinocytes. Angiogenesis, fibroplasia, and reepithelialization are all part of this stage, which is responsible for the lesion's closure. Within the first 48 hours after the beginning of the lesion, these processes begin in the microenvironment of the lesion and can last up to 14 days((Li et al.2007).

Blood flow changes as a result of vascular remodeling. Angiogenesis is a well-coordinated process that includes endothelial cell proliferation, basal membrane rupture and rearrangement, tubular structure migration and association, and perivascular cell recruitment. Angiogenesis has long been thought to be important in a variety of physiological and pathological processes, including embryogenesis, tumor growth, and metastasis (Rosen,2002).

According to Gonçalves et al., the subsequent growth of blood vessels involves the formation of collateral veins through two mechanisms: germination and cell division. (Gonçalves *et al.*2010). The vascular plexus that results is modified to distinguish between large and small blood vessels. Both accessory and smooth muscle cells are subsequently injected into the endothelium. The newly generated microvasulature allows fluid, oxygen, nutrients, and immune-competent cells to be transported to the stroma (Carmelie,2003). In addition to endothelium and lymphocyte cells' active participation in this biological process, pericytes are a cell group derived from the mesenchymal strain of smooth muscle cells, which was first reported many decades ago (Crocker,et al.1970).

The cells described above appear to be solitary entities that share the basal membrane of blood vessels and endothelial cells (Alon and Nourshargh 2013). Pericytes are light-colored connective tissue cells with long and thin cytoplasmatic processes that are found just outside the endothelium of blood capillaries and small venules into which the capillaries empty. Charles Rouget, according to Ribatti et al.2011, was the first to describe non-pigmented cells with contractible constituents in 1873. These authors, on the other hand, were unable to discolor them. Mayer, on the other hand, was able to see these cells in 1902 using methylene blue dye, which were later classified as pericytes by Zimmermann in 1923 because of their position on and surrounding blood vessels, with their processes wrapped around the basal surface of the endothelium. The pericyte makes focal contact with the endothelium by specialized junctures, which are lengthy cytoplasmatic extensions that stretch and surround the endothelial tube (Armulik et al.2011). Furthermore, through the deposition of matrix and/or the release and activation of signals that encourage endothelial cell differentiation

and compliance, such a cell alters the blood vessel's stability (Xian et al.2006,

Takakura,2006). Pericytes are mural cells found in the basal membrane of micro-blood arteries that run continuously along the endothelial basal membrane. Pericytes are mesenchymal or progenitor cell types that give rise to adipocytes, cartilage, bone, and muscle (Armulik,2011) Pericytes retain a mesenchymal potentiality in maturity that is sufficient to produce not just fibroblasts but also smooth muscle cells, according to research (Medrado et al.2010).

These cell elements can exhibit pluripotent cell properties, making them a valuable "cell reserve." Though pericytes' plasticity has yet to be thoroughly explored, Farrington-Rock et al. discovered that they have the ability to differentiate into osteoblasts, chondrocytes, fibroblasts, leiomyocytes, and adipocytes (Farrington et al.2004). This characteristic appears to be particularly relevant to tissue repair, considering that these cells can contribute to the total replenishing of scar tissue. Around four days after the injury, granulation tissue begins to form. Its name comes from the granular appearance of newly created tissue, which gives the nascent stroma its property.

The granulation tissue is formed by the following mechanisms, according to Calin et al. : an increase in fibroblastic proliferation; collagenous and elastic biosynthesis, which creates a three-dimensional extracellular network of connective tissue; and fibroblast production of chemotactic factors and IFN-beta. Integrin receptors are expressed by fibroblasts and endothelial cells, which allow them to enter the coagulation in the lesion region (Tonnesen et al.2000).

To comprehend the tissue repair process, various immune system peculiarities must be mentioned, such as the involvement of B lymphocytes and, more specifically, the multifunctionality of T lymphocytes. T lymphocytes are separated into two functional categories based on their morphology: CD4 (auxiliary T lymphocytes) and CD8 (suppressor/cytotoxic T cells). T CD4 cells are classified according to their cytokine production patterns, which include the Th1 subpopulation, which produces IL-2 and IFN gamma; Th2, which produces IL-4, IL-5, and IL-10; and Th17, which produces IL-17. 2 When a tissue lesion arises, the repair process is influenced by the inflammatory response of cells on the lesion's boundaries (keratinocytes), as well as a range of cytokines and growth hormones that affect migration, proliferation, and local cell differentiation. (Mason *et al*.2002).

According to (Medrado et al.2010), fibroplasia starts with the creation of granulation tissue, which is characterized by the proliferation of fibroblasts, which are the principal agents responsible for the deposition of the new matrix. Collagen is the major component of a developed connective tissue scar. Collagen-producing

fibroblasts are recruited from the dermis of the wound's border to generate the protein. The reestablishment of the basal membrane's integrity and function requires the creation of an unbroken basal membrane between the epidermis and dermis. Type III collagen, which is generated by fibroblasts in the granulation tissue, is prevalent during this first stage of repair (Isaac et al.2010).

The wound contraction process begins at this stage, according to Medrado et al. (2010), and is carried out by myofibroblasts, which are fibroblasts high in alpha smooth muscle actin. These cells, which have gathered on the wound's edges, perform contractive activities, causing the lesion's borders to contract toward the center. 27 The migration and mitogenic activation of endothelial cells causes angiogenesis in the extracellular matrix of the wound bed (Mendonça,2009).

The above-mentioned fibroblastic stage is accompanied with neovascularization. Irrigation of the wound's borders is critical for wound healing because it enables for an appropriate supply of nutrients, oxygen, and immune-competent cells to reach the stroma (Ruiter et al.1993,Tazima et al.2008). Parallel to all of the above, epithelial coating cells proliferate and move from the wound's edges in an attempt to close it, a process known as reepithelialization. Keratinocytes reepithelialize a wound by combining the proliferative stage with cell migration near the lesion (Li et al.2007). Keratinocytes migrate to the extremities of the lesion in the direction of the remaining skin.

Hair follicle epidermal cells eliminate coagulation and damaged stroma fast. The epidermal germ cells of the hair follicle, which generate the hair bulb, act as a reservoir for keratinocytes in the healing process, according to (Li et al.2007). There is a development and stretching of the keratinocytes' pseudopod projections, a loss of the extracellular matrix-cell and cell-cell contacts, a retraction of the tonofilaments, and the formation of actin filaments in the extremities of its cytoplasms about ten hours after the onset of the lesion. When migration stops, presumably as a result of contact-induced inhibition, the keratinocytes reattach to the substrate and rebuild the basal membrane. The differentiation process is then completed, resulting in the newly stratified epidermis. (Li *et al*.2007).

REMODELING STAGE:

Remodeling is the third phase of healing, which starts two to three weeks after the initiation of the lesion and can last a year or more. The remodeling stage's main goal is to maximize tensile strength by reorganizing, degrading, and resynthesising the extracellular matrix.

At this point in the healing process, an attempt is made to restore normal tissue structure, and the granulation tissue is gradually reformed, resulting in scar tissue that is less cellular and vascular and has a progressive rise in collagen fiber concentration. The maturation of the elements, as well as deep alterations in the extracellular matrix and the resolution of the acute inflammation, characterize this stage. When a monolayer of keratinocytes covers the surface of the lesion, epidermal migration stops, and a new stratified epidermis with a subjacent basal lamina is created from the wound's boundaries to its inner section (Martin,1997).

There is a deposition of the matrix at this point, followed by a change in its composition (Li et al.2007). Type III collagen degrades as the wound heals, but type I collagen synthesis increases. During the remodeling process, the amount of hyaluronic and fibronectic acid is reduced, which is degraded by cells and plasmatic metalloproteinase, and the rising type I collagen expression is processed at the same time (Gonçalves et al.2010). Many writers, including Sampaio and Riviti, have confirmed that the collagen fibers thicken and align at this last stage, resulting in increased tensile strength for the tissue.

The resolution step is critical for the lesioned tissue to regain functionality and a “normal” appearance (Shaw and, Martin 2009).. This is due to anti-inflammatory cytokines like IL-10 and TGF-1 not producing enough chemokines. Collagen synthesis is regulated by a variety of growth factors, including TGF-1 and FGF, which have a significant impact on the genic expression of this protein. Due to emigration processes, apoptosis, or other unknown mechanisms of cell death, the majority of blood vessels, fibroblasts, and inflammatory cells leave from the wound area during the maturation and remodeling processes.

As a result of this, a scar with a reduced number of cells forms. Later on, the granulation tissue fibroblasts change their phenotype and begin to express smooth muscle actin, earning them the moniker myofibroblasts (Medrado et al.2003, Calin et al.2010). According to (Calin et al.2010), myofibroblasts acquire certain contraction capabilities from smooth muscle cells and move closer to the wound's margins, where they are responsible for its contraction. Referent cells display well-developed bands of contractible microfilaments made of actin in this manner. Communication junctures keep them connected, and integrin receptors connect their cytoplasmatic actin filaments to fibronectin fibrils and collagen I and III in the extracellular matrix. It's vital to remember that in fibrosis, myofibroblasts are

the primary producers of extracellular matrix (Tazima et al.2008). The extracellular matrix, according to (Midwood et al.2008 and Badylak 2002), is not a static material and can play a significant role in this stage of tissue repair through interactions between its structural components and the various cell types present in the tissue. Proteins like collagen, fibronectin, and fibrin, among others, are structural components that offer signals and activate certain cell processes in the wound area. For example, fibronectin creates a scaffolding that allows for cell attachment and movement. Vitronectin, another sticky glycoprotein, can help the tissue contract due to the collagen produced by the fibroblasts. Because of the existence of these processes, promising therapeutic methods have focused on local regulation of cell/matrix interactions. It is important to note that exogenous and endogenous factors can modulate such occurrences and influence the healing process in all of the processes mentioned above. Systemic illnesses, such as diabetes, immunosuppression, and venous stasis, as well as those caused by exogenous agents, such as corticotherapy and smoking, can obstruct the wound's early closure. The formation of hypertrophic scars and keloids, in addition to these aggravating conditions, is a further complication. (Fonseca et al.2012).

2-3: Thrombin:

Thrombin has a long history of acting as a hemostatic agent. As early as 1892, descriptions of the usage of thrombin may be found in European literature (Brister et al 1994).

Barbers and boxers employed thrombin for hemostasis of shaving wounds and light lacerations early on. The use of thrombin in surgery has been documented since the 1940s. Since then, its use has skyrocketed, and thrombin is currently used in over 1 million patients in the United States each year, at a cost of US$250 million (Lawson 2006)**.** New breakthroughs in thrombin have recently occurred, including FDA approval of human thrombin and the development of a recombinant thrombin.

2-4: Mechanism of thrombin :

Thrombin contains a number of biological actions that help with coagulation and hemostasis that have been widely investigated. Exposed collagen and released tissue factor activate the intrinsic and extrinsic coagulation pathways in response to tissue injury and bleeding. Both mechanisms activate factor X, which then forms a compound with activated factor V to cleave the prothrombin protein into the active thrombin molecule.

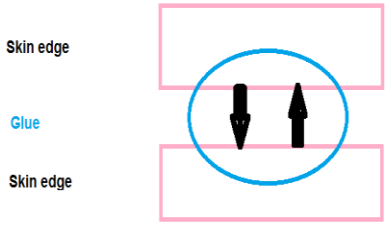

Fig.-1: The glue action for the wound edges.

The final coagulation step required to convert fibrinogen to fibrin is thrombin generation. This creates a hemostatic lattice at the injury site, preventing platelet aggregation and thrombus formation. Thrombin can act directly on a variety of cell types in addition to the coagulation cascade. It promotes vasoconstriction in smooth muscle cells, which contributes in hemostasis. It stimulates platelet aggregation at the thrombus location by stimulating platelets. Activated thrombin is a mitogen and chemoattractant for neutrophils and fibroblasts, as well as an inducer of VEGF production for tissue and vascular remodeling and repair (Brister et al .1994; Patterson et al .2001; Lawson 2006).

Thrombin can activate the anticoagulant system through protein C, which is interesting because it not only increases coagulation. The procoagulant properties of thrombin are activated when there is vascular damage, as mentioned above. When there is no arterial disturbance, on the other hand, thrombin interacts with thrombomodulin to activate protein C, which improves circulation by acting as an anticoagulant (Dahlback 2000). Thrombin stimulates and controls coagulation through a variety of mechanisms. We shall limit our discussion to its pro-thrombotic effect and how it has been used to reduce bleeding in a number of surgical procedures for the purposes of this essay.

Fig.-2 : Commercial topical skin adhesive

2-5: Conclusions :

Thrombin has a long history of usage in surgical hemostasis, and it has proven to be a helpful and successful auxiliary. Antibodies that cross react with numerous human coagulation proteins, the most important of which is factor V, have been convincingly connected to the development of early bovine thrombin formulations. Multiple examples of life-threatening bleeding and other problems have resulted from bovine-induced antibodies against human coagulation factors. Human thrombin, which was recently approved by the FDA as an alternative to bovine thrombin, has the theoretical risk of viral transmission. The recent development and FDA licensing of a recombinant protein thrombin product offers yet another potential alternative to bovine thrombin, with the same efficacy but without the risk of antigenicity.

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جامعة القادسية
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بحث تخرج
مقدم إلى فرع الطب الباطني كجزء من متطلبات شهادة البكالوريوس في علوم الطب والجراحة البيطرية

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