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Comparative Study of Auto and Xenograft for Reconstruction of Experimentally induced Cerebral Meningeal Defect in Dogs

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Supervised By
Professor Dr.

Osama Hazim Ismail Al-Hyani

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Comparative Study of Auto and Xenograft for Reconstruction of Experimentally induced Cerebral Meningeal Defect in Dogs

A Dissertation Submitted
By

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In
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Supervised By Professor Dr.

Osama Hazim Ismail Al-Hyani

2024 A.D. **1445 A.H.**

قُلِ ٱللَّهُمَّ مَـٰلِكَ ٱلْمُلْكِ تُؤْتِى ٱلْمُلْكَ مَن تَشَاءُ وَتَنزِعُ ٱلْمُلْكَ مِمَّن تَشَاءُ وَتُعِزُّ مَن تَشَاءُ وَتُذِلُّ مَن تَشَاءُ بِيَدِكَ ٱلْخَيْرُ إِنَّكَ عَلَىٰ كُلِّ شَىْءٍ قَدِيرٌ

سورة ال عمران

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Abstract

This project was designed to evaluate The efficiency of using different grafted tissues to reconstruct induced cerebral meningeal defects in dogs. Thirty-six local breed adult dogs were used in this experimental study. The animals were divided randomly into four main equal groups, each group consisted of nine animals. All animals were anesThetized by using a mixture of 10 % ketamine HCL at a dose of 10mg/kg and 2% xylazine at a dose of 2mg/kg respectively in The thigh muscles with The injection of atropine sulfate at a dose of 0.05mg/kg as a pre-anesThetic. A small defect was induced in The cerebral meningeal for each dog after cranirctomy. The induced menengeal defect was closed by applying different biomaterials, according to The following:

First group: The meningeal defect in this group was closed by application The fascia of The temporalis muscle as autograft. **Second group:** The meningeal defect was closed by application apiece of peritoneum taken from The same animal as autograft also. **Third group:** In this group, a cellular ovine esophageal mucosa was used to close The Meningeal defect as a xenograft. **Fourth group:** Lyophilized bovine pericardium was used in this group as a xenograft to close The Meningeal defect.

The grafted tissues in all animals were fixed on The meningeal defect using fibrin glue instead of suturing. The follow up evaluation was achieved by monitoring postoperative clinical signs for each dog especially those related with abnormal nervous signs such as hearing changes, nausea, vomiting, abnormal vision and eyeball movement, muscle spasm, or any abnormal body position. In addition, The gross and histopathological changes, estimation of cerebrospinal fluid pressure, levels of glucose, protein, and total cell count of cerebra spinal fluid in all groups at 15^{th}, $30^{th,}$ and 60^{th} postoperative day were studied also. The statistical analysis of

histopathological scoring, cerebrospinal fluid pressure, levels of glucose, protein and total cell count of cerebrospinal fluid were dependent also.

All animals after The surgical operation were survived without development of any complications especially, those related with The appearance of abnormal nervous signs, food and water intake was normally without The appearance of any change in Their behaviors.

Grossly, The site of craniectomy in all animals was healed and occluded completely with connective tissue during all periods of The study externally. In addition, no cerebrospinal fluid leak was noticed at The site of craniectomy postoperatively. Also, at The end of The study, The meningeal defect was closed internally in all animals of all types of The grafted tissues used in this study sealed and connected with The meninges of The host completely.

The histological study in all animals revealed by The formation of granulation tissue with infiltrations of inflammatory cells and angiogenesis. The statistical analysis of histopathological scoring was revealed a significant difference at $p \leq 0.05$ in group four than oTher groups in The degree of angiogenesis and infiltration of inflammatory cells, which characterized by more angiogenesis, and little infiltration of inflammatory cells in The early stages of healing process.

In all animals, The level of protein and glucose in cerebrospinal fluid, in addition to The cerebrospinal fluid pressure appeared within The normal ranges between all groups during all periods of The study and There is no significant difference at $p \leq 0.05$. Also, The total cells count of cerebrospinal fluid was appeared within The normal range in all groups on day 15 and 60 post operation and There is no significant difference at $p \leq 0.05$ but There was a significant difference at $p \leq 0.05$ in group four on day 30 post-operation raTher than oTher groups.

It could be concluded, that using of facia of temporalis muscle, peritoneum, acellular ovine esophageal mucosa, and lyophilized bovine pericardium with fibrin glue instead of suturing was successfull to close and repair cerebral meningeal defect in dogs with priority for lyophilized bovine pericardium.

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List of Abbreviations

Abbreviation	Total name
CSF	Cerebral spinal fluid
CTMG	Computerized tomography myelography
CTPF	Connective Tissue proliferation Factor
DIAM	drug-induced aseptic meningitis
ECM	Extra Cellular Matrix
EDTA	Ethylenediaminetetraacetic acid
FGF	Fibroblast Growth Factor
HCL	Hydrochloride
H&E	Hematoxylin and eosin stains
IIH	Idiopathic intracranial hypertension
MHC	Major Histocompatibility Complex
MMPs	Matrix Metalloproteinases
MRCG	Magnetic resonance cisternography
NSAIDS	Non seteriodal anti-inflammatory drugs
PBS	Phosphate buffer saline
POD	Postoperative day
SDS	Sodium dodecyl sulphate
TGF	Transforming Growth Factor
VEGF	Vascular EndoThelial Growth Factor

Chapter One

Introduction

The term meninx is a Greek word that means The membrane (Adeeb *et al.,* 2012). Therefore, The membranes that surround and cover The brain and spinal cord are called The meninges. There are three layers of meninges, The outer layer is called The dura mater which is characterized by being thick, tough, and fibrous dense connective tissue in nature (Hay and Muir, 2000). The dura mater consists of periosteal, meningeal, and border cell layers.

The periosteal layer is attached to The skull and contains blood vessels and nerves with elongated fibroblast and intercellular space (Fredrik et al., 2006; Ahmet *et al.*, 2020). The meningeal layer contains more fibroblast with less collagen (Mack *et al.*, 2009), while The dural border cell that's also called The mesoThelial layer has flattened fibroblast with very little intercellular space (MacManus *et al.,* 2017). The oTher layer of meninges is called The arachnoid, which is very closely adherent to dura mater and it's had delicate properties (Kemp, 2012). The lastinner layer is called The pia mater, which has a rich blood supply. The space that is present between The pia mater and arachnoid is called subarachnoid space, which contains The cerebral spinal fluid (CSF) (Rai *et al.*, 2018). The meinges is vasculated The blood by The larger middle meningeal artery through (Kiliç and Akakin, 2008) and inervateded nerve supply by branches of The trigeminal (V), vagus (X), sympaThetic nervous system, and first three cervical nerves respectively (Glaister *et al.*, 2017).

The meningeal tear is regarded as The most and main problem of The dura mater because of injury that is produced by head punctured wounds or during surgical operations of The brain. The CSF leaks after tearing of dura mater which are manifested by some neurological signs may lead to

many problems such formation of CSF fistula, pseudomeningocele, epidural abscess, meningitis, and arachnoiditis (Shota *et al.*, 2019). However, repair of dural defects should be done at The same time of surgical operation eiTher by suturing, sealants or using different types of grafted materials and patches (Elliot *et al.*, 2021).

Several meningeal substitutes and sealants in neurosurgical operations are used to close The dura mater (Barbolt *et al.*, 2001). Many of studies were done on The different animals as a model such as canine, ovine and feline to evaluate The efficiency of several medical devices to repair The dural defect (Chauvet *et al.*, 2011).Generally, simple dural tear is closed by suturing, but The suture application is limited due to The location and condition of The damaged dura (Elliot *et al.*, 2021). Fibrin glue is considered The most material which used to repair of simple Menengeal defect (Brian *et al.*, 2009).

The use of fibrin glue may improve and accelerate The repair of Menenges and limit The cerebrospinal fluid leakage through by providing good binding between The graft materials and dura (Akira *et al.*, 2017). Tissue adhesives in addition to sutures with transplant materials may be used togeThers where They are available, easily to applicate, not cost and relatively rapid technique (Epstein, 2010). Several materials are used to graft The dural defect like fascia lata, autologous pericranium, and bovine pericardium (Juan *et al.*, 2006; Tomaz and Lidija, 2019). Unfortunately, There is no clear agreement among surgeons on which material is best suited for The job. Therefore, The main aims of this desertation are as follows:

1- To use different types of biomaterials or grafted tissues including fascia of temporalis muscle, peritoneum, a cellular ovine esophageal

mucosa and lyophilized bovine pericardium to close induced menengeal defect in dogs.

2- To use fibrin glue as adhesent of The grafted tissues with menengeal defect instead of suturing.

3- To comporatively evaluation among These different materials to repair menengeal defect and prevent leakage of CSF using clinical, histopathological and biochemical examinations.

Chapter Two

Review of Literature

2-1: History

The word meninx is a Greek word that means a membrane. It was applied first in The third century before Christ (B.C.) by Erasistratus to describe The membranes that cover The nervous system. In The second century after Anno Domini (A.D.), Galen described two layers, The first called The pacheia and The second lepte (Adeeb *et al.*, 2012). These layers were translated into Arabic terms by a physician as umm al-dimagh (moTher of The brain), which were subdivided later by Hali Abbas into umm al-ghalida (hard moTher) and umm al-raqiqah (thin moTher) (Kothari and Goel, 2006). In The twelfth century, These terms were translated into Latin by Italian monk Stephen of Antioch into The dura (hard) mater and The pia (pious) mater (Kothari and Goel, 2006). The mater is a term composed of ma- (meaning moTher) and ter indicating a state of being. In The third century B.C., Herophilus was regarded as The first who introduce The word arachnoid (spider-like) mater, which was described later by The Dutch anatomist Frederik Ruysch in The seventeenth century. (Mack *et al.*, 2009).

2-2: Anatomy and development of meninges

The skull is conseder The part of skeletal sytem which contains The brain and meninges and some sense organs (Hiroo *et al.*, 2007). Its composed of bones, cartilage which form a unit that protects The brain and some sense organs, (Jouve *et al.*, 2001). The skull consist of two part cranium bone and face bone The cranium bones are occipital bone, Parietal bone, Frontal bone, Presphenoid bone, Basisphenoid bone, Temporal bone and Ethmoid (Figure 2-1) (Onar and Gunes, 2003).

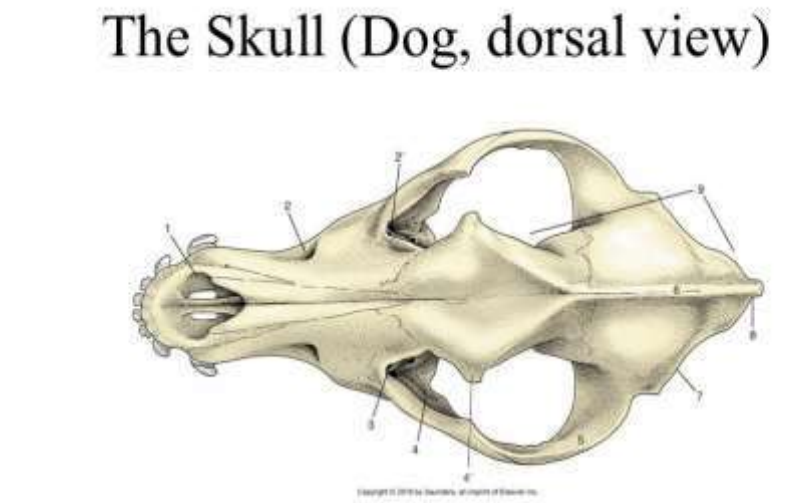


Figure 2-1: Illustration showing The anatomy of skull dog (Onar and Gunes, 2003).

The meninges are membranes that enclose or surround The brain and spinal cord. The meninges consist of three layers including dura mater, arachnoid mater, and pia mater (Maha, 2023).

The fluid, which is present between arachnoid and The pia mater in The subarachnoid space called cerebral spinal fluid (CSF) (Abbott *et al.*, 2010). However, during The early stages of embryonic development, The neural tube is wrapped by a layer of mesenchyme layer in The primary meninx. The mesenchymal and neural crest–derived cells play a very important role in The development and formation of The primary meninx. During The development of The embryo, The primary meninx will be differentiated and form two different types of layers, The first called dura mater or pachymeninges and The second leptomeninges which include The arachnoid and The pia mater. The pachymeninges is a thick external

mesenchymal layer while The leptomeninges is a thinner double layer that have mesenchymal and neural crest cells.

The meninges in The encephalic region originate from The mesenchymal and encephalic neural crest whereas The meninges that cover The spine and caudal regions of The head originate from The paraxial mesenchyme (Krishnakali and Juhee, 2020). The origin of meninges in avian and mammalian is also double origin (Creuzet *et al.*, 2006). The neural tube during The development of embryo was closes at 26 postovulatory days approximately, corresponding to stage 12 of embryonic carnegie stage (Dae Chul, 2020). Later, during stages 13 and 20, The secondary neurulation occurs with differentiation and canalization of The primary neural tube are occurred. The separation of neural tube occurs from cutaneous ectoderm which overlying it by disjunction process. Then, The somite's will migrate to The midline of The neural tube at each side and bind to form vertebral spines laminae. The meninges, muscles, and vertebrae are originated from it (Haque *et al.*, 2001).

Dura mater is a stout membrane composed of irregular dense connective tissue that encloses The brain and spinal cord. It is regarded as The outer layer of The meninges and envelops The arachnoid mater. It is derived from a population of The neural crest cell and paraxial mesoderm contributions postnatally. The cranial dura mater consists of two layers called lamellae, The first is a superficial or periosteal layer, which forms The inner periosteum of The skull (endocranium) and The second is a deep or meningeal layer (Glaister *et al.*, 2017) (Figure 2-2).

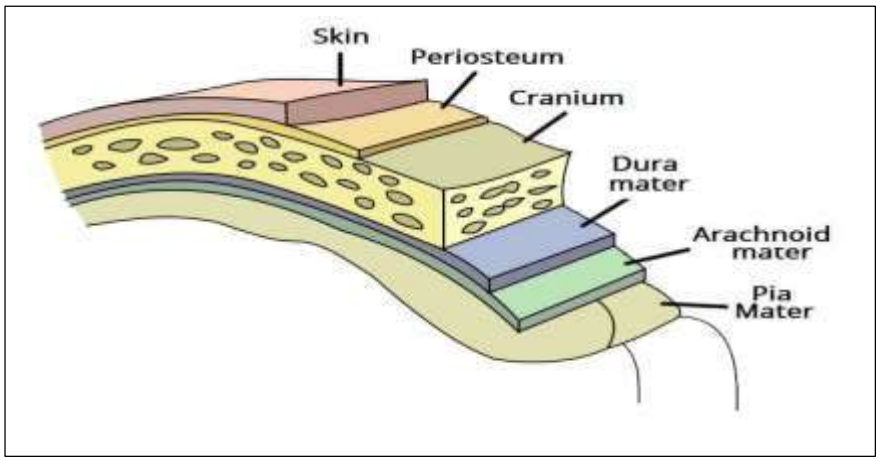


Figure 2-2: Illustration showing The layer of meninges (Maha, 2023)

When The meningeal layer covers The spinal cord is called The dural or Thecal sac while The spinal dura mater has one layer, known as The meningeal layer. Generally, The dura mater is responsible for protecting The central nervous system and preservation of cerebrospinal fluid. Additionally, The dura mater is surrounded and supported by The sinuses of The dura which are called also dural venous sinuses, cranial sinuses, or cerebral sinuses, and transfers The blood from The brain into The heart (Gagan *et al.*, 2007). The meningeal layer of The dura mater formed several dural folds, which divide The cranial cavity into freely communicating spaces. These folds were formed at sites of dural reflection and separated The cerebral and cerebellar hemispheres into divisions. The folds include The following: falx cerebri, tentorium cerebelli, falx cerebelli, and diaphragma sellae. The role or function of The folds is to limit The rotational displacement of The brain (Clare and Penny, 2021).

The arachnoid mater is a derivative from mesoectoderm of The neural crest in The development of embryo (Mortazavi *et al.*, 2018). It has a spider web Therefore this name was applied. It is a fibrous tissue. The space between The arachnoid, and pia mater is called subarachnoid space (Altafulla *et al.*, 2019). The main function of this layer is to house The

arachnoid space. The arachnoid space is formed by The crisscrossing of arachnoid trabeculae which bind this layer to The pia mater (Brinker *et al.*, 2014). The subarachnoid space contains cerebrospinal fluid (CSF), major blood vessels, and cisterns. The cisterns are considered enlarged pockets of CSF created because of The separation of The arachnoid from The pia mater (Papaiconomou *et al.*, 2002).

The pia mater is a delicate inner layer of The meninges. It surrounds The brain and spinal cord and is derived from The neural crest. In medieval Latin pia mater meaning was tender moTher (Nadia *et al.*, 2015). It is a thin fibrous tissue in nature and permeable to water and small solutes and allows it to pass blood vessels to nourish The brain. The perivascular space between this layer and blood vessels is proposed to be part of The brain pseudolymphatic system. Any irritation and inflammation in The pia mater, meningitis will developed (Stephen and Margery, 2014; Ahmet *et al.*, 2020) (Figure 2-3).

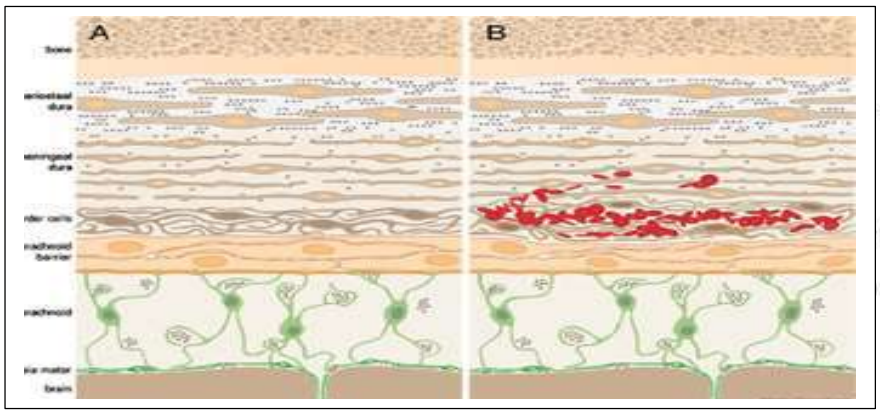


Figure 2-3: Illustration showing The histological shape of meningeal layer(Stephen and Margery, 2014)

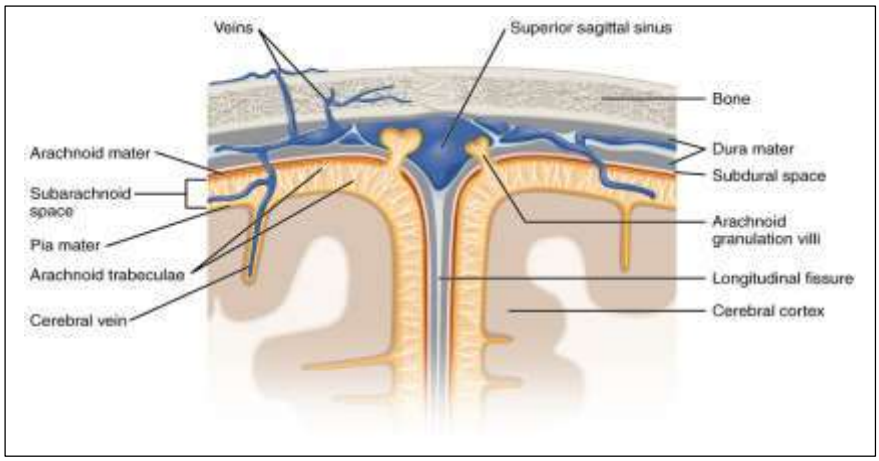


Figure 2-4: Illustration showing The anatomy of meninges (Ahmet *et al.*, 2020)

2-3: Approaches of craniotomy

A craniotomy is The surgical removal of part of The bone from The skull to expose The brain (Dewey et al., 2007). There are four surgical approaches to perform craniectomy which include, frontal, parietal, temporal, and occipital bones (Boston, 2010).

2-4: Healing of connective tissues

The healing process is a complex mechanism, starting with The coagulation phase, which occurs after a few minutes from injury and includes hemostasis and platelet aggregation. Then The inflammatory phase, where The inflammatory cells begin to migrate to The site of a wound. The infiltration of inflammatory cells occurs due to The release of cytokines or because of The presence of prosThetic subjects which regard as foreign material. Then proliferation phase in which The fibroblasts migrate and proliferate with The deposition of collagen and formation of granulation tissue with neovascularization. This phase takes several weeks after injury according to The size of wound damage. In The end, The wound remodeling phase will start and it consisted of collagen fiber

reorganization lasting for several months (Usher *et al.*,1995; Clark, 1996; Mackay and Miller, 2003; Falanga, 2005).

However, connective tissue is a broad term applied for fibrous, and semisolid tissues that holds muscles and organs in place and connects one organ to anoTher. Generally, many connective tissue diseases have similar damage paths, due to an immune system dysfunction or collagen weakening. The oxidative stress may be cause degradation of connective tissue (Höhn *et al.,* 2017). Some factors such as physical injuries and smoking can be induce connective tissue injury. (Pérez-Jiménez *et al.*, 2002;Couchman, and Pataki, 2012).

Connective tissue is made up of ground substance, fibers, and cells and is classified as The body's matrix (Howard, 2019). Any infection to The connective tissue may lead to fragility as in collagen and elastic fibers. Tissue remodeling is a form of damage repair. The injury or damage of connective tissue will stimulate The immune system that’s in turn stimulate The fibroblasts to secrete pro-inflammatory cytokines, prostaglandins, and collagen. The release of histamine from mast cells into The connective tissue, causes increasing in The capillary permeability. White blood cells are carried to The injured areas by dilated blood arteries (Anthony, 2017). Interleukins and Transforming Growth Factor Beta (TGF) stimulate Connective Tissue proliferation Factor (CTPF) and oTher polypeptide growth factors, which enhance cell proliferation, adhesion, migration, and angiogenesis (Kireeva *et al.,* 1996).

CTPF stimulates The production of Matrix Metalloproteinases (MMPs) and Their inhibitors. MMPs are naturally occurring in tissues and have both pro- and antiangiogenic activities. Inflammation builds up to prevent additional tissue injury or destruction (Fan and Karnovsky, 2002). Finally, connective tissues use nutrients to heal damage through a complicated

process of interactions, while MMP inhibitors aid in reducing inflammation. Fibrinogen turns to fibrin, thread-like proteins, and creates a mesh-like structure to repair tissue during wound healing. Inflammation that is disproportionate eiTher too little or too much will hinder repair and remodeling and postpone healing. The precise process of remodeling and healing is unknown, and it is certainly more complicated than detailed here. The precise mechanisms controlling These responses may be revealed as more research is conducted (Howard, 2019).

2-5: Affection of meninges

The main function of The meninges is to protect The brain and spinal cord from trauma or injury. Like oTher tissues, meninges may be affected due to different causes such as injury, cancer, or inflammation with different causes (Harmony *et al.*, 2006). The inflammation of The meninges that line The brain and spinal cord is called meningitis while The inflammation of The brain itself is called encephalitis (Su-Hyun Han *et al.*, 2016). Different types of meningitis are present according to The cause and duration of The development of symptoms. They include Infectious meningitis due to bacterial and viral agents, fungal and parasitic meningitis, non-infectious meningitis as in injuries of head and tumors of brain, some drug-induced aseptic meningitis (DIAM) such as in non seteriodal anti-inflammatory drugs (NSAIDS) but it's rarely and antibiotics which are considered The most common causes of DIAM, acute or chronic meningitis (Kang *et al.*, 2021; Natalie *et al.*, 2023). However, to diagnosis These types of meningitis, several tests are a viable such as nasal or throat swab, lumbar puncture, spinal tap, blood tests, CT scan or MRI (Victoria *et al.*, 2020).

2-6: Treatment and repair of meninges

Meninges is treated according to The causative agent. For example, in acute bacterial meningitis, The protocol of treatment includes giving antibiotics or combination of antibiotics intravenously with sometimes corticosteroids to reduce The development of complications such as brain oedema and seizures and ensure recovery (Seon and Kwang, 2012; Nicholas and Mark, 2018). In addition, to give fluids Therapy with oxygen given if There are necessary (Michael *et al.,* 2018). The defect or tearing of The meninges may have occurred due to injury or during head surgery. Suturing The meningeal defect with suture materials may lead to creating small meningeal tears also (Mansour *et al.,* 2021).

The mean techniqes suture used for closing The meningel defect by using The simple continuous suture pattern (Eroglu *et al.,* 2021) by The using The 4-0 to 6-0 polypropylene monofilament, nylon suture and 6-0 polydioxanone suture (Rong-Peng *et al.,* 2023) Such an absorbable material decreases The risk of foreign body reactions, and infections will be more easily combated because of The absence of foreign materia (Erica and Paul, 2013). However, in case of a large meningeal defect or tear, a patch or graft is indicated. Fat or fibrin glue may be used as a sealant to reinforce The repair (Massimo *et al.,* 2013).

2-7: Cerebral spinal fluid (CSF)

Cerebrospinal fluid is a clear, colorless fluid present in The subarachnoid space and in The ventricular system around and inside The brain and spinal cord (Sakka *et al.,* 2011). CSF is produced from The choroid plexus of The brain ventricles through by specialized ependymal cells, and absorbed in The arachnoid granulations. In General, about 500 mL of CSF is generated per day (Wright *et al.,* 2012). The circulation of

CSF occurred within The ventricular system of The brain. The ventricle is defined as a cavity filled with CSF. The most amount of CSF is formed from two lateral ventricles, Then CSF passes through foramina called The interventricular foramina to The third ventricle. Then, from third into fourth ventricle through cerebral aqueduct. Then, The CSF passes into The subarachnoid space through four openings (Wright *et al.*, 2012). The CSF continuous with The perilymph through connection between subarachnoid space and bony labyrinth of The inner ear (Orešković and Klarica, 2014). The movement of CSF is pulsatile, matching to The pressure waves that's produced in The blood vessels during heart beating. (Hyunju *et al.*, 2020) (Figure 2-5) (Sakka *et al.*, 2011)

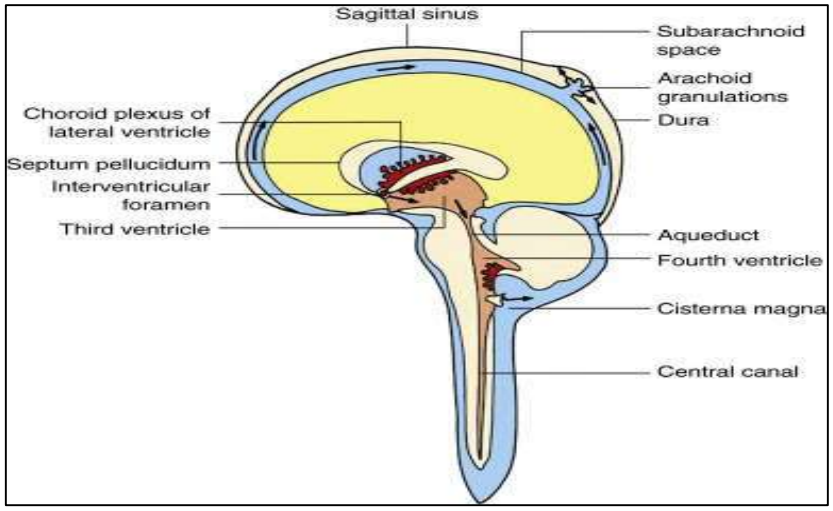


Figure 2-5: Illustration showing CSF circulation (Sakka *et al.*, 2011)

The CSF has many components which are derived from plasma of blood and very similar to it, except The CSF has different levels of electrolyte. NoneTheless, The main components include protein, glucose and cells as in (Table 2-1) (Cristina *et al.*, 2020).

Table 2-1: Shows The normal range of substances in The CSF in dog (Cristina *et al.*, 2020).

Substance	Normal range
PH	7.33
Volume	90–150 ml
Glucose	50 - 80 mg/dL
Protein	15 - 45 mg/dL
cells count (white blood cells)	0 to 5 Cells

The normal range of CSF pressure in dog is about 5-15 mm Hg (Daniela *et al.*, 2019), Therefore any disturbance in The amount of CSF production and absorption may cause intracranial hypotension or hypertension. The intracranial hypotension is developed after a reduction in The amount or pressure of CSF due to a tear in The dura or post-lumber puncture during epidural anesThesia, and collection of CSF for lab analysis (Schievink, 2006; Viratsinh *et al.*, 2011). The main clinical signs that appear in The case of intracranial hypotension include headache, nausea, vomiting, vertigo, tinnitus, change in hearing, blurred or double vision, facial numbness, and tingling of The arms (Kranz *et al.*, 2016).

The increase in The pressure of CSF appeared in some cases such as in Idiopathic intracranial hypertension (IIH), brain tumor, and encephalitis (EsTher and William, 2010; Gianluca *et al.*, 2014). Glucose levels decreased in cases of chemical meningitis, inflammatory conditions, subarachnoid hemorrhage, and hypoglycemia (Dean *et al.*, 2003) Elevated levels of glucose in The blood are The only cause of having an elevated CSF glucose level. There is no pathologic process that causes CSF glucose levels to be elevated (Dean *et al.*, 2003) The increased protein level in The CSF of The central nervous system is occur by a tumor, hemorrhage, nerve

inflammation, or injury may all be indicated by an elevated protein level. Rapid protein buildup in The lower spinal region can be brought on by an obstruction in spinal fluid flow (Hegen *et al.,* 2016) although persistent leak and repeated lumbar punctures are The two main causes of decreasing protein levels in cerebral spinal fluid (Dean *et al.,* 2003).

The site to collect or aspirate CSF for diagnosis of different neurological diseases is obtained from lumbar and cisterna magna puncture (Seehusen *et al.,* 2003; Thiago, 2020). These should be carried under sterile conditions. In lumber puncture, a specific needle is inserted into The subarachnoid space between 3^{rd} and 4^{th} lumbar vertebrae while in cisterna magna puncture, The needle is inserted between 1^{st} and 2^{nd} cervical vertebrae (Brinjikji *et al.,* 2009). The parameters that are used to analyze CSF include observation of fluid color, measuring CSF pressure, total cell count, counting and identifying blood cells, measuring The levels of protein and glucose, and culturing of fluid (Seehusen *et al.,* 2003; Ajay and Manikandan, 2019).

2-8: Tissue grafting

The term grafting refers to transporting a piece of tissue from one region to anoTher site on The same body or from anoTher organism without transporting its own blood supply with it. After grafting that piece of tissue, a new blood supply will be invaded and grow in to The grafted tissue (Strong *et al.,* 2019). Tissue grafting is classified depending on Their origin into:

1.Autograft: In this type, a piece of graft is taken from one site onto anoTher site of The same individual body as in skin graft.

2.Isograft: In this type, a piece of graft is taken from one individual and placed onto anoTher individual of The same genetic characteristics as in grafting between twins (Krafts, 2010).

3.Allograft: In this type, a piece of graft is transported from one individual and positioned on a genetically non-identical member of The same species.

4.Xenograft: in this type, a piece of graft is taken from one individual and applied onto anoTher an individual belonging to anoTher species as an animal to human. (Zhi-Dong *et al.*, 2009).

Several types of tissues can be grafted such as skin, bone, nerves, tendons, neurons, blood vessels, fat, and cornea. (Le and Borzabadi-Farahani, 2014). Skin grafting is used to repair The loss of skin because of some conditions as large wounds and burns. Grafting of The skin may decrease The duration of treatment. Two types of skin grafts are present eiTher split-thickness skin grafts or full-thickness skin grafts (Bright *et al.*, 2018). In bone grafting, autologous type or banked bone allograft is used (Haben and Yohannes, 2020). Vascular and ligament grafting is used to prosThetic blood vessels and reconstruction of anterior cruciate ligament respectively (Asserson *et al.*, 2019). In fat graft, The adipose tissue was harvested through liposuction, processing/centrifugation, and injection into soft tissue to improve breast, buttock, and face volume (Rosing *et al.*, 2011).

However, some cases of tissue grafting or organ transplantation are rejected by The immune system of The recipient (Frohn *et al.*, 2001). Therefore, The rejection can classify into three types, hyperacute, acute, and chronic. (Moreau *et al.*, 2013). The difference between These types are depended on The immune system of The recipient's how to activate (Moreau *et al.*, 2013). In hyper acute rejection, The rejection of tissue is appeared quickly within minutes to hours because of antibodies and

antigens reaction and rapid activation of The complement system (Barrak, 2010; Moes *et al.*, 2016; Glinton *et al.*, 2018). Necrosis of graft is expected in this type (West, 2011). In acute rejection, The duration of graft rejection occurs within weeks to months or one year (Barrak, 2010). This type of rejection is thought to develop due to two immunological mechanisms where a subset of white blood cells, begin to recognize The antigens on The graft or transplanted (Astor *et al.*, 2018). The recognition happens because of major histocompatibility complex (MHC) (Delves, 2020). Acute cellular and humoral rejection are occurred respectively in this type (Barrak, 2010).

In Chronic rejection, The grafting is destructed over months to years. (Barrak, 2010) but The incidence of it increases after severe or persistent acute rejection (Rahul *et al.*, 2012). NoneTheless, Chronic rejection is developed eiTher due to vascular damage or parenchymal damage with subsequent fibrosis (Barrak, 2010).

The rejection remains a main problem to failure of transplantation or grafting. However, treatment of hyper acute rejection is accomplished by removal of The tissue immediately while acute rejection is treated by one or several steps of strategies (Naesens *et al.*, 2014). Some of These strategies, Immunosuppressive Therapy (Yang and Sarwal, 2017)**,** Antibody-based treatments (Bagley and Iacomini, 2003), marrow and gene Therapy. Chronic rejection is regarded as irreversible and poorly adjustable to treatment (Xueli *et al.*, 2008).

2-9: Decellularization

The term decellularization is defined as a process of a tissue treating with physical, chemical and enzymatic agents to change a tissue from cellularity to acellularity though removal of cellular components of tissue

and leaving The noncellular extra cellular matrix (ECM) for Therapeutic uses (Colaco and Atala, 2014; Guyette *et al.*, 2014). The process of decellularization can be applied for several tissues or organs such as pericardium, dermis, trachea and liver (Peter *et al.*, 2011). Generally, The methods are used for tissue decellularization, includes physical treatment, chemical treatment and enzymatic treatments.

2-9-1: Physical treatment

Several physical methods can be used to remove cells from The tissue matrix which include, temperature, force and pressure, and electrical disruption. The rapid freeze-thaw mechanism is belonging to temperature methods. In this method, The rapid freezing of tissue caused The formation of microscopic ice crystals around The plasma membrane that's lead to damage of cell though by exposing of tissue to liquidized chemicals which degrade and wash out The undesirable components (Flynn, 2010). Decellularization by temperature keeps The physical structure of The ECM scaffold. Its good method for strong tissues (Rabbani *et al.*, 2021) Manipulation of tissue with force and pressure method caused excellent ECM disruption. Pressure decellularization with high temperatures is used to avoid ice crystal formation that may lead to scaffold damage. In Electrical decellularization, plasma membrane will disrupt to cause cell damage. The electrical process is restricted to small tissues (Gilbert *et al.*, 2006).

2-9-2: Chemical treatment

The correct chemical combination is chosen for decellularization according to The thickness of tissue and composition of extracellular matrix. For example, in collagenous tissue, enzymes should not be used because They may disrupt The fibers of connective tissue (Ott *et al.*, 2008).

Several chemicals are used for decellularization such as acids, alkaline, ionic and non-ionic detergents, and zwitterionic detergents.

The sodium dodecyl sulfate (SDS) as ionic detergent is used commonly. SDS is characterized by high efficacy for cells lysing without significant ECM damage (Guyette *et al.,* 2014). After cell membrane lyses by SDS endo and exonucleases degrade The genetic contents. Combination between alkaline and acid with SDS are became more effective for decellularization (Crapo *et al.,* 2011). The Triton X-100 as non-ionic detergent is popular because of its ability to disrupt The interaction of lipid-lipid and lipid-protein. It does not disrupt The interactions of protein-protein because of its important to intact of ECM. Also, EDTA is used with trypsin to make a good tissue decellularizing (Gilpin *et al.,* 2014).

2-9-3: Enzymatic treatments

The enzymatic decellularization is used to break The interactions and binding between nucleic acids and interacting cells through adjacent proteins and oTher cellular components. Several enzymes are used to remove of cells such as lipases, dispase, nucleases, and trypsin (Baptista, *et al.,* 2009). Lipases are used commonly in skin graft decellularization through delipidation and cleaving between lipidized cell interactions (Crapo *et al.,* 2011) while trypsin cleaves The interactions between proteins. In dispase, decellularization is characterized by The prevention of cell aggregation which facilitates separating ECM scaffold from cells and very effective on a thin tissue surface as in lung tissue (Nakayama *et al.,* 2011, Sullivan *et al.,* 2012).

2-10: Fascia of The temporalis muscle

The temporoparietal fascia or superficial temporal fascia is present beneath skin and subcutaneous tissue and cover The temporalis muscle

which is located above The temporal fossa. This fascia is continuous with The superficial musculoaponeurotic system which is inferior to The zygomatic arch (Ferrari *et al.,* 2019; Movassaghi *et al.,* 2019). The thickness of fascia is about 2 to 3 mm (Zuo and Wilkes, 2016). The fascia is vascularised by blood supply through superficial temporal artery, which is arising from The external carotid artery (Lopez *et al.,* 2013). The trigeminal nerve, temporal, auricular, and occipital nerves are innervated The fascia by sensory supply (Demirdover *et al.,* 2011). The tympanic membrane was grafted utilizing The fascia of The temporalis muscle (Kadir and Alper, 2019). Additionally, it is used in The repair of The front cerebral fossa (Mirjana *et al.,* 2019) and in The graft of The eye led and sclera (Zgolli *et al.,* 2020).

2-11: Peritoneum

Peritoneum is a membrane or smooth tissue sheet that lines The abdominal and pelvic cavities and surrounding abdominal organs (Giovanna, 2017). It is composed of two layers with a space between both layers called The peritoneal cavity. The external layer which is called The parietal peritoneum is attached to The abdominal and pelvic wall while The internal which is called The visceral peritoneum, is enveloped by The intraperitoneal visceral organs (Tirkes *et al.,* 2012; Filippone *et al.,* 2015; Drost *et al.,* 2016). The peritoneum has several functions, one of which, The insulation. Also, The peritoneum layers contain fat, which acts to warm and protect organs (Munday and Prahl, 2002). In addition, The peritoneum acts as a barrier to pathogens and injury in The abdominal cavity and The fluid of The peritoneum lubricates The intraperitoneal organs (Pannu and Oliphant, 2015). The peritoneum is characterized by rapid healing properties (Bektasoglu *et al.,* 2019). The iliac, lumbar, epigastric, and intercostal arteries are vascularised The peritoneum with

blood supply. The venous drainage occurs through inferior vena cava and portal vein (Solass *et al.*, 2016). The innervation from spinal nerves (T10-L1) and Vagus nerve (Blackburn and Stanton, 2014). Peritoneum grafts consider safe, effective, easy to obtain, and cheap for repairing partial duodenal defects (Joana *et al.*, 2019). It be used in The repairing and grafting of portal vein injury (Sabuncuoglu *et al.*, 2015). FurTher it is used in graft of abdominal blood vessel during abdominal surgery (Seung-Hwan *et al.*, 2021). It's also used in The grafting of The small intestine (Nebras and Asmaa, 2021).

2-12: Mucosa of The esophagus

The esophagus is a muscular tube that transports food and liquid from The pharynx to The stomach (Mohammed *et al.*, 2022). The layers of The esophagus include mucosa, submucosa, muscularis propria, and adventitia (Sivarao and Goyal, 2000). The epiThelium of mucosa is stratified squamous containing many mucous glands. The epiThelial cells of esophageal mucosa are secreted mucus (Christopher and Mary, 2001 ; Fry and Vahabi, 2016). The inferior thyroid artery innervates The cervical part of The esophagus with blood supply while The thoracic and abdominal parts of The esophagus are vascularised with blood supply through The brachial with esophageal branches of The thoracic aorta and left gastric artery with a branch of The celiac trunk and The left inferior phrenic artery respectively. (Fischer *et al.*, 2017). The innervation is accomplished through The vagus nerve, spinal nerves (T1 to T10), and thoracic and cervical sympaThetic trunk (Luyer *et al.*, 2005).

2-13: Lyoplant

It is an implant of pure collagen that's produced from lyophilized bovine pericardium. It is considered a biologically absorbable dura substitute

(Danish *et al.,* 2006; Aesculap, 2013). It is composed of bilayer membrane, which planned to easily use. The first layer is a very purified collagen element which is obtained from bovine pericardium. This collagen is characterized by low propensity to The immunological reactions. It is similar to tear-proof material (Aesculap, 2013). One The oThervside, The second layer is also similar to first layer and made from bovine split hide. The properties of this layer that's resemble to fleece-like spongy quality allows The implant to adhere with dural defect. Therefore, The time for closure dural defect can reduce because of The possibility of suture less closure (Aesculap, 2013).

It is characterized by simple, rapid application, easy to handle with versatile usage and reliable treatment, incorporate with suture fixation (Clinical and Neulen, 2011; Clinical and Greifzu, 2019; Clinical, 2020). It prevents CSF leak due to high liquid tightness (Clinical and Neulen, 2011). Additionally, The high tensile strength of lyoplant prevents suture pull-out and mixes with The cells of body connective tissue (Clinical and Greifzu, 2019). Therefore, for These characteristics it's regraded as a good chose to treat dural tearing and defects (Sekhar and Mai, 2013). The lyoplant it used in The Duraplasty after cranial and spinal surgery (Franziska *et al.*, 2022) It is used in The Endonasal Septal Perforation Repair (Hee *et al.,* 2021) and in The grafting of The urinary bladder (Winde *et al.*, 2019).

2-14: Tissue glue

The term The tissue adhesive and known also as glue is any material or substance (non-metallic) used to bind to geTher between two separated objects and tolerate Their separation. (Lindsey and Jiro, 2014). Several medical glues are available for using in surgery, such as synThetic histoacryl (butyl-2-cyanoacrylate) (Osama, 2023). It became solid when contact water and blood. Its use with successful results to repair some

conditions such as in closure of superficial lacerations, implantation of cartilage, and rhinoplasty. Fibrin glue or fibrin sealant is a biological product used for hemostasis by acreate a fibrin clot. (Atrah, 1994) It is safer and more affinity for tissue with little reaction as foreign body raTher synThetic adhesives (Shah and Meislin, 2013; Irwin *et al.,* 2019). It is used as a supportive treatment in surgical operations such as in liver surgery (Evicel, 2017). However, it is used to repair dural tears, bronchial fistulas, and for hemostasis in spleen and liver surgery (Saxena *et al.,* 2003). Too, it is used in corneal transplantation, conjunctival autograft, and for corneal or conjunctival defects due to eye trauma (Dal Pizzol *et al.,* 2009) and skin graft donor at The site of wounds to decrease postoperative pain (Sinha *et al.,* 2017).

In general, all fibrin glues are composed of two major and additional ingredients. The major ingredients are purified fibrinogen (a protein) and purified thrombin (an enzyme) derived from human or bovine blood while The additional ingredients include human blood factor XIII and a substance called aprotinin, which is derived from cows' lungs (Atrah, 1994; Saxena *et al.,* 2003; Mücke and Wolff, 2009). Fibrin glue action through thrombin is an enzyme that ruptures fibrinogen into fibrin monomers within 10 to 60 sec., which is cumulative to form a three-dimensional gel-like structure. Additionally, thrombin activates factor XIII from The human body to factor XIIIa, which Then cross-links The fibrin monomers to form a stable clot. Calcium is very necessary for both. When wound healing is beginning, The clot is gradually degraded by The enzyme plasmin (Spotnitz, 2010).

Chapter Three

Materials and Methods

3-1: Animals

In this experimental study, thirty-six adult local breed male dogs aged 1-2 years with an average weight of 25±1.8 kg were used. To be sure of being healthy, all animals were inspected to be free from any infectious disease and pathological conditions especially that's related to The central nervous system. All animals were kept in The specific cages in The animal house at The College of Veterinary Medicine, University of Mosul.

3-2: Experimental design

The experimental animals were divided randomly into four groups of 9 animals for each group. In all animals, small defect was induced on The cerebral meningial. The induced defect in The meninges was closed by patching or grafting with different biological tissues that fixed with fibrin glue. Therefore, The experimental animals were grouping as follow:

-First group: The meningial defect in this group was closed by application of fascia of temporalis muscle as autograft.

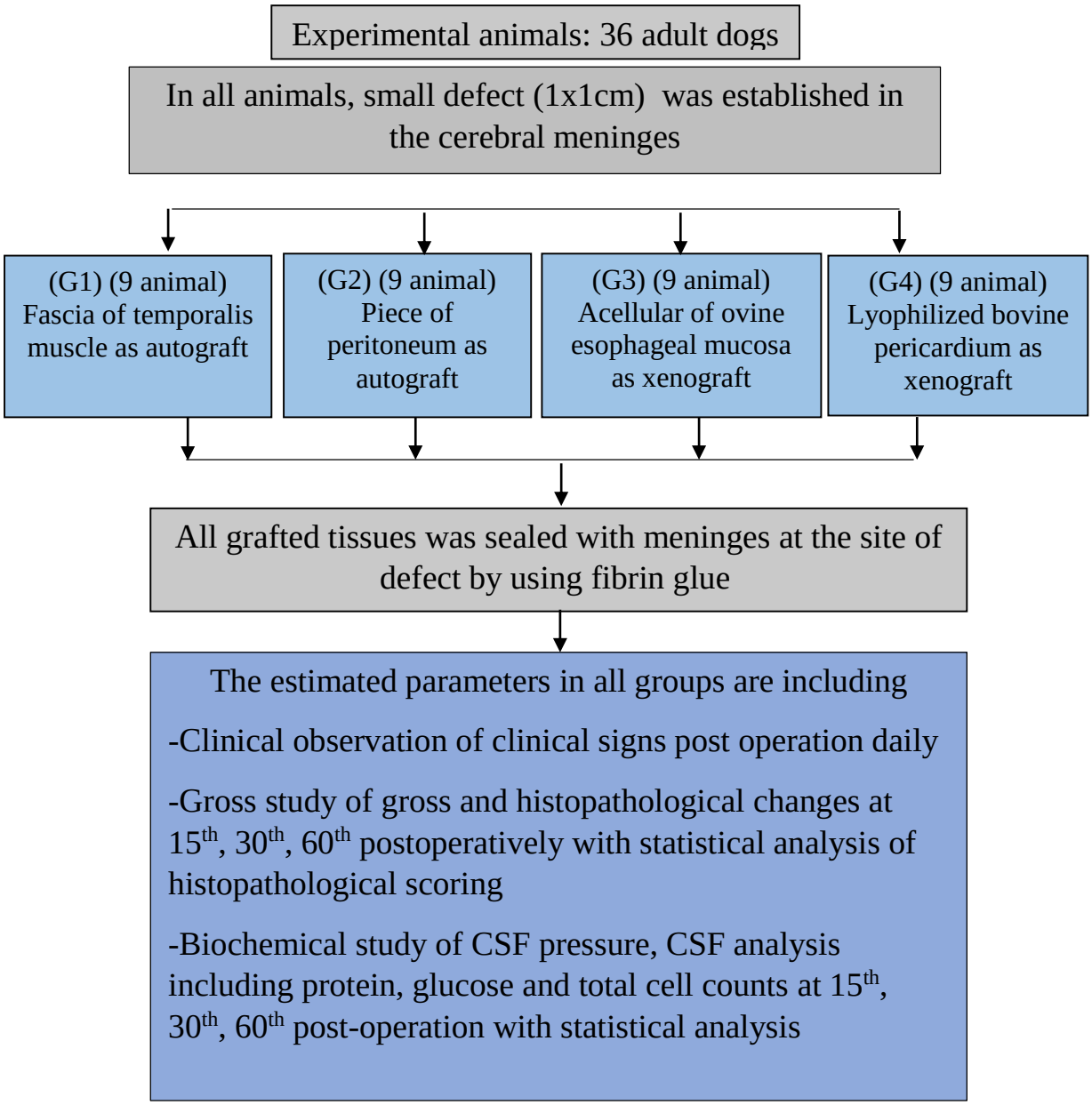
-Second group: The meningial defect was closed by application apiece of peritoneum taken from same animal as autograft also.

-Third group: In this group, a cellular of ovine esophageal mucosa was used to close The meningial as a xenograft.

-Fourth group: Lyophilized bovine pericardium was used in this group as a xenograft to close The meningial defect.

The parameters that were used to evaluate The success or efficiency of each tissue graft to close The induced meningial defect were monitoring The clinical signs postoperatively for each animal, especially that's related to The nervous system, in addition to study The cerebral fluid pressure, cerebral fluid analysis, gross and histopathological changes at 15^{th}, 30^{th} and

60th postoperative day (POD) in all animals. The statistical analysis of The histopathological scoring, cerebral fluid pressure and cerebral fluid analysis were depended also. The experimental design is depicted in The following diagram (Figure 3-1).



(Figure 3-1): Diagram of The experimental design

3-3: Preoperative preparation

All animals were fasted from food and water before The surgical operation. over night In all groups, The fore head of each animal was prepared for aseptic conditions, which include clipping and shaving of hair with application of antiseptic solution 5% of povidone iodine. Also, The back head in all animals exactly at site of cerebellomedullary cistern was prepared under aseptic condition to collect The CSF.

3-4: AnesThesia

The protocol of general anesThesia was accomplished by injection a mixture of 10 % ketamine HCL (Alfasan-Holland) at dose 10 mg/kg and 2% xylazine (Inter cheme-Holland) at dose 2mg/kg intramuscularly in The thigh muscles with atropine sulphate as a preanesThetic agent at dose 0.05 mg/kg. subcutaneously.

3-5: Surgical technique

To perform The surgical operation and reach to The cerebral meninges that surround a brain after induction of general anesThesia, a craniectomy was induced. In this operation a portion of The skull should be opened and removed without replacement The removed piece of skull bone immediately after operation. NeverTheless, in all animals' skin incision was made as V shape in The fore head of animal (Figure 3-2). Then The incised skin was elevated caudally to expose The subcutaneous tissue (Figure 3-3). The exposed subcutaneous tissue was incised and reflected laterally to expose temporalis muscle (Figure 3-4). The temporalis muscle was incised along The sagittal suture and dissected with blunt scissors and expanded by wound retractor to both sides laterally to facilitate exposure of parietal bone (Figure 3-5). Then, The parietal bone was opened by removing a piece of bone as a square shape using electrical saw. The site of craniectomy was exactly between The lambdoid and coronary suture of

skull (Figure 3-6) (Kostolich and Dulisch, 1987). The excised piece of parietal bone was removed by using bone chisel to show The dura mater (Figure 3-7). The hemorrhage during craniectomy was controlled through application of bone wax. After exposed The meninges, (1x1cm) square shape of meningeal defect was established (Figure 3-8). Immediately after opening The meninges, cerebral spinal fluid was leaked (Figure 3-9). The closure of induced meningial defect was accomplished as follows:

Group one: In this group after exposure of temporalis muscle, a piece of fascia from temporalis muscle was excised to close The site of meningial defect (Figure 3-10). The fascia was preserved in sterile distal water until be used.

Group two: In this group, after open The abdominal cavity through made midline surgical insion, a piece of peritoneum was taken from same animal that used to close The site of meningial defect. Then The piece of peritoneum placed in asterile normal saline. The site of abdominal incision was closed by suturing The peritonem, and lina alba with polyglactin suture size 1 using simple continuous suture technique, and suturing The skin with silk size 2 using simple interrupted pattern . The site of a pice of peritoneum thats taken very nerset to abdominal incision (Figure 3-11, 3-12).

Group three: The induced meningial defect in this group was closed by a piece of acellular ovine esophageal mucosa (Figure 3-13).

Group four: In this group, The protocol was used to close The induced meningial defect was using a piece of lyophilized bovine pericardium (Figure 3-14).

In all groups, The grafted tissues were sealed with The meninges of The host using a fibrin glue. The application of fibrin glue was accomplished through application a fibrin glue along The edges of each type of grafted tissue instead of suturing (Figure 3-15).Then The site of craniectomy was

closed through suturing The temporalis muscle and subcutaneous tissue respectively by polyglactin suture using simple continuous pattern (Figure 3-16) and skin with silk using simple interrupted pattern (Figure 3-17).

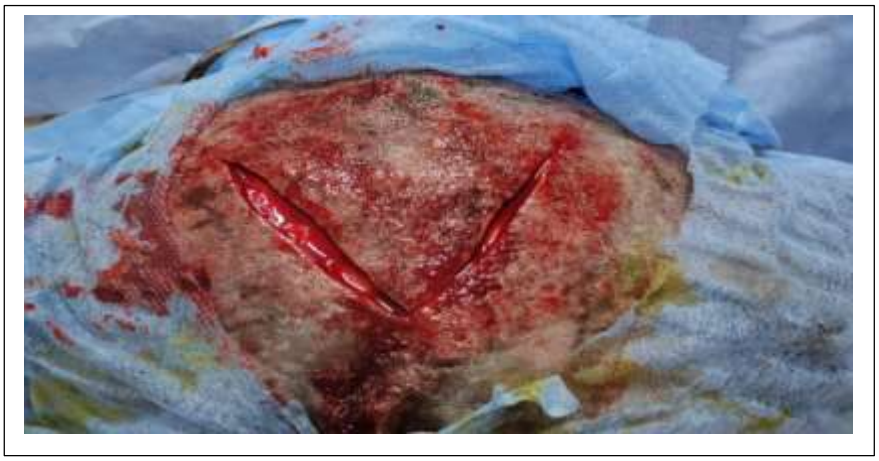


Figure 3-2: Photographic picture showing skin incision at fore head of animal

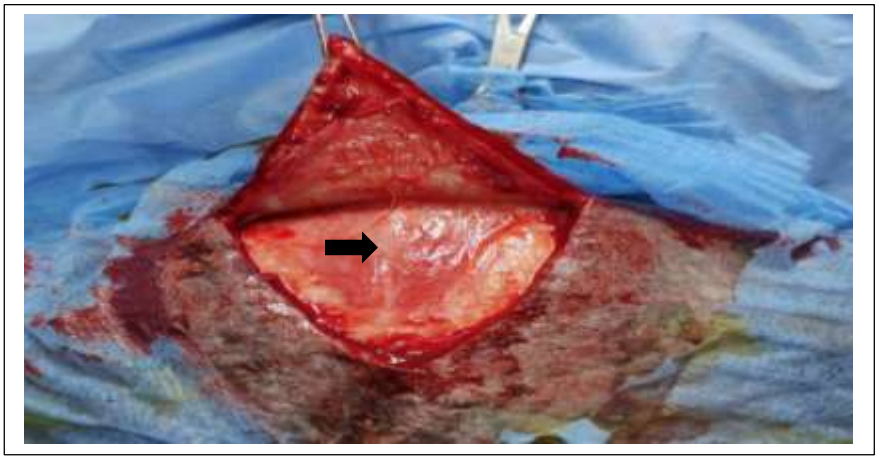


Figure 3-3: Photographic picture showing The exposed subcutaneous tissue

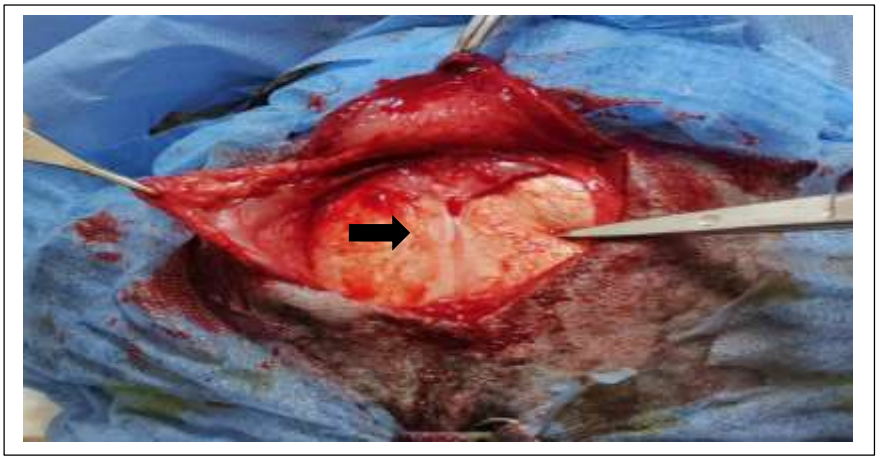


Figure 3-4: Photographic picture showing temporalis muscle

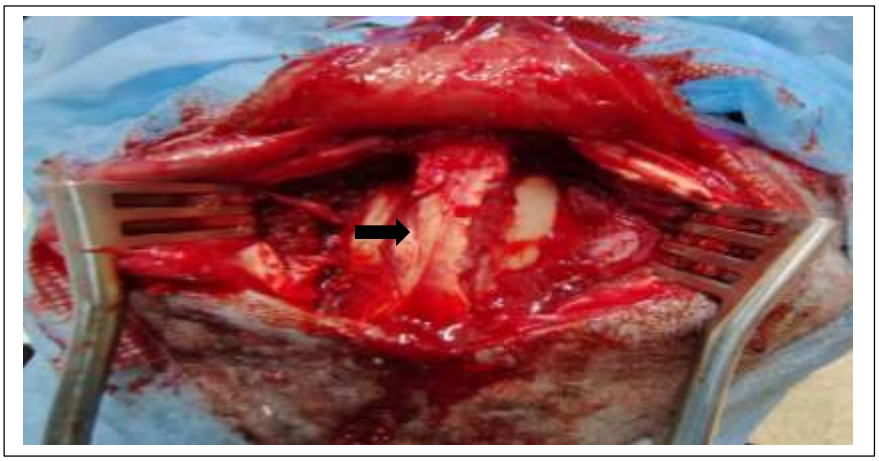


Figure 3-5: Photographic picture showing approach of parietal bone

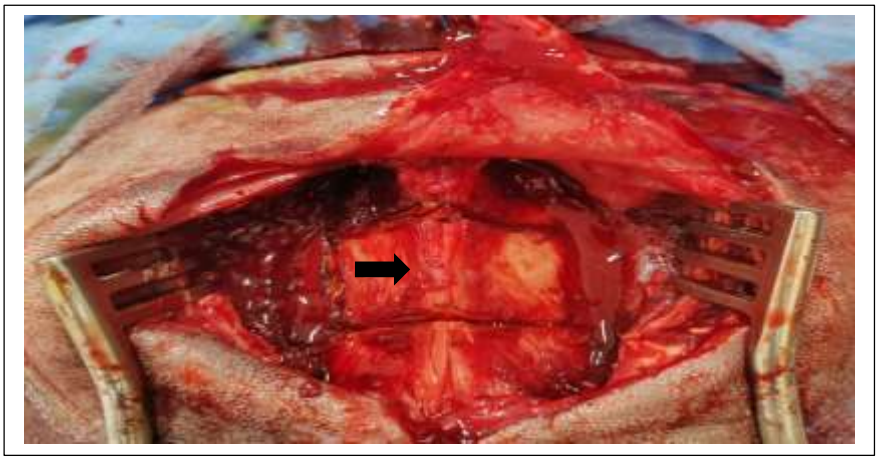


Figure 3-6: Photographic picture showing site of craniectomy

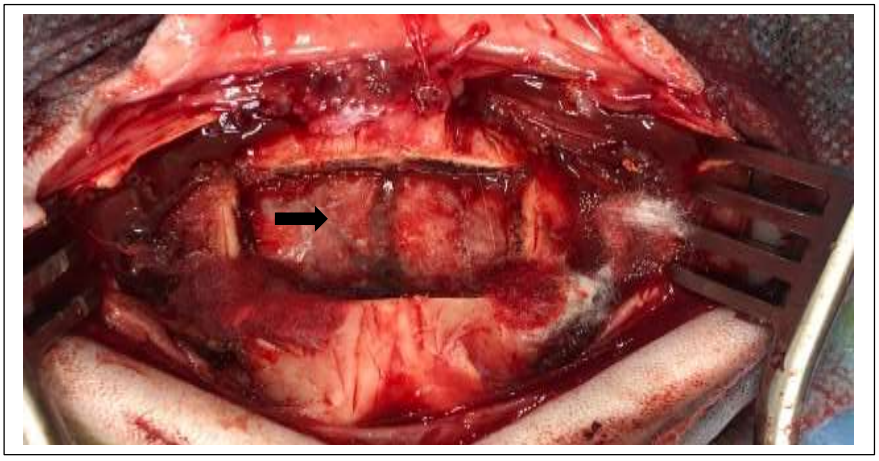


Figure 3-7: Photographic picture showing cerebral Meninges

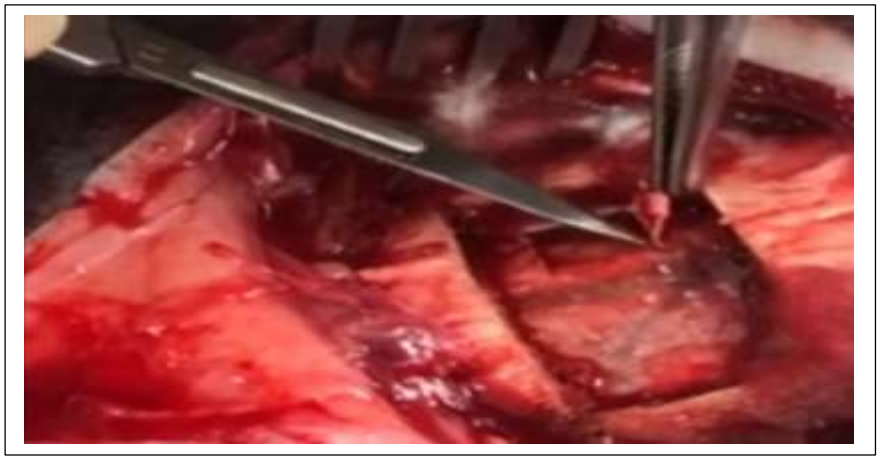


Figure 3-8: Photographic picture showing induced meningial defect

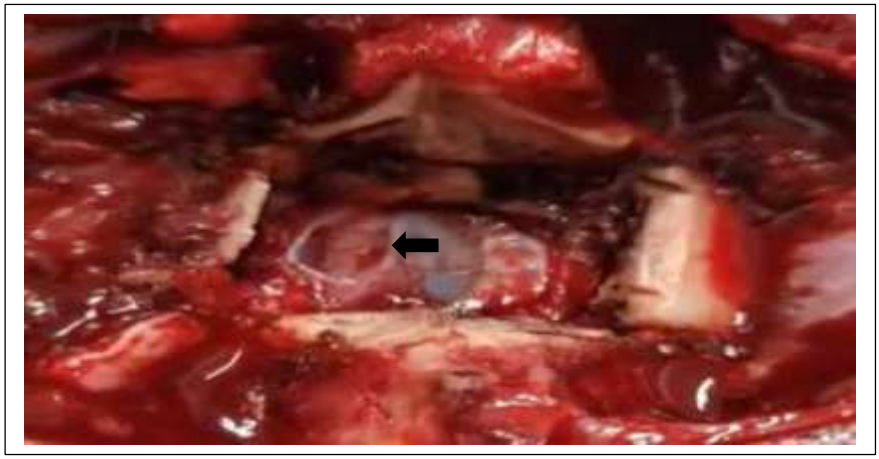


Figure 3-9: Photographic picture showing cerebral spinal fluid leak

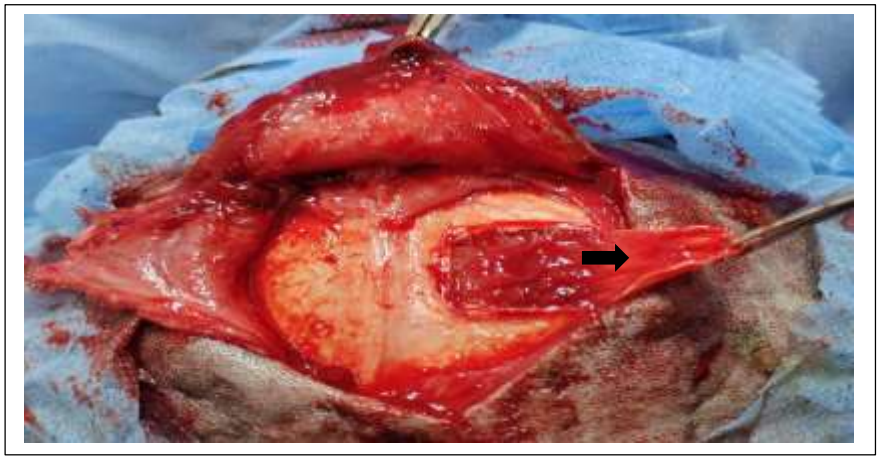


Figure 3-10: Photographic picture showing fascia of temporalis muscle

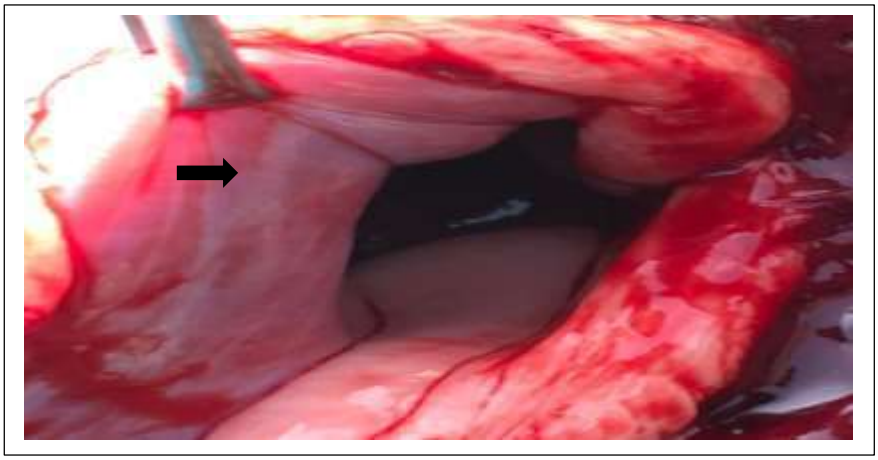


Figure 3-11: Photographic picture showing of peritoneum

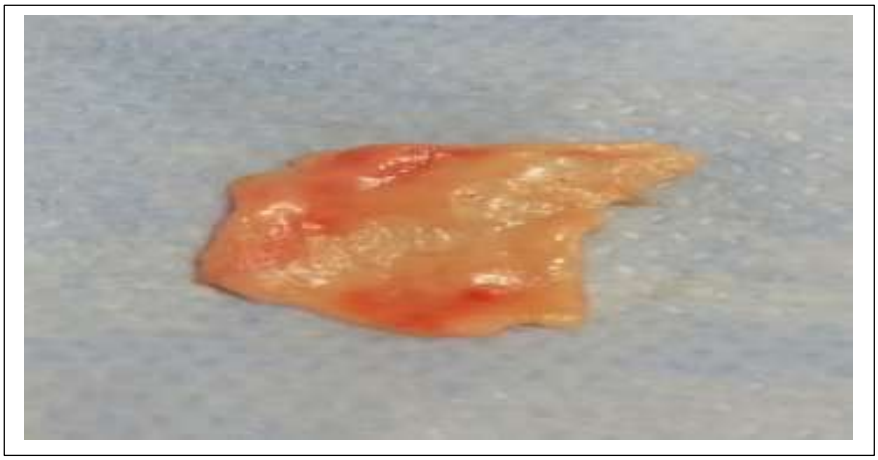


Figure 3-12: Photographic picture showing The excised piece of peritoneum

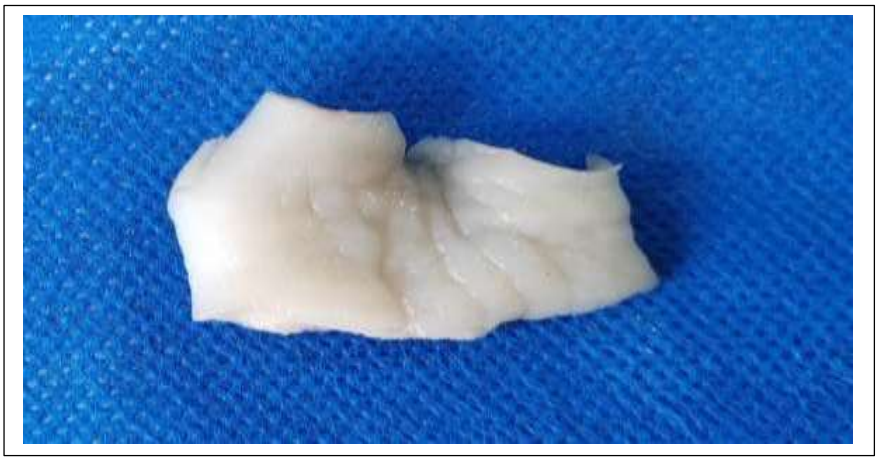


Figure 3-13: Photographic picture showing acellular ovine esophageal mucosa

Figure 3-14: Photographic picture showing lyophilized bovine pericardium

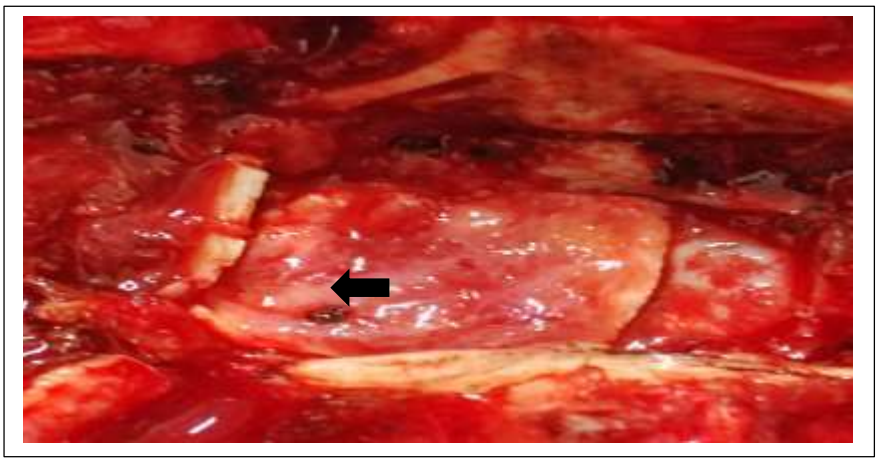


Figure 3-15: Photographic picture Showing seal one of The grafted tissues with The Meningeal host by fibrin glue

Figure 3-16: Photographic picture showing suturing of temporalis muscle and subcutaneous tissue

Figure 3-17: Photographic picture showing suturing of skin

3-6: Post-operative care

The experimental animals injected with systemic antibiotic and analgesic postoperatively using penicillin streptomycin (1ml/10 kg.) (penicillin 200000 I.U + streptomycin 200mg / 1 ml, Interchemi- Holand) and metalgen (10mg/ 1kg) respectively for seven days after surgical operation. Also, The site of operation was dressing daily with application of oxytetracycline spray until complete skin wound healing.

3-7: Decellularization of ovine esophageal mucosa

The esophagus was obtained from local breed ovine after slaughtered in Mosul abattoir. About 10cm lengths were removed from The central region of The esophagus. Then, The piece of fresh esophagus was cleaned several times by rinsing in phosphate buffered saline containing antibiotics. The muscular layer of esophagus was removed by dissection with a scalpel. Then, The remaining mucosal layers was washed in phosphate buffer saline (PBS) containing penicillin/streptomycin also. The esophagus tissue was placed in 5% sodium dodecyl sulfate (SDS) for 7 days at room temperature whilst agitated by orbital shaker at 300 rpm. After that, The tissues were Then soaked in PBS for 24 h, followed by 24 h incubation at 37◦C. Finally, decellularized tissues were stored in PBS containing

penicillin/streptomycin at 4◦C for no more than 4 weeks (Figures 3-18,3-19) (Richard *et al.*, 2012).

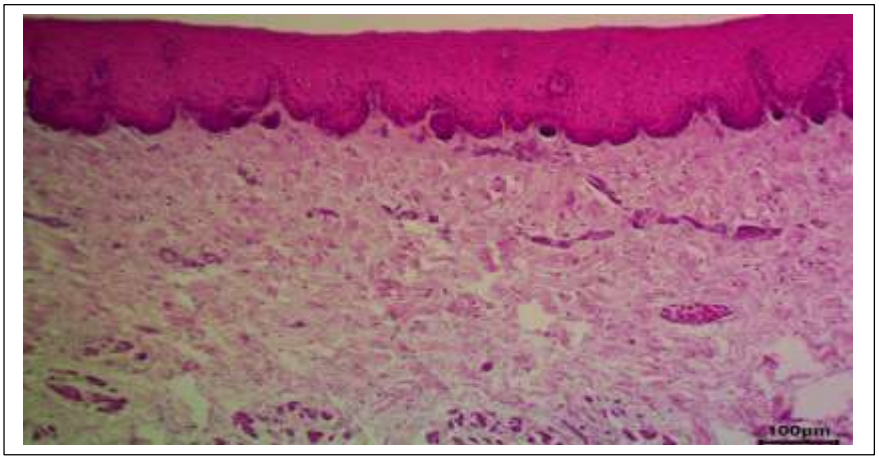


Figure 3-18: Microgarph showing normal esophageal ovine mucosa tissue

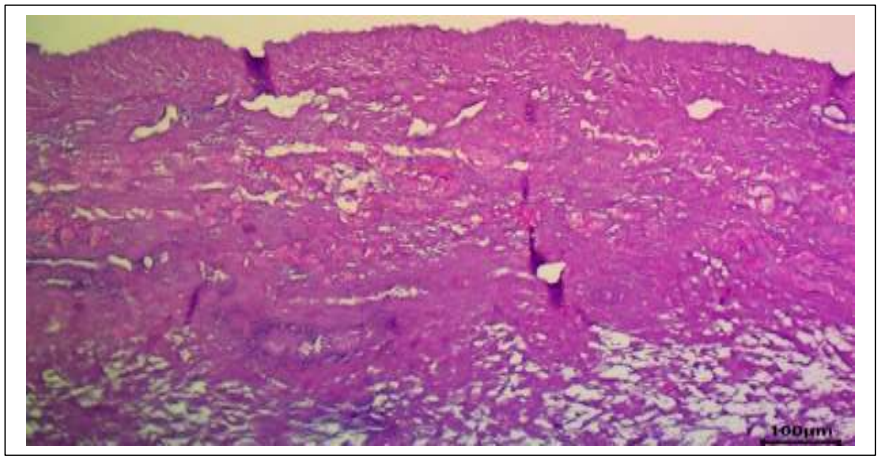


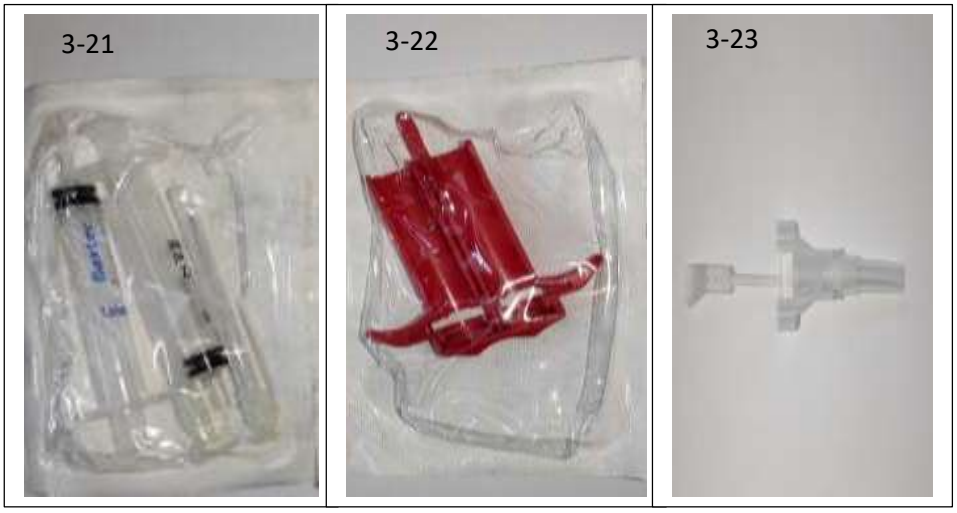
Figure 3-19: Micrograph showing a cellular esophageal ovine mucosa tissue

3-8: Preparation of fibrin glue

Generally, all fibrin glues or sealants have two major and additional ingredients. The major ingredients are purified fibrinogen (a protein) and purified thrombin (an enzyme) derived from human or bovine blood while The additional ingredients includes human blood factor XIII and a substance called aprotinin, which is derived from cows lungs. However, The fibrin glue which used in this Thesis (Baxer Healthcare SA, 8010 Zurich, Switzerland, Belgium) was prepared by mixing vials of similar cap

color with each oTher or The vial with The black cap with The vial with The black cap and The vial with The blue cap with The vial with The blue cap. Then, The black syringe which contains a mixture formed from reconstitute calcium chloride dihydrate solution with human thrombin lyophilized and The blue syringe which contains a mixture formed from reconstitute synThetic aprotinin solution with sealer protein concentrate lyophilized were placed in especial disposable device to mix all components of fibrin glue with each oTher (figures 3-20, 3-21, 3-22, 3-23).

Figure 3-20: Photographic picture showing The compartments of fibrin glue (Baxter-Belgium)



Figures 3-21, 3-22, 3-23: Photographic picture showing The disposable plastic device for
mixing fibrin glue compositions (Baxter-Belgium)

3-9: Estimation of cerebral spinal fluid pressure

Generally, The best methods to diagnose any CSF leaks is accomplished by magnetic resonance cisternography (MRCG) and computerized tomography myelography (CTMG). Due to un availablilty of These techniques, monitoring of CSF pressure by using a caTheter as modified technique was depended to ensure There is no any CSF leaks where a small, flexible tube was placed and fixed on The calculated ruler and connected with spinal needle after insertion of it's in The subarachnoid space. The animal must be placed on one side and on one level. Additionally, The tube that's used to collect CSF should be placed in vertical position to The animal and spinal needle and left for short time to track changes in The CSF pressure (Figure 3-24) (Malgorzata *et al.*, 2019).

Figure 3-24: Photographic picture for estimation of CSF pressure

3-10: Collection of cerebral spinal fluid

The CSF was collected in this work under general anesThesia from cerebellomedullary cistern, which located at The back of The animal head. The main landmarks were depended to collect cerebrospinal fluid from cistern, included The external occipital protuberance, cranial aspect of The dorsal spine of The axis and The transverse processes of The atlas. noneTheless, after induction of general anesThesia The back of The neck

was shaved and disinfected. Then a spinal needle is inserted at The base of The skull, and into The spinal column, penetrating The dura mater and arachnoid membranes to The subarachnoid space. Then CSF will be escape or leak through a spinal needle into sterile plain tube. About 5 ml was collected to made CSF analysis (Figure 3-25) (Kulkarni *et al.*, 2009).

Figure 3-25: Showing CSF collection

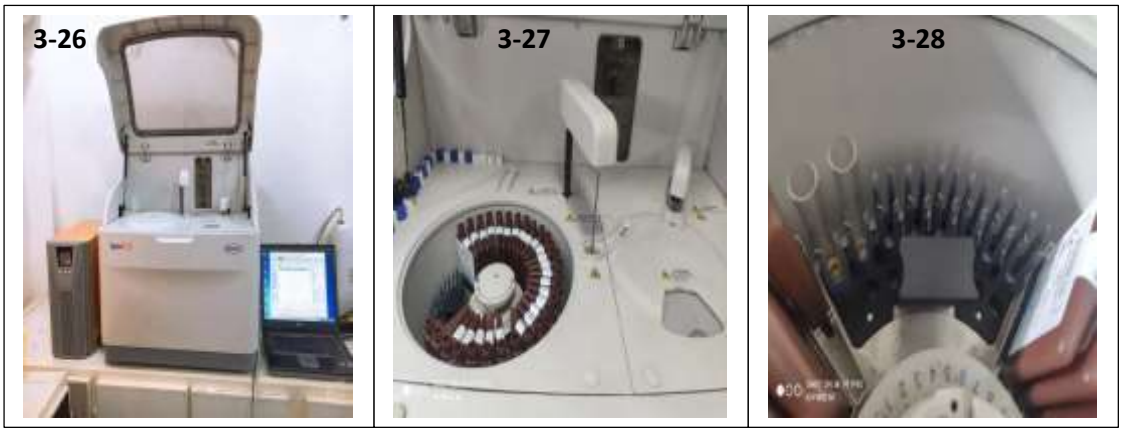
3-11: Cerebral spinal fluid analysis

The main components of The CSF adopted during The analysis of CSF to evaluate The efficiency of each type of The used grafted tissue work includes: level of protein and glucose with estimation The total cells count (Anna *et al.*,, 2021) .

3-11-1: Estimation of CSF glucose

1 ml of CSF was taken from The collected sample of CSF and putting in a sterile glass tube. Then, glass tube which contain CSF sample was placed inside a device spin 120 (Figures 3-26, 3-27, 3-28). The reagent that’s used in this study to estimate The level of CSF glucose called, glucose spin reagent (Figure 3-29). The reaction between The sample of

CSF and glucose spin reagent will be provide The data of analysis (Weber *et al.*, 2012).



Figures 3-26, 3-27, 3-28: Photographic picture showing device spin 120 (Spinreact- WK-81105776- Germany).

Figure 3-29: Photographic picture showing glucose spin reagent (spinreact- 17176- Spain)

3-11-2: Estimation of CSF protein

The device which used in this work to estimate The level of CSF protein is called, The device Fujifilm (Figures 3-30, 3-31). However, 1 ml of CSF was putting in The eppendorf tube. Then, a disposable fuji dri-chem slide (Figure 3-32). and auto tips (Figure 3-33). with eppendorf tube which contains The sample of CSF were put in The device Fujifilm (Figure 3-34).

The chemical reaction between CSF sample and fuji dri-chem slide will give The end result of analysis (Roerig *et al.*, 2013).

Figures 3-30, 3-31: Photographic picture showing The device Fujifilm (Fujifilm corporation- 67156826- Japan)

Figure 3-32: Photographic picture showing the fuji dri-chem slide (Fujifilm – 1850- Vietnam)

Figure 3-33: Photographic picture showing auto tips (Fujifilm – 1850- Vietnam)

Figure 3-34: Photographic picture showing auto tips( ), fuji dri-chem slide( ) and eppendorf tube( )

3-11-3: Estimation of CSF total cells count

To estimate total cells count of CSF, hemocytometer chamber was used. Each chamber was composed from 5 mini chambers as square shape, 4 peripheral and 1 central (figure 3-35). To read white cells (lymphocyte, monocyte, neutrophils and eosinophils) 25micron of CSF sample was applied on 1 peripheral mini chamber with addition to its 75micron of new methylene blue. Then, The sample was left for 10 minutes to fix and Then The hemocytometer chamber washing by tap water and left The sample to dry. After that, 25 microns of oily drop was applied on The chamber with putting cover slide. The results were recorded under microscope using lens with power (100x). While, The central mini chamber was used to read only The red cells, here The methylene blue didn't used (only The CSF sample) (Hachiro *et al.*, 2007)

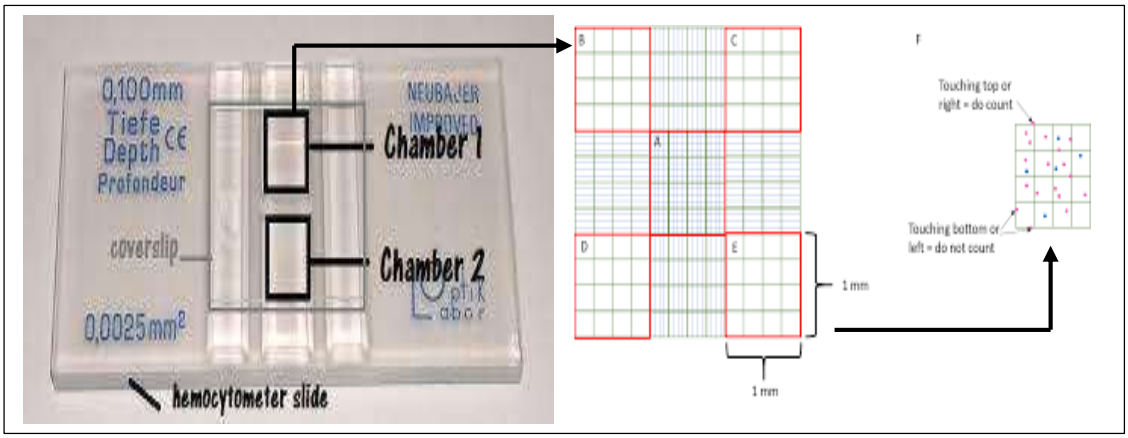


Figure 3-35: Iluustration showing hemocytometer chamber

3-12: Assessment of meningeal defect healing

The assessment of meningeal defect healing was depended on The following parameters after euthanizing all animals by giving high dose of anesThesia as follow:

A-Observations of clinical signs daily post operation especially that's related to The central nervous system.

B-Study gross and histopathological changes at 15th, 30th and 60^{h} postoperative days with statistical analysis of histological scoring. Specimens of The graft area with The cortex of The brain were obtained on The 15th, 30th, and 60th days after euthanizing three animals of each group in each period for macroscopic observation, and histopathological evaluation where The samples fixed in 10% formalin and stained with hematoxylin and eosin (H&E) stain.

The histopathological scores were analyzed statistically by pathologist using Kruskal-Wallis One Way Analysis of Variance on Ranks test and used Pairwise Multiple Comparison Procedures (Tukey Test) at $p \leq 0.05$. We used Sigma Plot software program for statistical analysis.

The histological sections were scored according to The following criteria (Sultana *et. al.*, 2009; Gupta and Kumar, 2015).

1-Intensity of granulation tissue.

2-Intensity of Angiogenesis.

3-Intensity of inflammatory reaction.

Table 3-1: Showing The histopathological scoring

Criteria	1	2	3	4
Granulation tissue	Absent	Discrete	Moderate	Intense
Angiogenesis	Absent	Discrete	Moderate	Intense
Severity of inflammation	Sever	Moderate	Few	Absent

C- Study The level of protein, glucose, and total cells count of spinal fluid with cerebral spinal fluid pressure in all groups at 15^{th}, 30^{th} and 60^{th} postoperatively also. The level of protein, glucose, and total cells count with cerebral spinal fluid pressure were analyzed statistically by One Way Anova with utilized post hoc Duncan's multiple comparison at $p \leq 0.05$.

Chapter Four

Results

4-1: Clinical signs

The site of operation externally in all animals was suffered from swelling post operation. The swelling was disappeared within The first week postoperatively. However, all animals were stilled alive without appearance of any complications especially that's related to The development of abnormal nervous signs. In addition, The animals were eaten and drink water normally and no any change in Their behavior was shown.

4-2: Gross changes

In all animals, The site of craniectomy externally was occluded completely with connective tissue during all periods of The study. In addition, no any CSF leak was noticed at The site of craniectomy postoperatively. At The end of The study, The dural defect was closed completely in all animals internally where all types of The grafted tissues sealed with The host meninges that prevent leaks of CSF (Figures 4-1- 4-24).

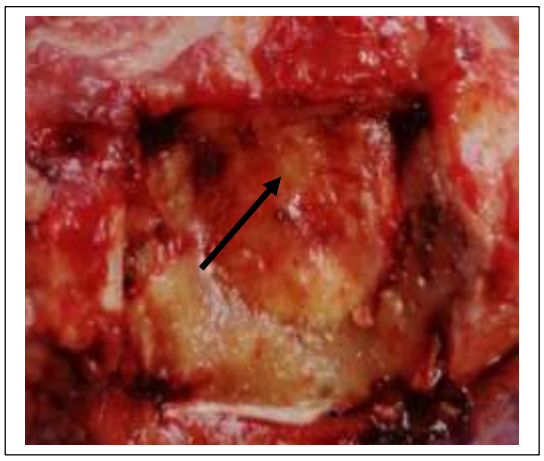


Figure 4-1: Photographic picture showing the closing of site of meningeal defect on15th POD in G1in external part (Fascia of temporalis muscle as autograft)

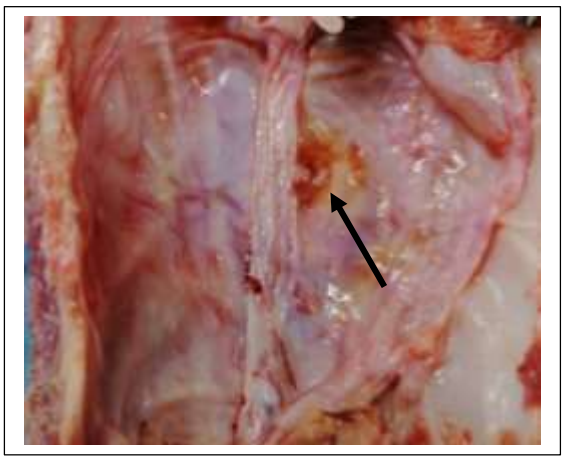


Figure 4-2: Photographic picture showing the closing the site of meningeal defect after 15th POD in G1 in the internal part

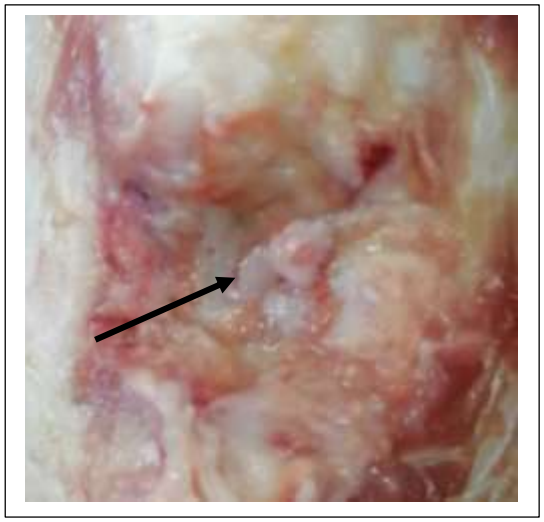


Figure 4-3: Photographic picture showing closing the site of meningeal defect on 30th POD in G1 from external part

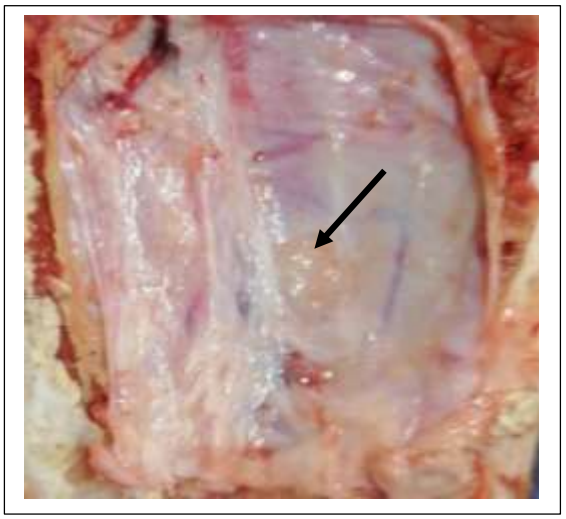


Figure 4-4: Photographic picture showing the closing site of meningeal defect after 30th POD in G1 in the interal part

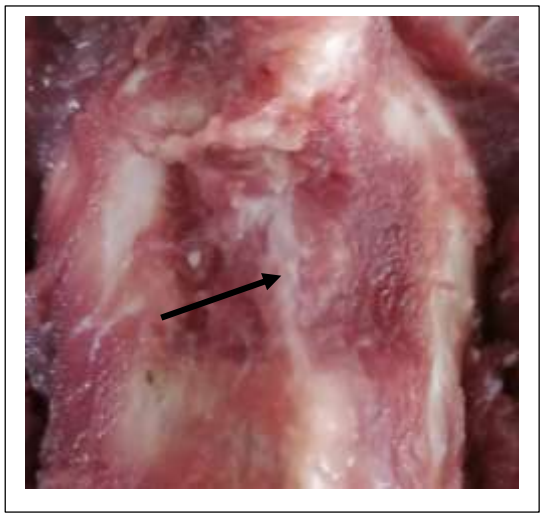


Figure 4-5: Photographic picture showing complet closing the external site of operation after 60th POD in G1

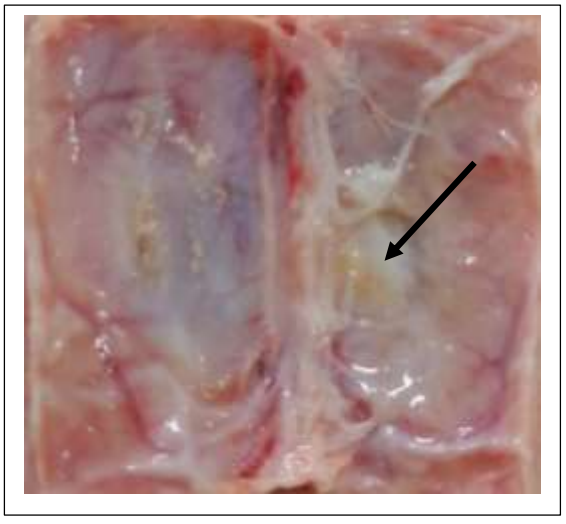


Figure 4-6: Photographic picture showing the complet closing site of meningeal defect after 60th POD in G1

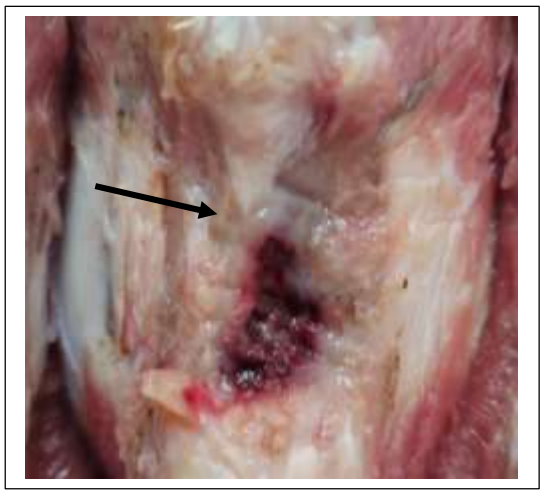


Figure 4-7: Photographic picture showing the complet closing the external site of operation after 15th POD in G2 (Peritoneum as autograft)

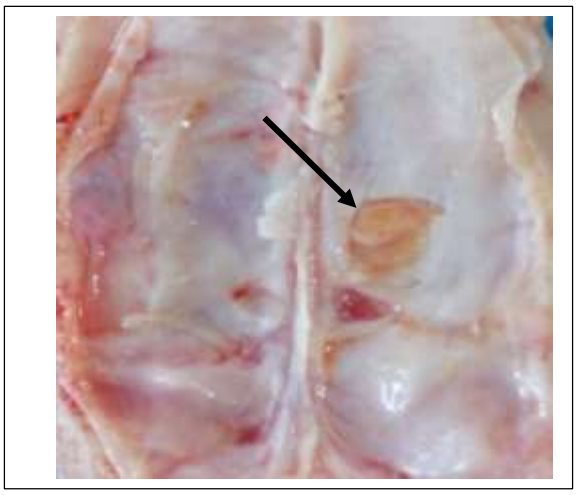


Figure 4-8: Photographic picture showing the complet closing the site of meningeat defect after 15th POD in G2 from internat part

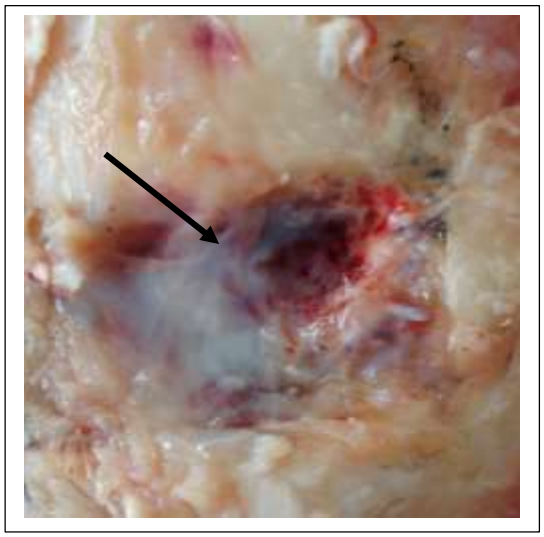


Figure 4-9: Photographic picture showing the complet closing of external part for the site of operation after 30th POD in G2

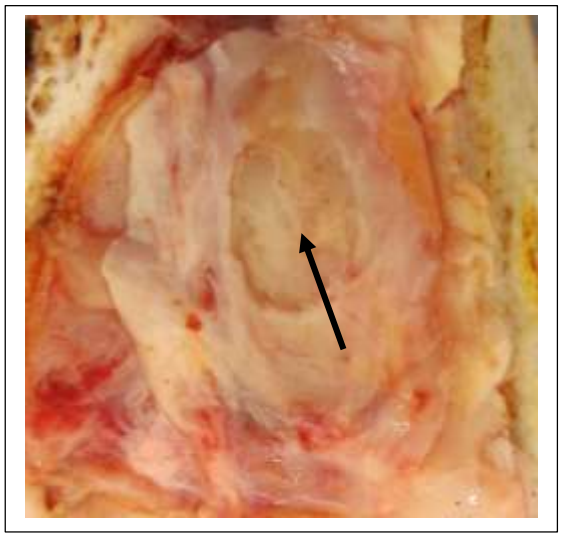


Figure 4-10: Photographic picture showing complet closing the internal part in the site of meningeal defect after 30th POD in G2

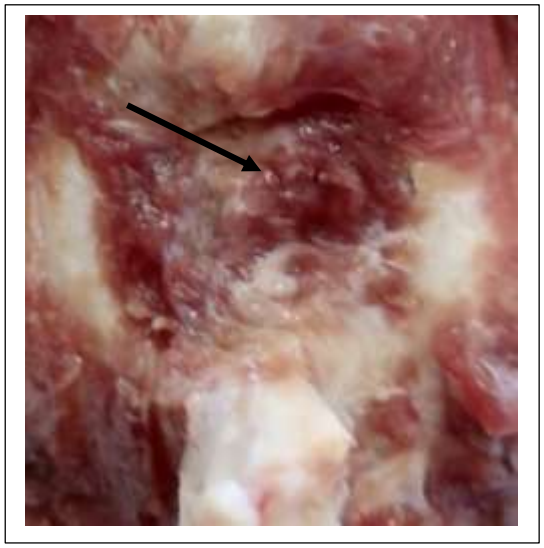


Figure 4-11: Photographic picture showing the complet closing the site of operation after 60th POD in G2

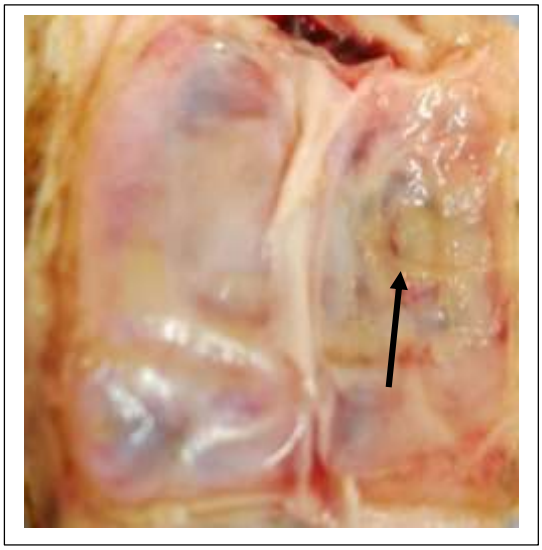


Figure 4-12: Photographic picture showing the complet closed the site of meningeal defect after 60th POD in G2

Figure 4-13: Photographic picture showing the closed the site of operation after 15th POD in G3 from external part (Acellular of ovine esophageal mucosa as xenograft)

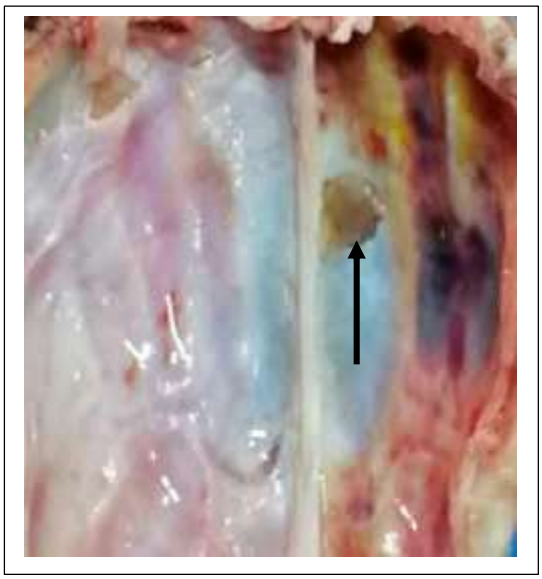


Figure 4-14: Photographic picture showing the closing internal part of meningeal defect after 15th POD in G3

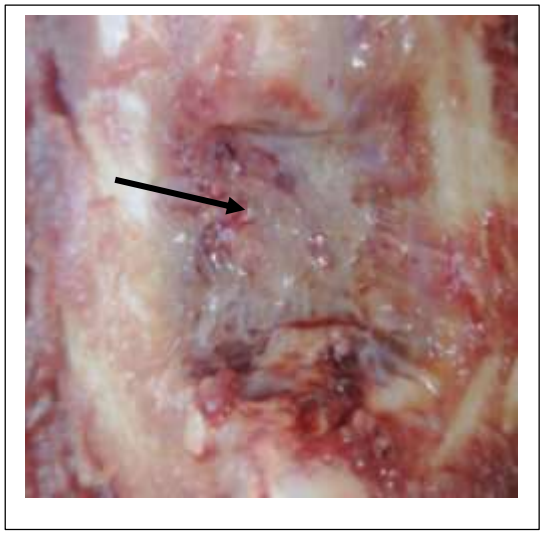


Figure 4-15: Photographic picture showing the complet closing the site of operation after 30th POD in G3

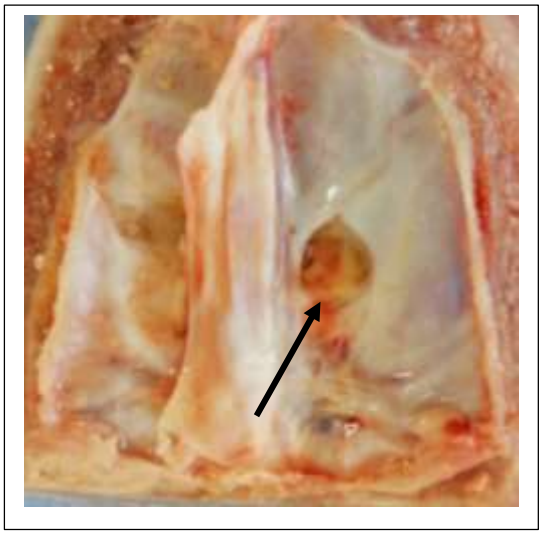


Figure 4-16: Photographic picture showing the closed the internal site of meningeal defect after 30th POD in G3

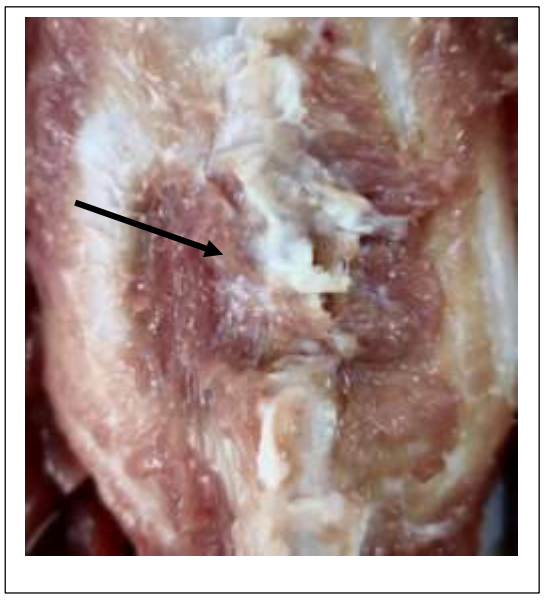


Figure 4-17: Photographic picture showing the complet closed the site of operation after 60th POD in G3

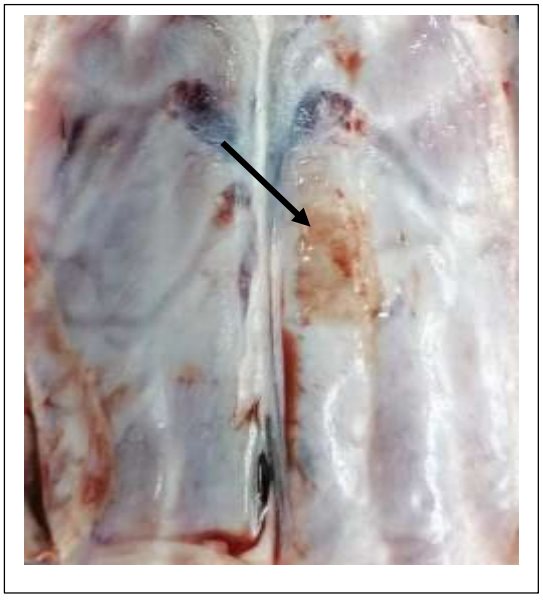


Figure 4-18: Photographic picture showing the complet closed the site of meningeal defect after 60th POD in G3

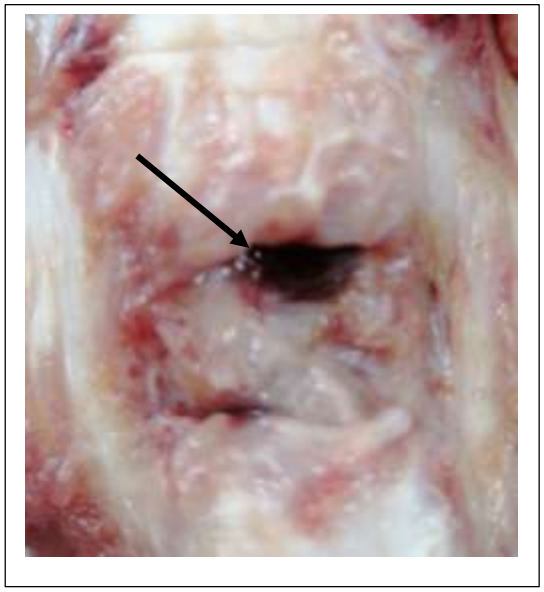


Figure 4-19: Photographic picture showing the closing of operation after 15th POD in G4 from external part (Lyophilized bovine pericardium as xenograft)

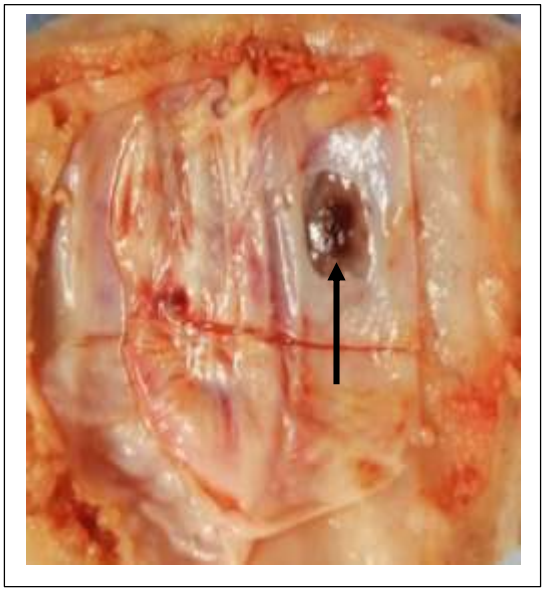


Figure 4-20: Photographic picture showing the site of meningeal defect after 15th POD in G4 from internal part

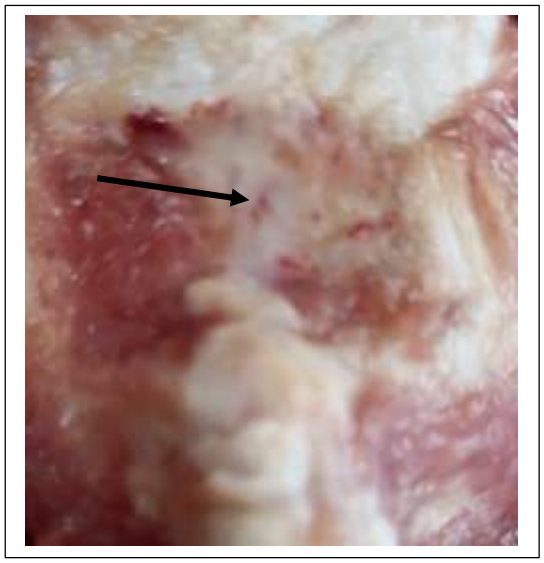


Figure 4-21: Photographic picture showing closed the site of operation after 30th POD from external part in G4

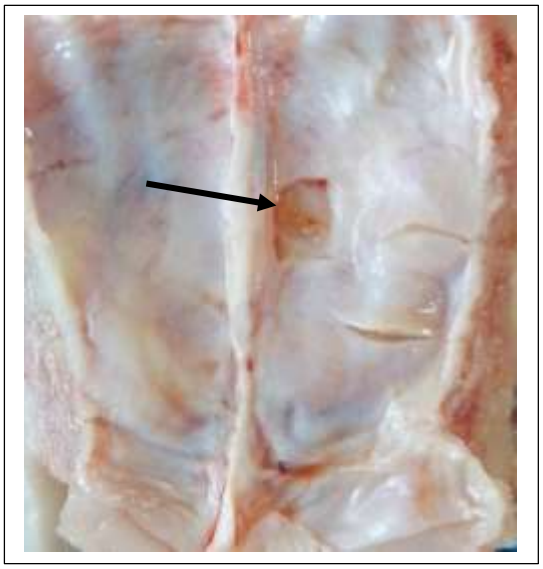


Figure 4-22: Photographic picture showing closed the site of meningeal defect after 30th POD in G4 in the internal part

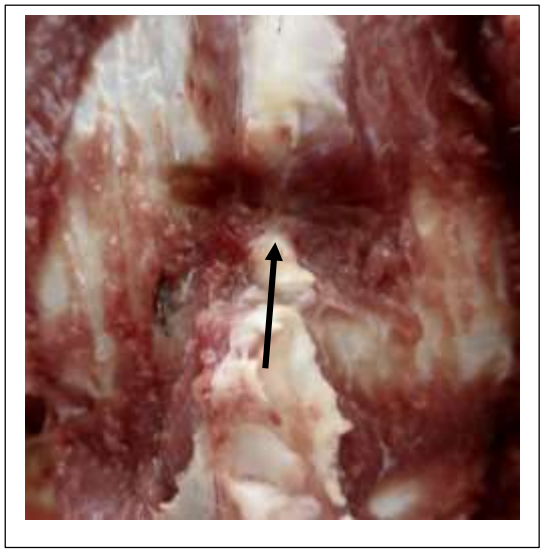


Figure 4-23: Photographic picture showing the complet closing the site operation after 60th POD in G4 from external

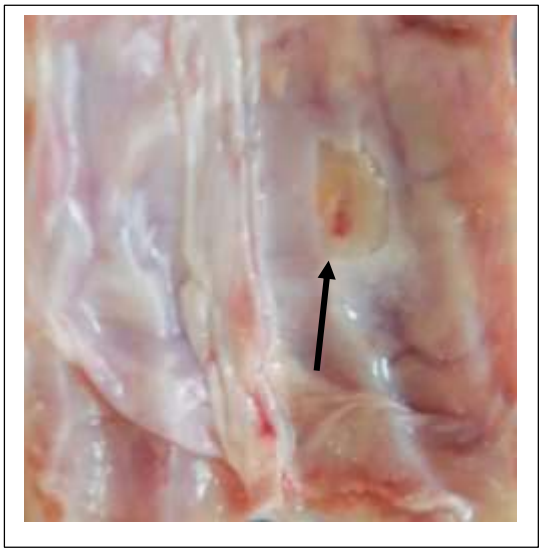


Figure 4-24: Photographic picture showing the closing the site of meningeal defect after 60th POD in G4 from internal part

4-3: Histopathological changes

In The fascia of temporalis mucle group one, The histopathological section at The grafting site after 15th POD was characterized by proliferation of granulation tissue, newly blood vessels formation and infiltration of inflammatory cells with deposition of eosinophilic proteinaus material within The connective tissue (Figures 4-25,4-26,4-27). At 30th POD, The histopathological changes showed maturation of granulation tissue, newly blood vessels and reduction in The

infiltration of inflammatory cells (Figures 4-28,4-29,4-30). At 60th POD, The histopathological section was revealed more granulation tissue maturation with infiltration of inflammatory cells, mild angiogenesis and some area of

fibrin glue remnant with presence of foreign body giant cell (Figures 4-31,4-32,4-33,4-34). Normal histological architecture of brain cortex section during all period of The study was shown (Figure 4-35).

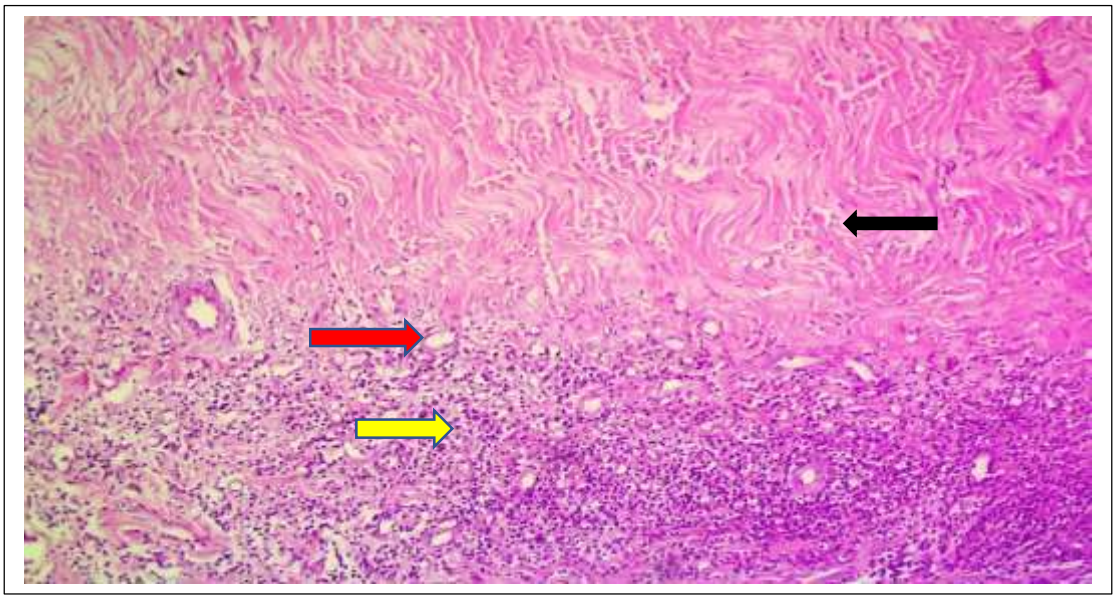


Figure 4-25: Micrograph at 15th POD in G1 shows proliferation of granulation tissue (black arrow), newly blood vessels (red arrow) and infiltration of inflammatory cells (yellow arrow). (H&E.100X)

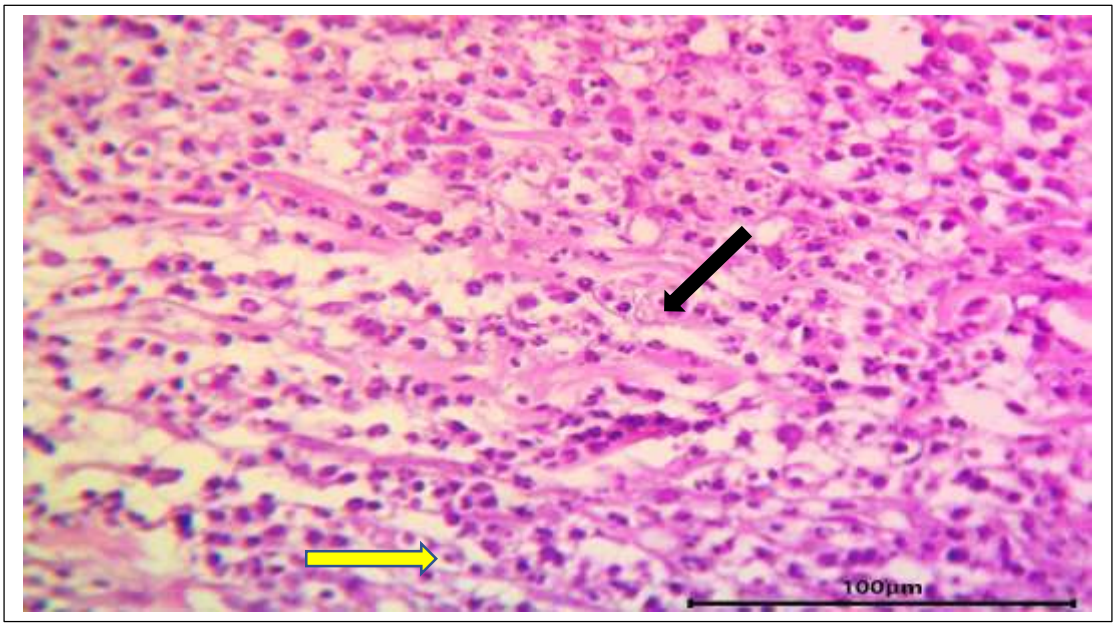


Figure 4-26: Micrograph at 15th POD in G1 shows proliferation of granulation tissue (black arrow) and infiltration of inflammatory cells (yellow arrow). (H&E.400X)

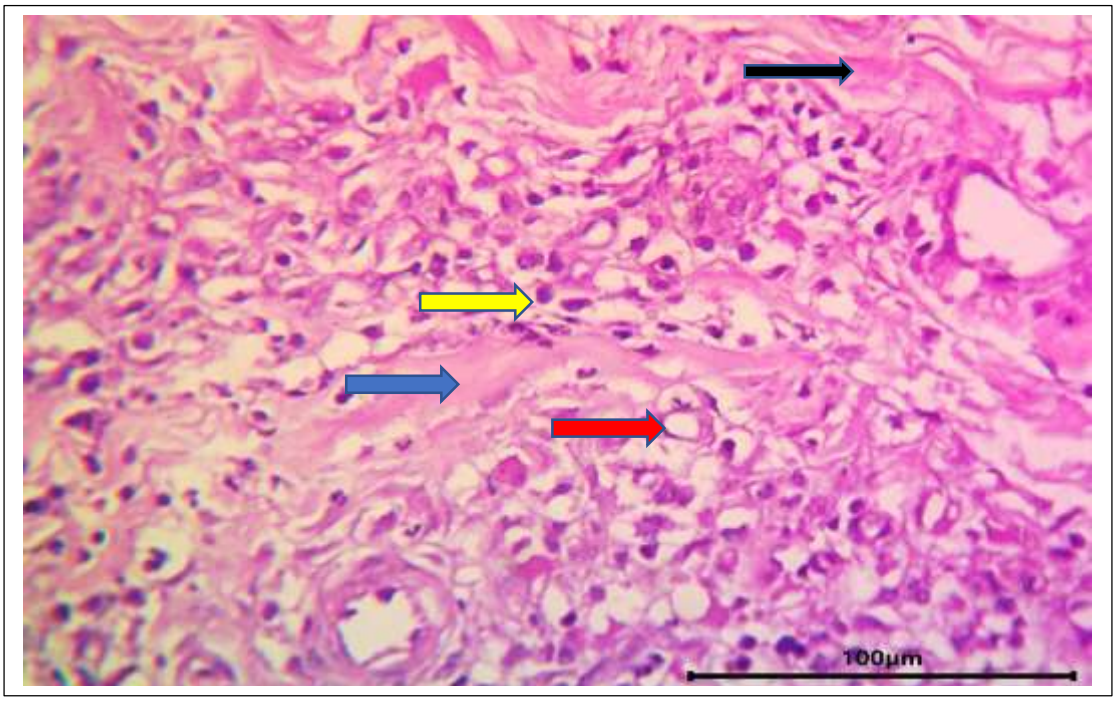


Figure 4-27: Micrograph at 15th POD in G1 shows proliferation of granulation tissue (black arrow), newly blood vessels (red arrow), diffused infiltration of inflammatory cells (yellow arrow) and deposition of proteinitious material (blue arrow). (H&E.400X)

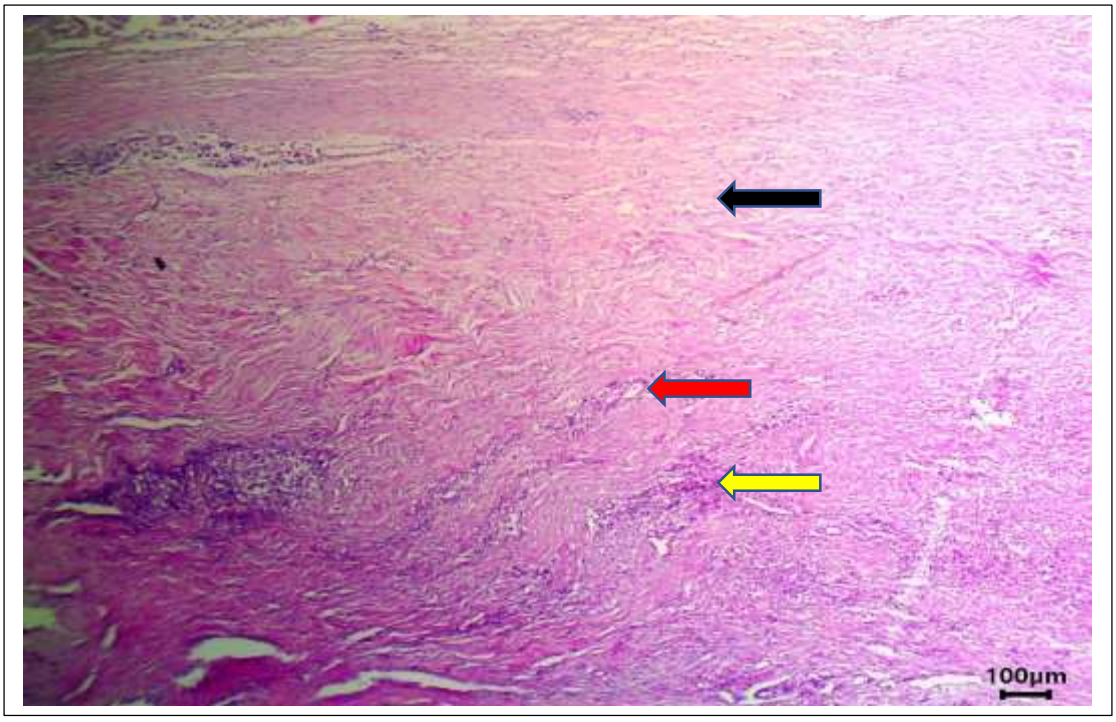


Figure 4-28: Micrograph at 30th POD in G1 shows maturation of granulation tissue (black arrow), newly blood vessels (red arrow) and reduction of inflammatory cells infiltration (yellow arrow). (H&E.40X)

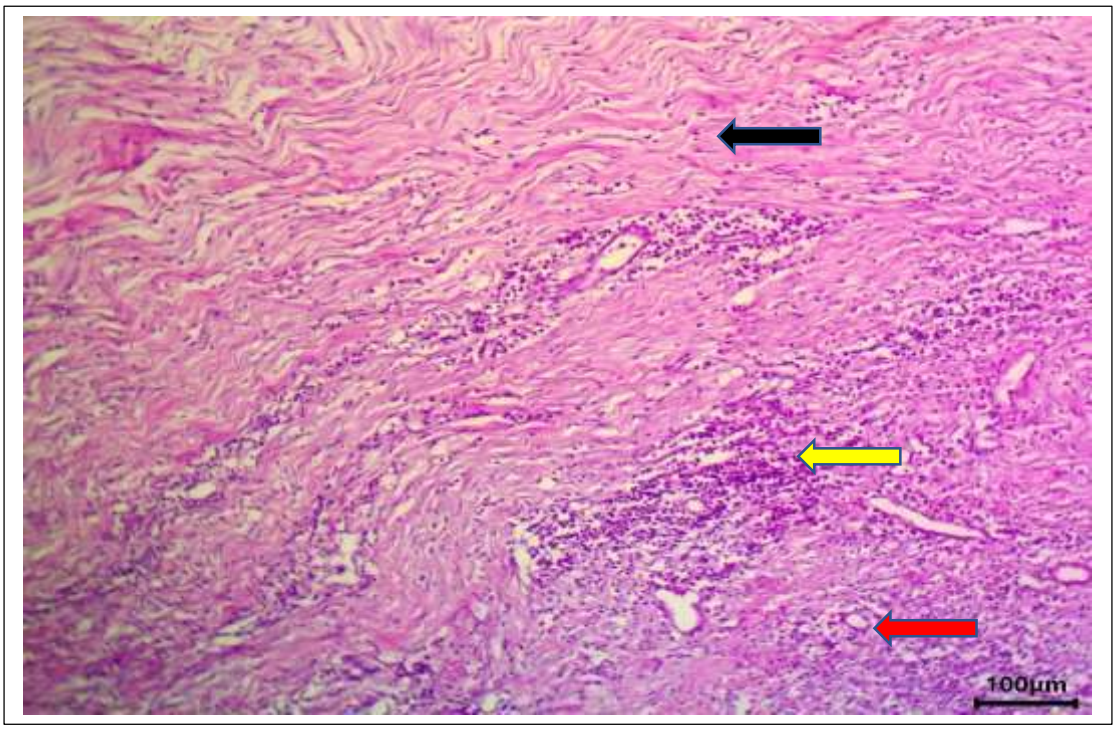


Figure 4-29: Micrograph at 30th POD in G1 shows maturation of granulation tissue (black arrow), newly blood vessels (red arrow) and infiltration of inflammatory cells (yellow arrow). (H&E.100X)

Figure 4-30: Micrograph at 30th POD in G1 shows maturation of granulation tissue (black arrow) and infiltration of inflammatory cells (yellow arrow). (H&E.400X)

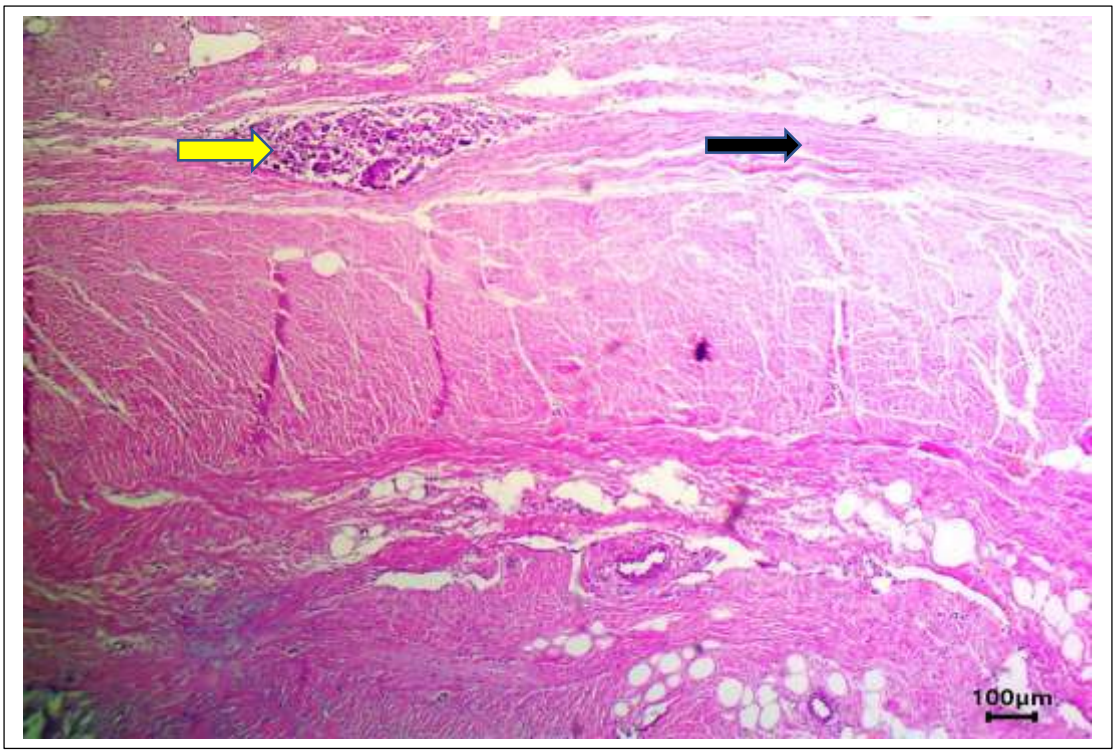


Figure 4-31: Micrograph at 60th POD in G1 shows maturation of granulation tissue (black arrow) and remnant of fibrin glue (yellow arrow). (H&E.40X)

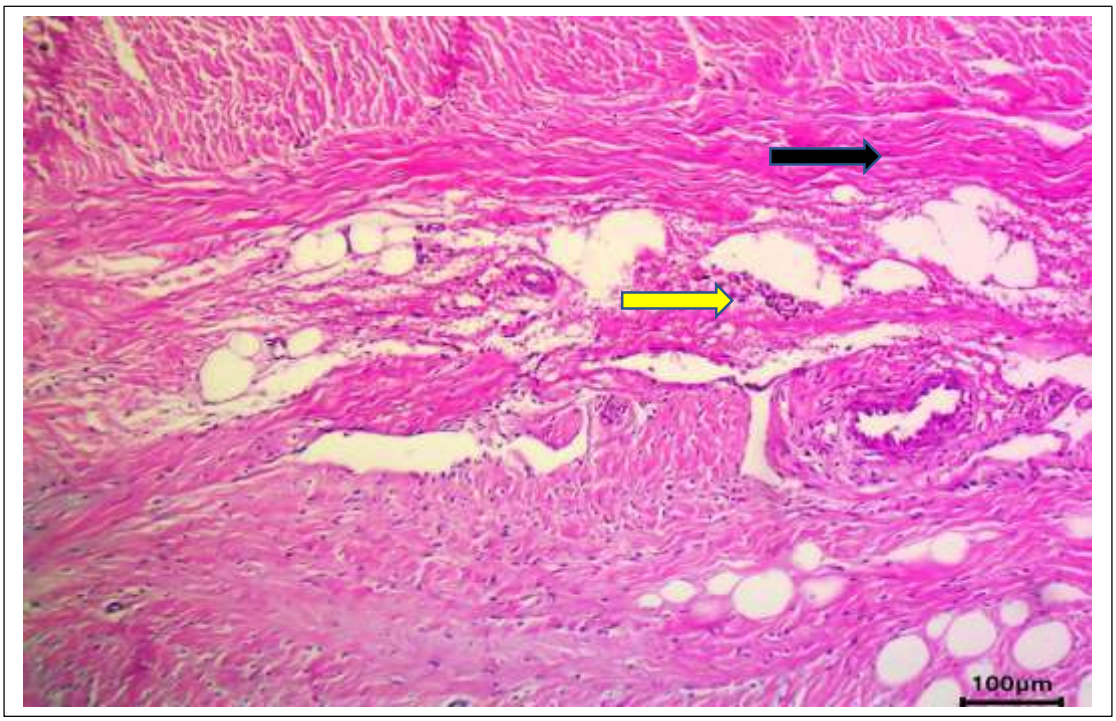


Figure 4-32: Micrograph at 60th POD in G1 shows maturation of granulation tissue (black arrow) and few number of infiltration of inflammatory cells (yellow arrow). (H&E.100X)

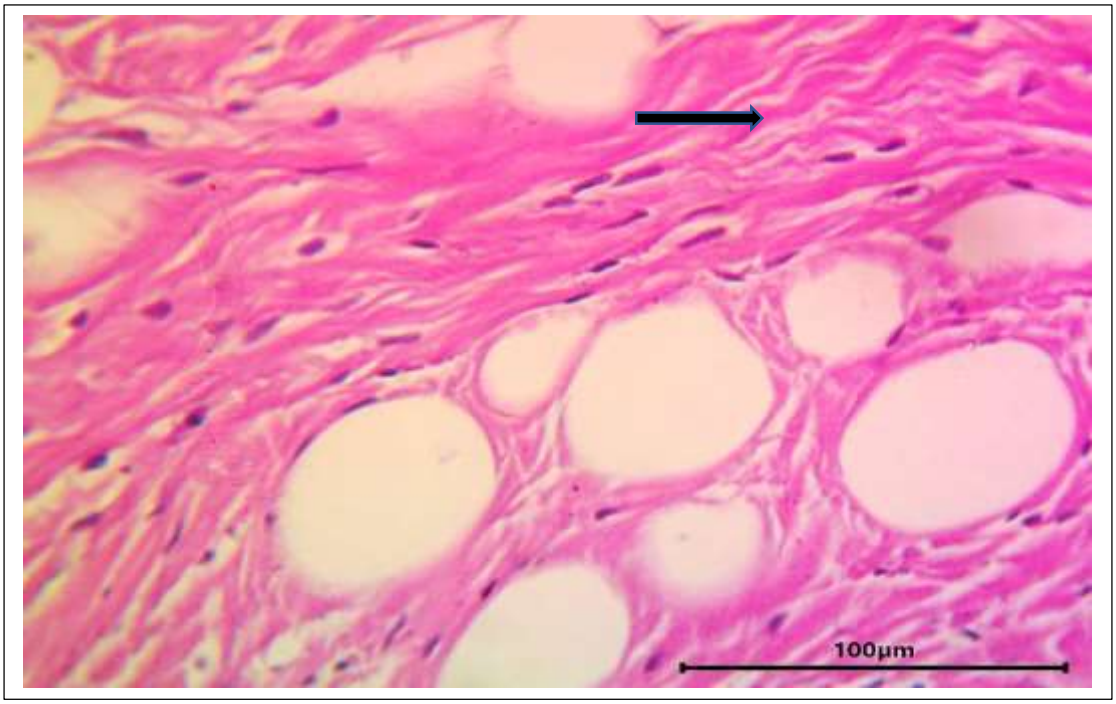


Figure 4-33: Micrograph at 60th POD in G1 shows mature granulation tissue (black arrow). (H&E.400X)

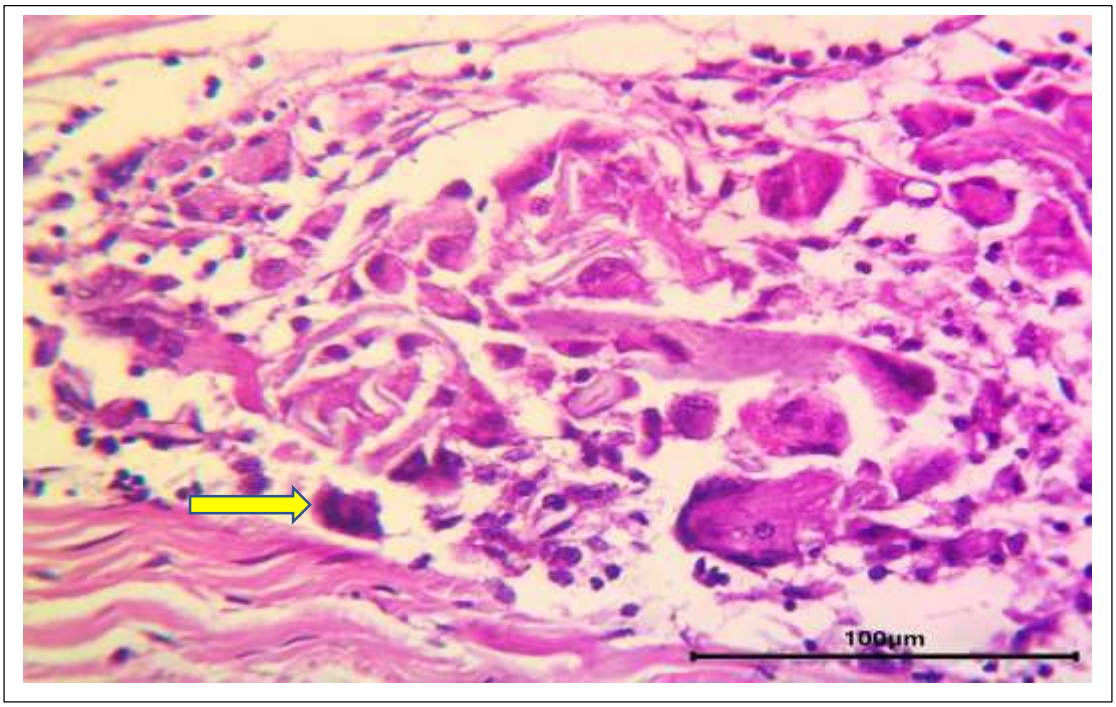


Figure 4-34: Micrograph at 60th POD in G1 shows foreign body giant cell (yellow arrow) (H&E.400X)

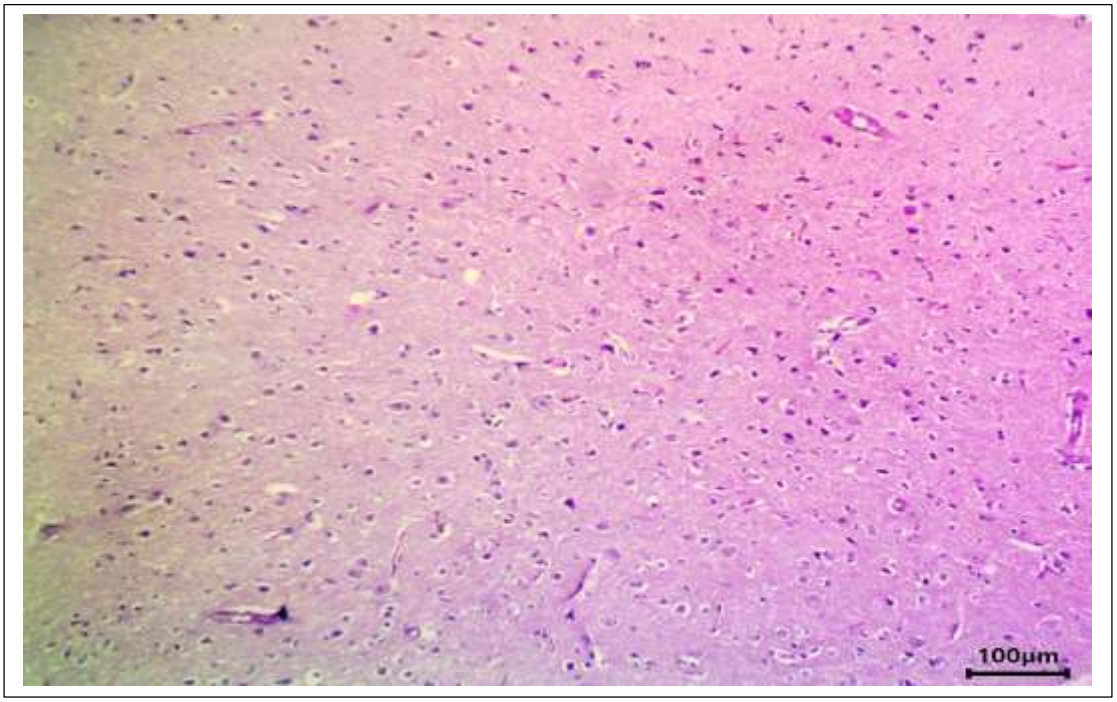


Figure 4-35: Micrograph at 60th POD in G1 shows normal braine cortex, neurons and glial cells (H&E.100X)

In The peritoneum group two, The histological section at The grafting site after 15th POD was characterized by formation of granulation tissue, sever inflammatory cells infiltration, more angiogenesis and deposition of eosinophilic protaintious materials within The proliferative connective tissue (Figures 4-36,4-37,4-38). At 30th POD, There are maturation in The granulation tissue, pronounced angiogenesis and reduction in The inflammatory cells' infiltration (Figures 4-39,4-40). At 60th POD, The histopathological section was showed mature granulation tissue, very few infiltrations of inflammatory cells and angiogenesis (Figures 4-41,4-42). In addition, There was normal histological architecture of brain cortex was showed during all period of The study also (Figure 4-43).

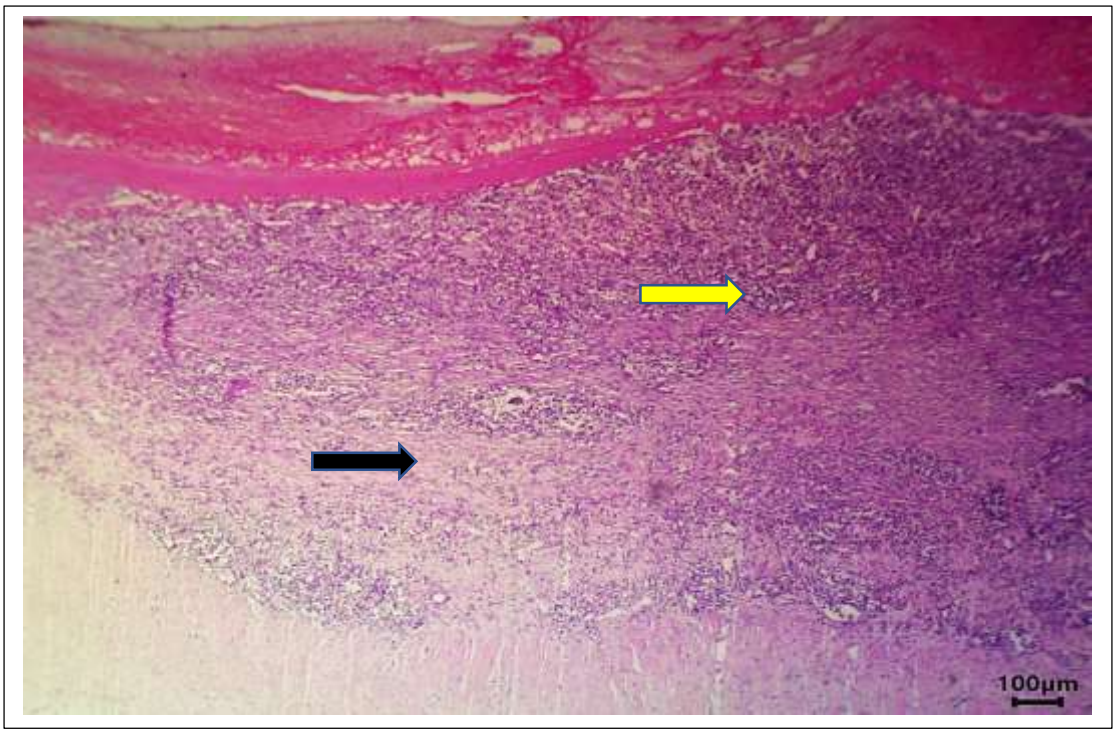


Figure 4-36: Micrograph at 15th POD in G2 shows proliferation of granulation tissue (black arrow) and sever infiltration of inflammatory cells (yellow arrow) (H&E.40X)

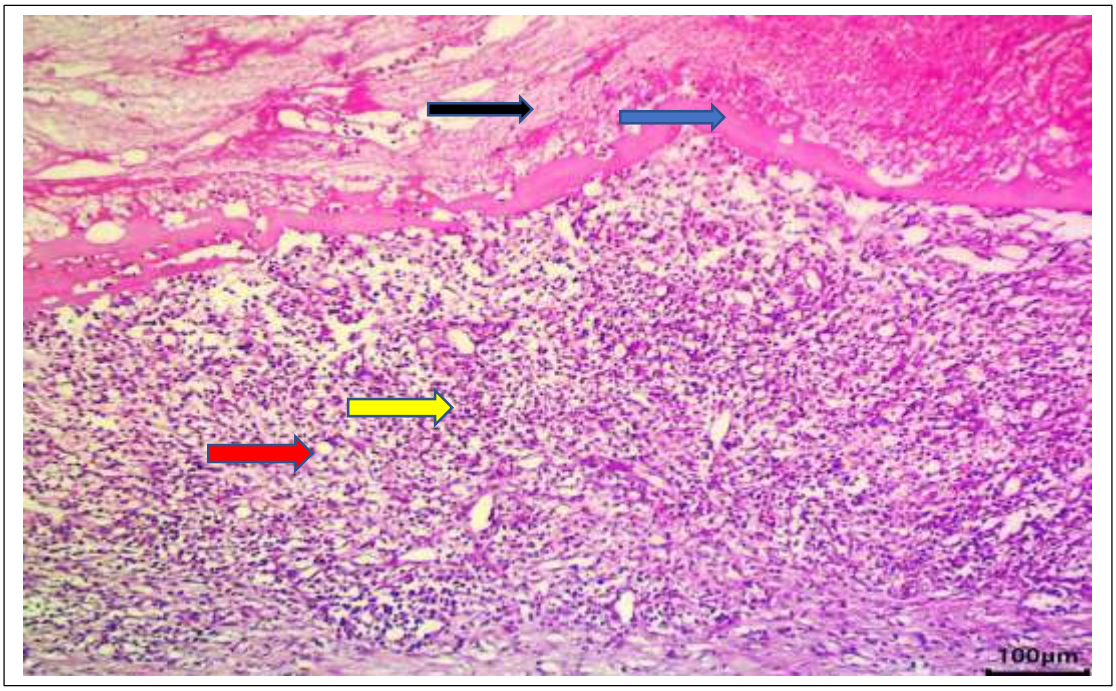


Figure 4-37: Micrograph at 15th POD in G2 shows proliferation of granulation tissue (black arrow), sever infiltration of inflammatory cells (yellow arrow), deposition of poteinitious material (blue arrow) and newly blood vessels (red arrow). (H&E.100X)

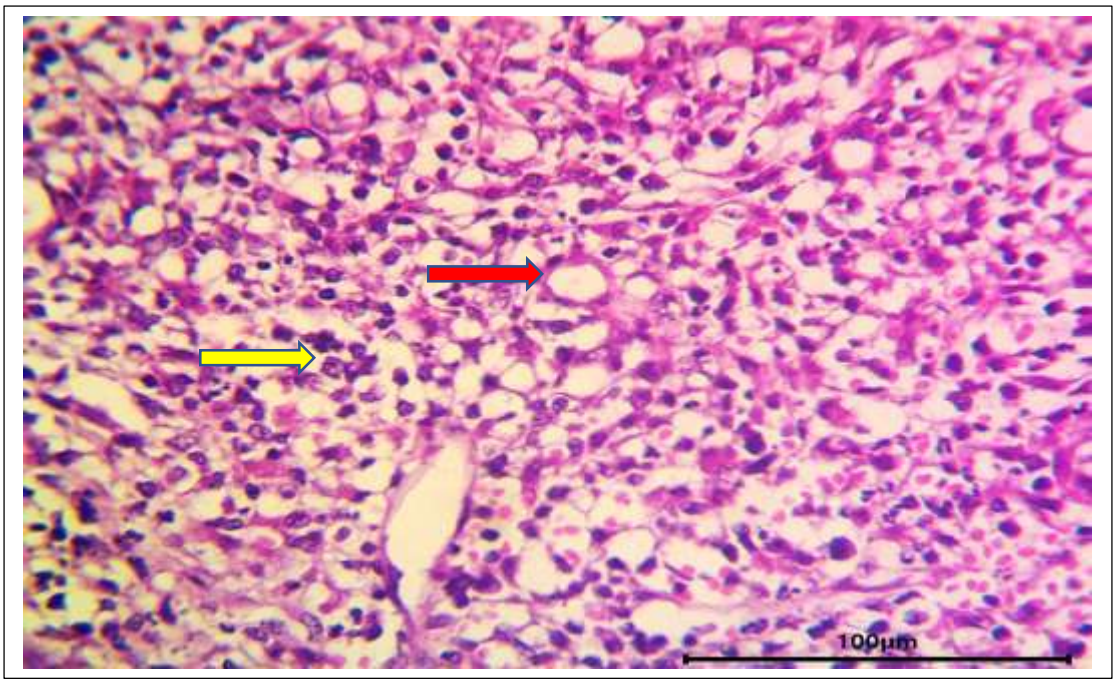


Figure 4-38: Micrograph at 15th POD in G2 shows infiltration of inflammatory cells (red arrow) and newly blood vessels (yellow arrow). (H&E.400X)

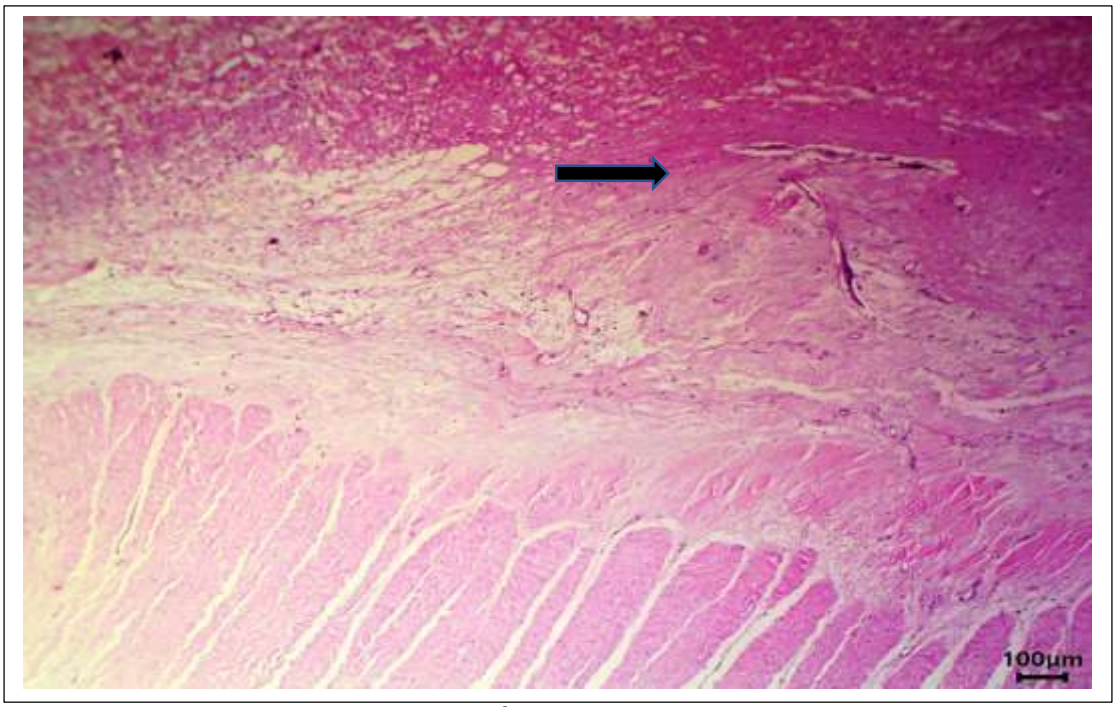


Figure 4-39: Micrograph at 30th POD in G2 shows maturation of The granulation tissue (black arrow) ((H&E.40X)

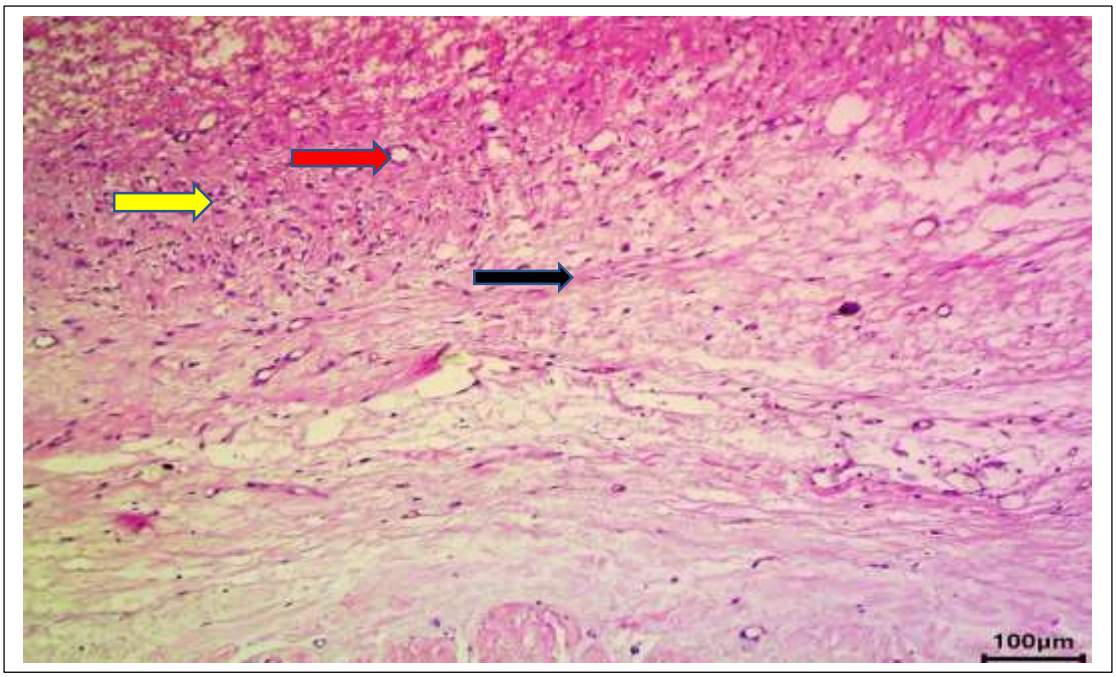


Figure 4-40: Micrograph at 30th POD in G2 shows mature granulation tissue (black arrow), angiogenesis (red arrow) and little infiltration of inflammatory cells (yellow arrow). (H&E.100X)

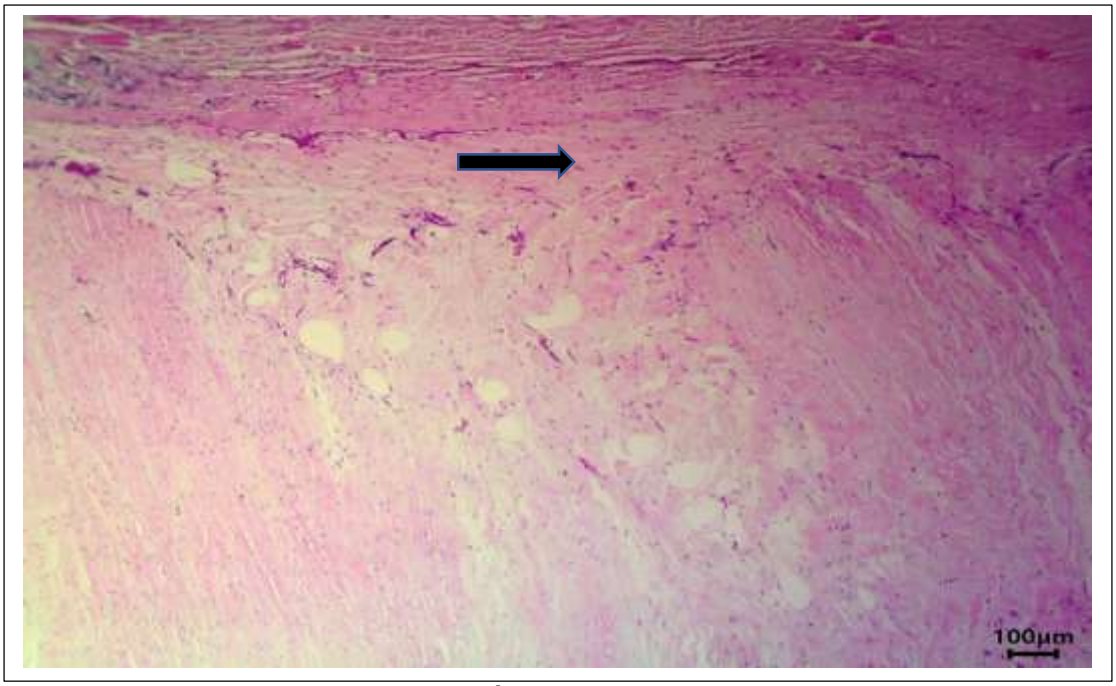


Figure 4-41: Micrograph at 60th POD in G2 shows mature granulation tissue (black arrow). (H&E.40X)

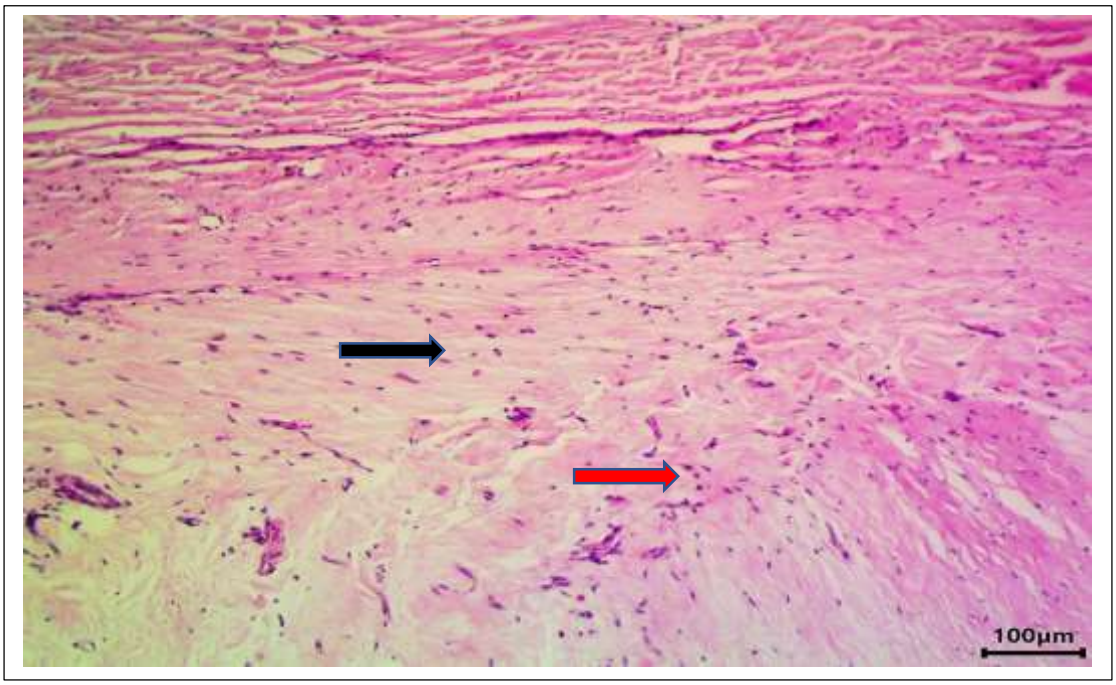


Figure 4-42: Micrograph at 60th POD in G2 shows mature granulation tissue (black arrow) and few infiltrations of inflammatory cells (red arrow). (H&E.100X)

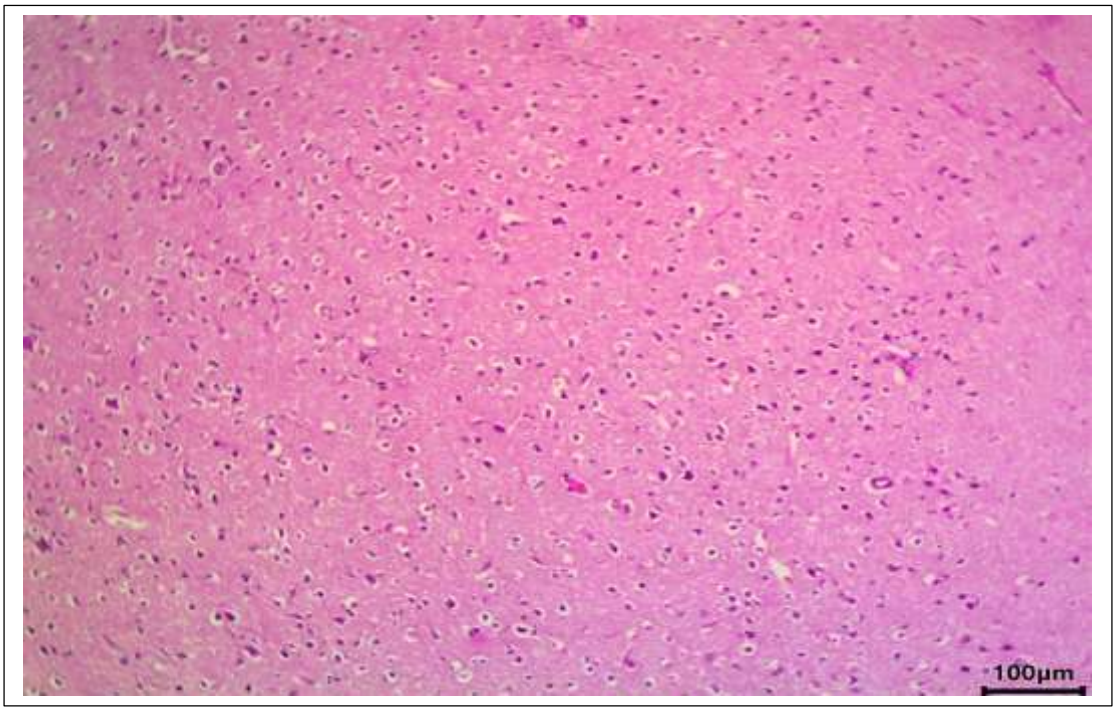


Figure 4-43: Micrograph at 60th POD in G2 shows normal brain cortex, neurons and glial cells (H&E.100X)

In The acellular ovine esophageal mucosa group three, The histological section at The grafting site after 15th POD was revealed proliferation of granulation tissue, sever inflammatory cells infiltration and newly blood vessels formation (Figures 4-44,4-45,4-46). At 30th POD, The histopathological sections were characterized by formation of granulation tissue, decrease in The inflammatory cells' infiltration and mild angiogenesis (Figures 4-47,4-48,4-49). At 60th POD, There were more maturation of granulation tissue with slight infiltration of inflammatory cells and few angiogenesis (Figure 4-50). In addition, There is normal histological architecture of brain cortex was showed during all period of The study also (Figure 4-51).

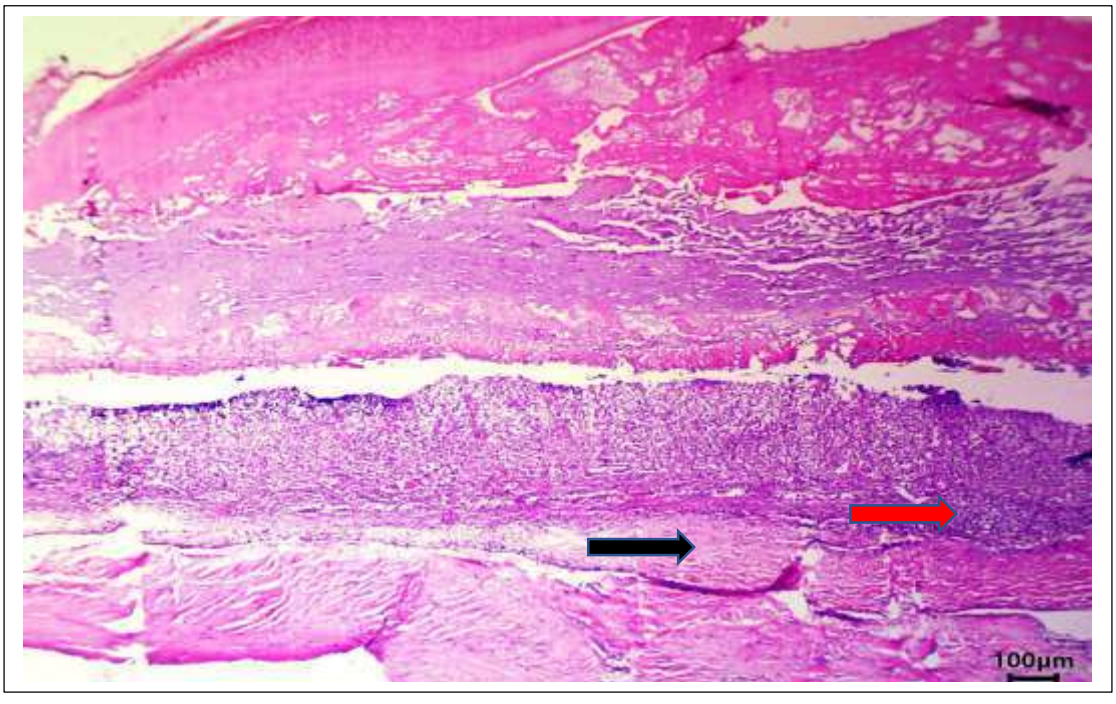


Figure 4-44: Micrograph at 15th POD in G3 shows proliferation of granulation tissue (black arrow) and sever infiltration of inflammatory cells (red arrow). (H&E.40X)

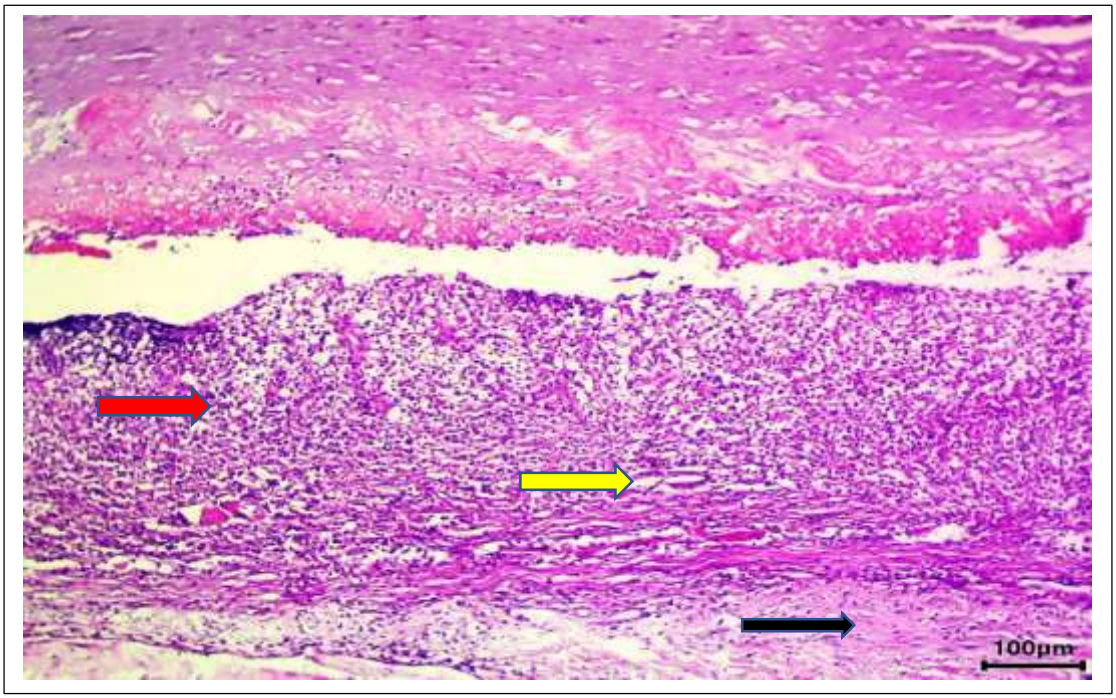


Figure 4-45: Micrograph at 15th POD in G3 shows sever infiltration of inflammatory cells (red arrow), granulation tissue (black arrow), newly blood vessels (yellow arrow) (H&E.100X)

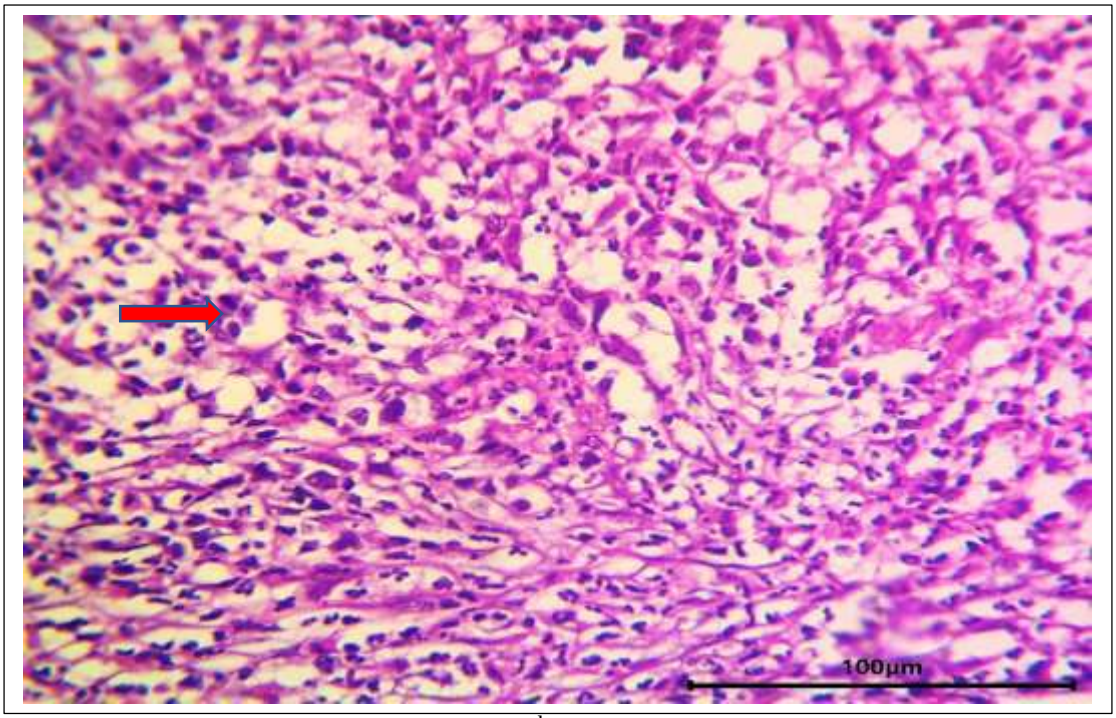


Figure 4-46: Micrograph at 15th POD in G3 shows infiltration of inflammatory cells (red arrow). (H&E.400X)

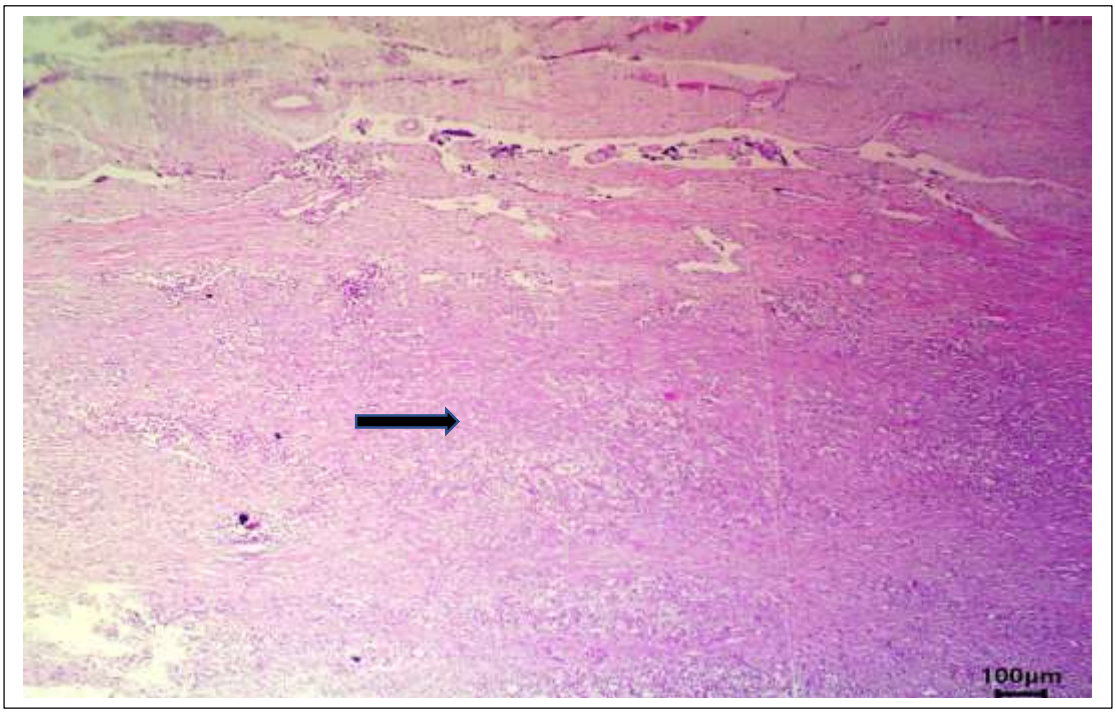


Figure 4-47: Micrograph at 30th POD in G3 show maturity of granulation tissue (black arrow). (H&E.40X)

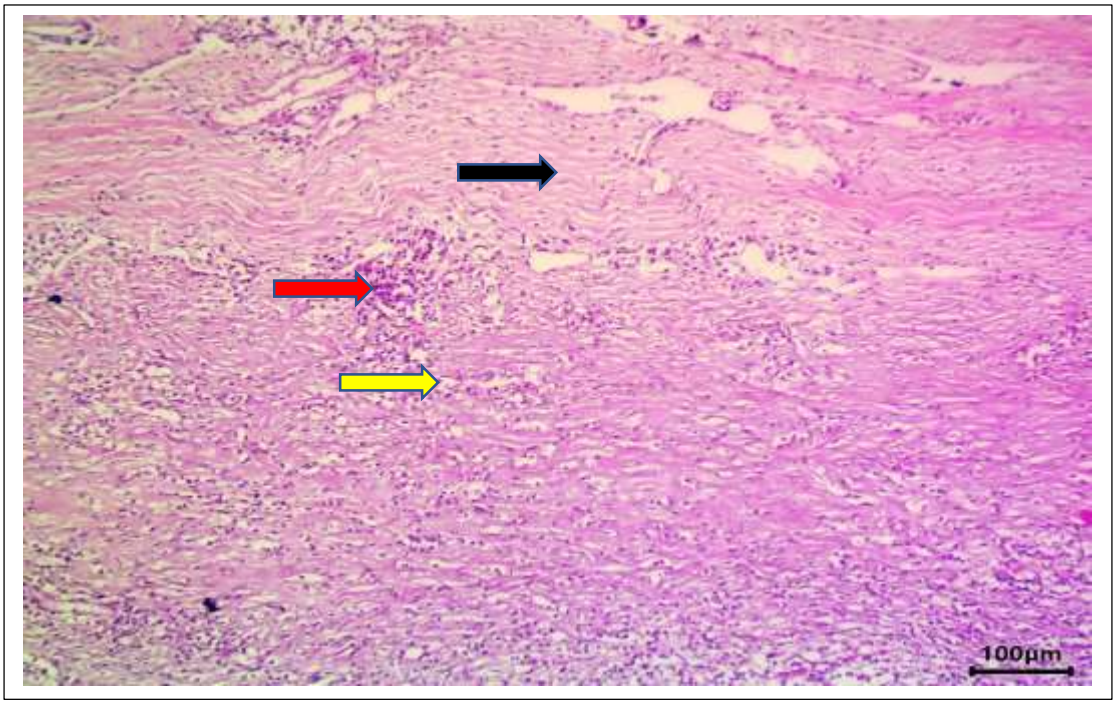


Figure 4-48: Micrograph at 30th POD in G3 shows maturity of granulation tissue (black arrow), infiltration of inflammatory cells (red arrow) and newly blood vessels (yellow arrow). (H&E.100X)

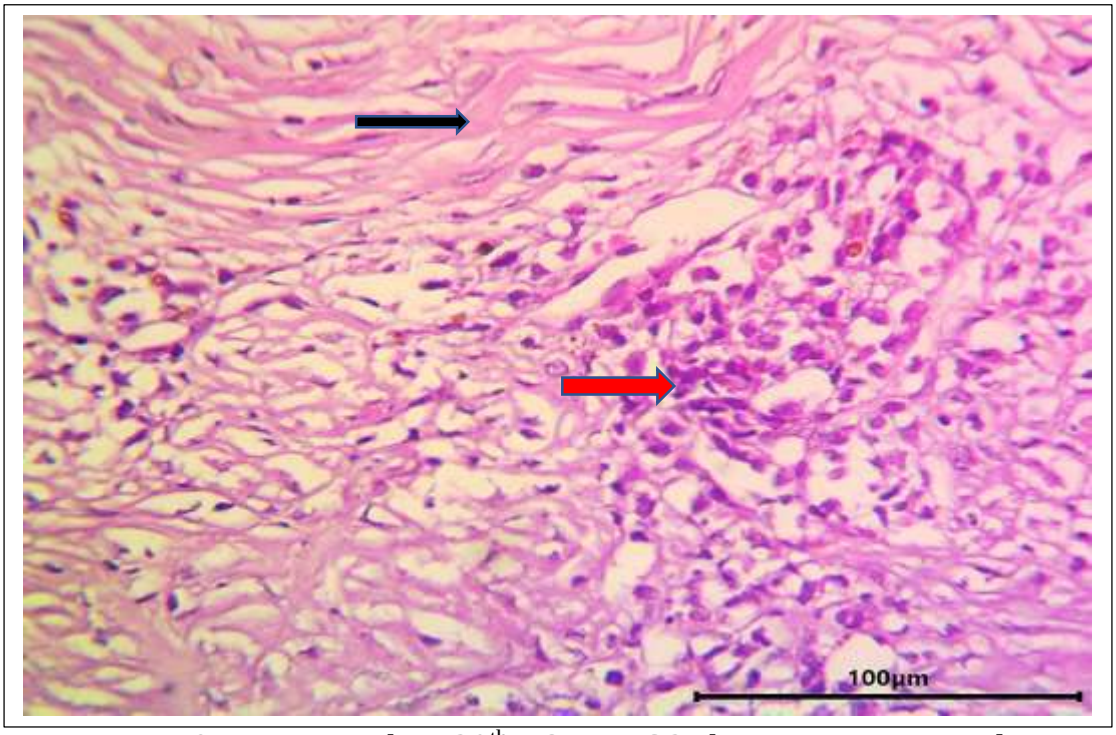


Figure 4-49: Micrograph at 30th POD in G3 shows mature granulation tissue (black arrow) and inflammatory cells (red arrow). (H&E.400X)

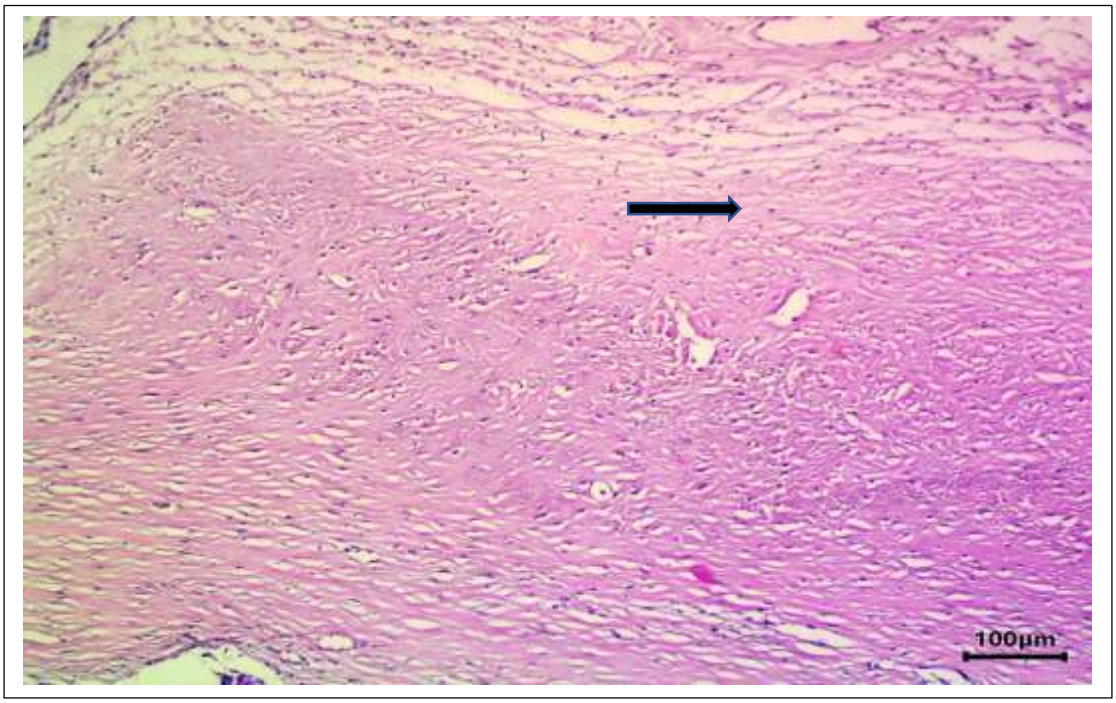


Figure 4-50: Micrograph at 60th POD in G3 shows mature granulation tissue (black arrow). (H&E.100X)

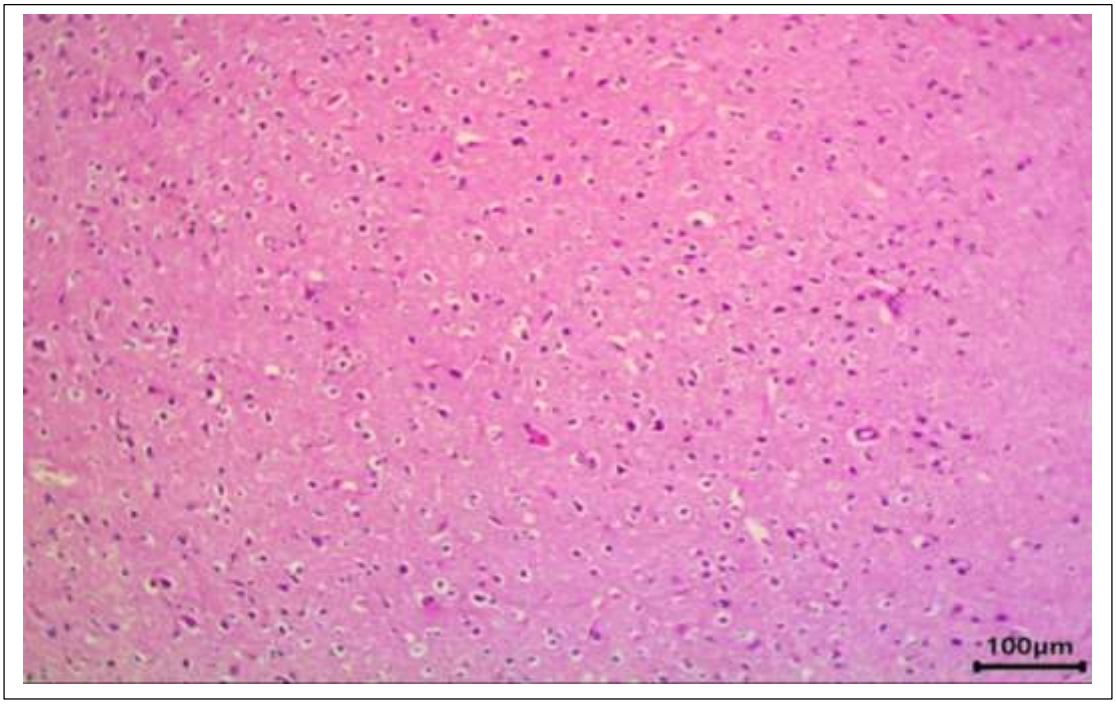


Figure 4-51: Micrograph at 60th POD in G3 shows normal brain cortex, neurons and glial cells . (H&E.100X)

In The lyophilized bovine pericardium group four, The histological section at The grafting site after 15th POD was characterized by proliferation of granulation, angiogenesis and few infiltrations of inflammatory cells (Figures 4-52,4-53,4-54). At 30th POD, There is more maturation of granulation tissue with very few infiltrations of inflammatory cells and angiogenesis with deposition of eosinophilic pretentious material within connective tissue (Figures 4-54,4-56,4-57,4-58). At 60th POD, The histopathological changes were characterized by increase in The granulation tissue maturity (Figures 4-59,4-60,4-61). Normal histological architecture of brain cortex was showed during all period of The study (Figure 4-62).

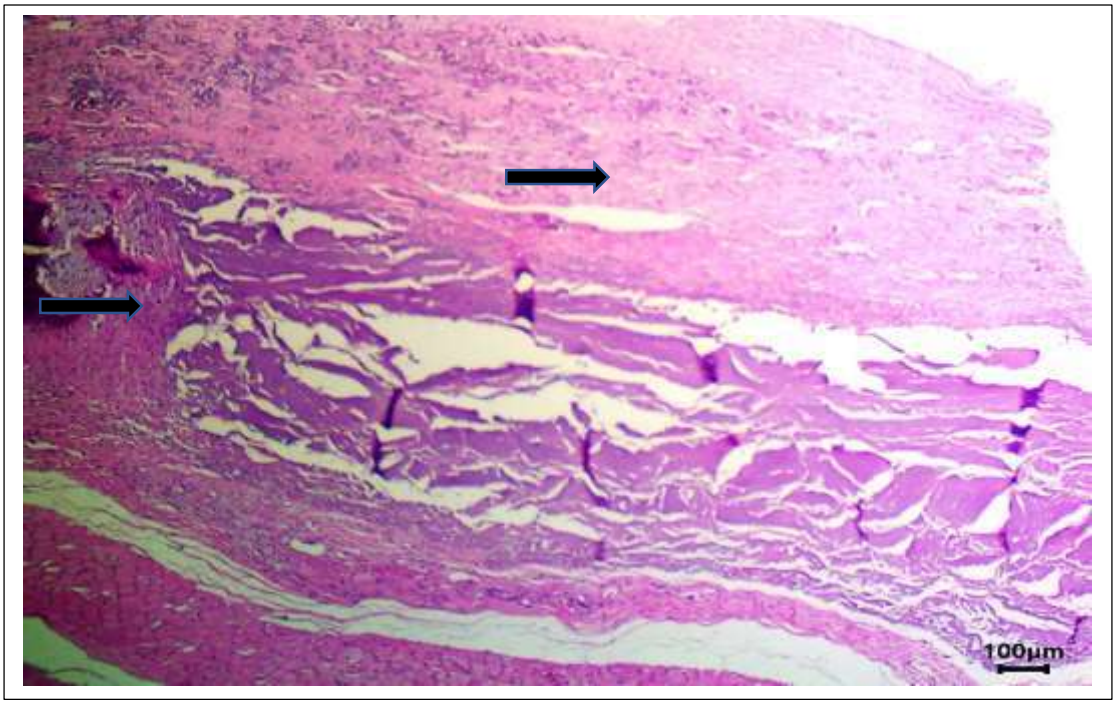


Figure 4-52: Micrograph at 15th POD in G4 shows formation of granulation tissue (black arrow). (H&E.40X)

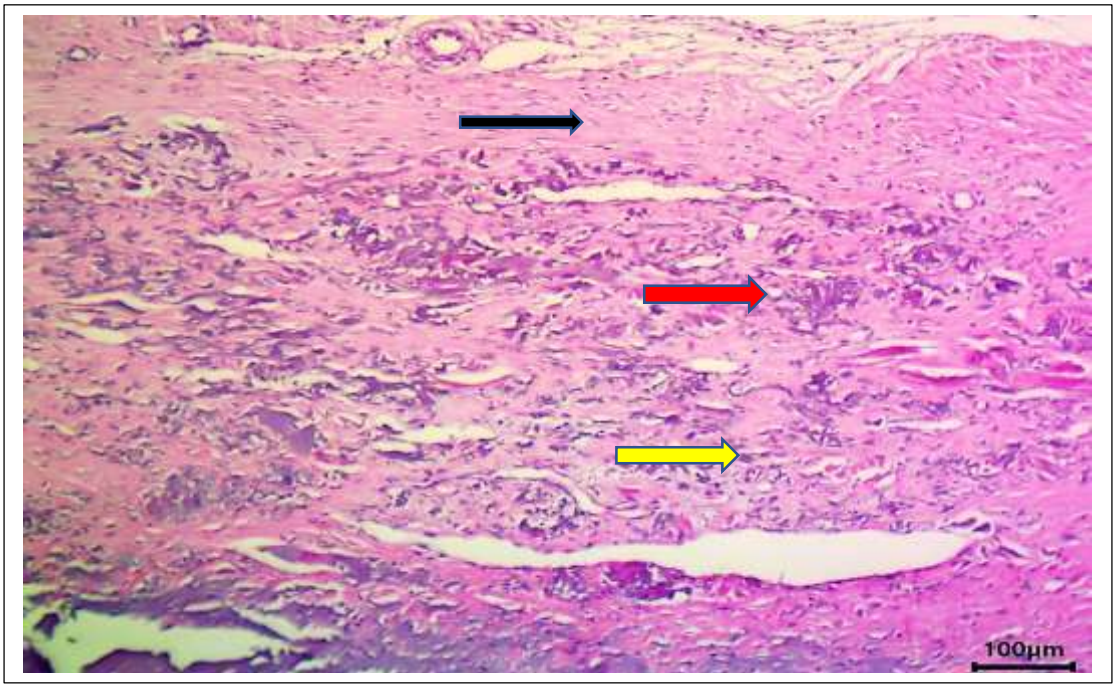


Figure 4-53: Micrograph at 15th POD in G4 shows granulation tissue (black arrow), newly blood vessels (red arrow) and few infiltrations of inflammatory cells (yellow arrow). (H&E.100X)

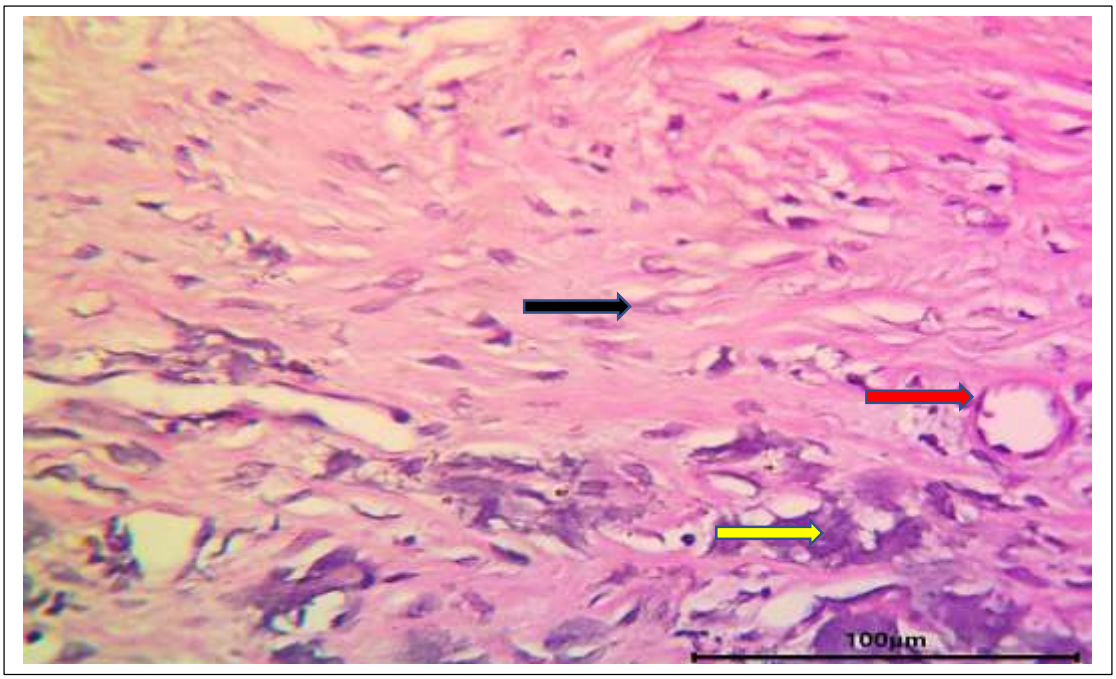


Figure 4-54: Micrograph at 15th POD in G4 shows proliferation of granulation tissue (black arrow), newly blood vessels (red arrow) and remnant of fibrin glue (yellow arrow). (H&E.400X)

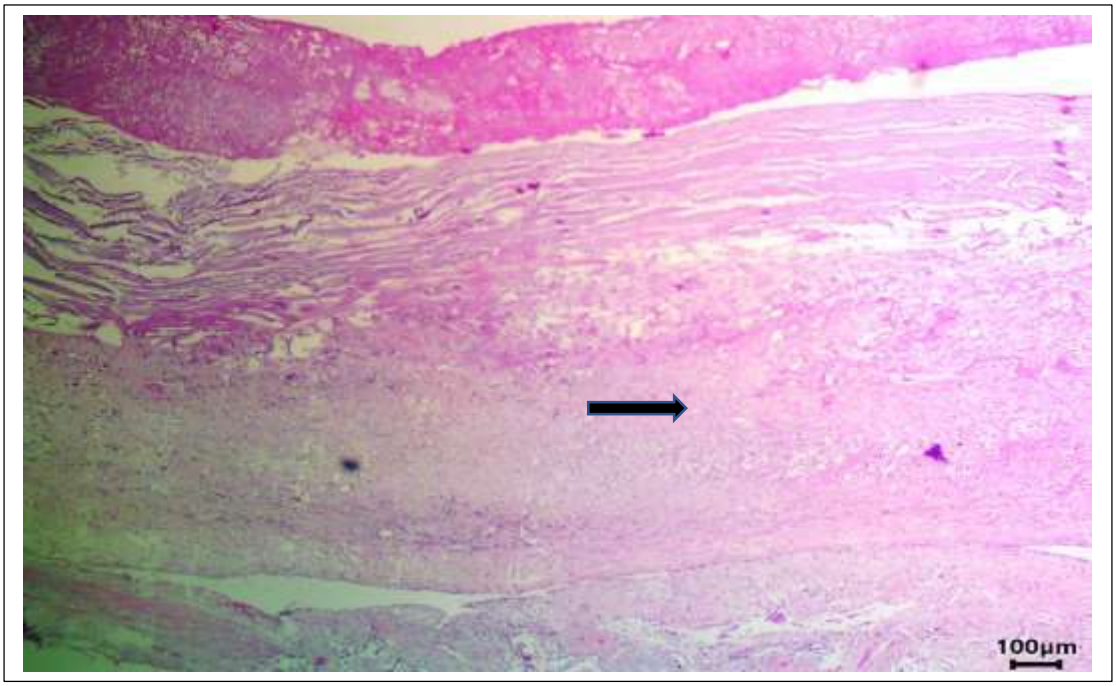


Figure 4-55: Micrograph at 30th POD in G4 shows maturity of granulation tissue (black arrow). (H&E.40X)

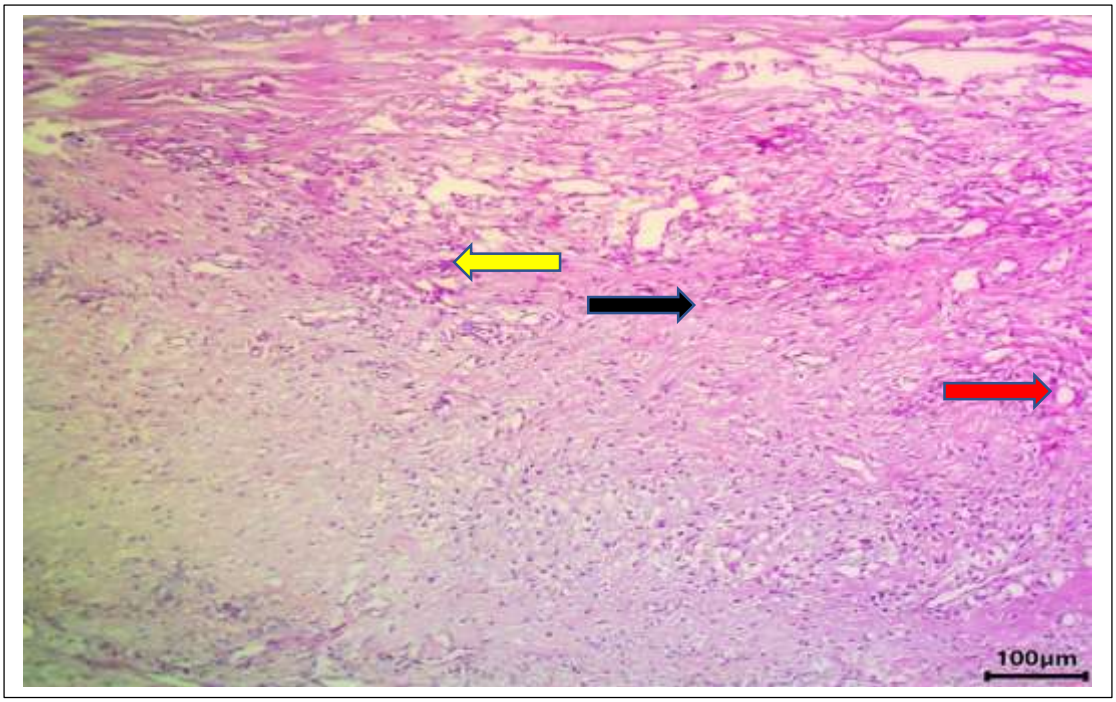


Figure 4-56: Micrograph at 30th POD in G4 shows mature granulation tissue (black arrow), few infiltrations of inflammatory cells (yellow arrow) and angiogenesis (red arrow) (H&E.100X)

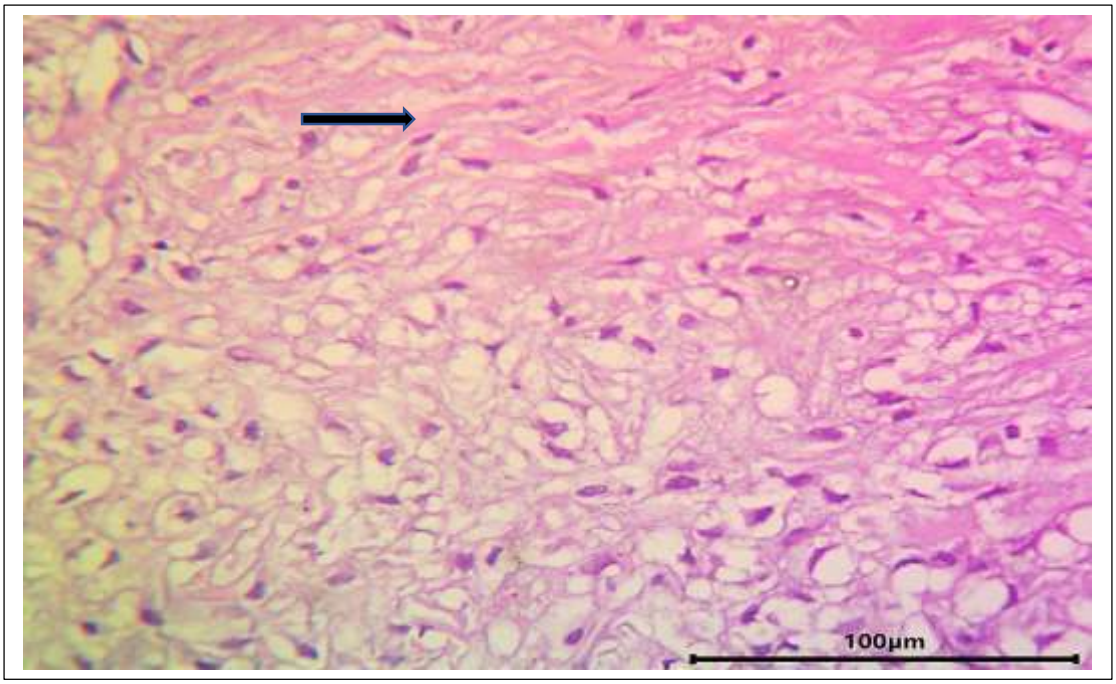


Figure 4-57: Micrograph at 30th POD in G4 shows mature granulation tissue (black arrow). (H&E.400X)

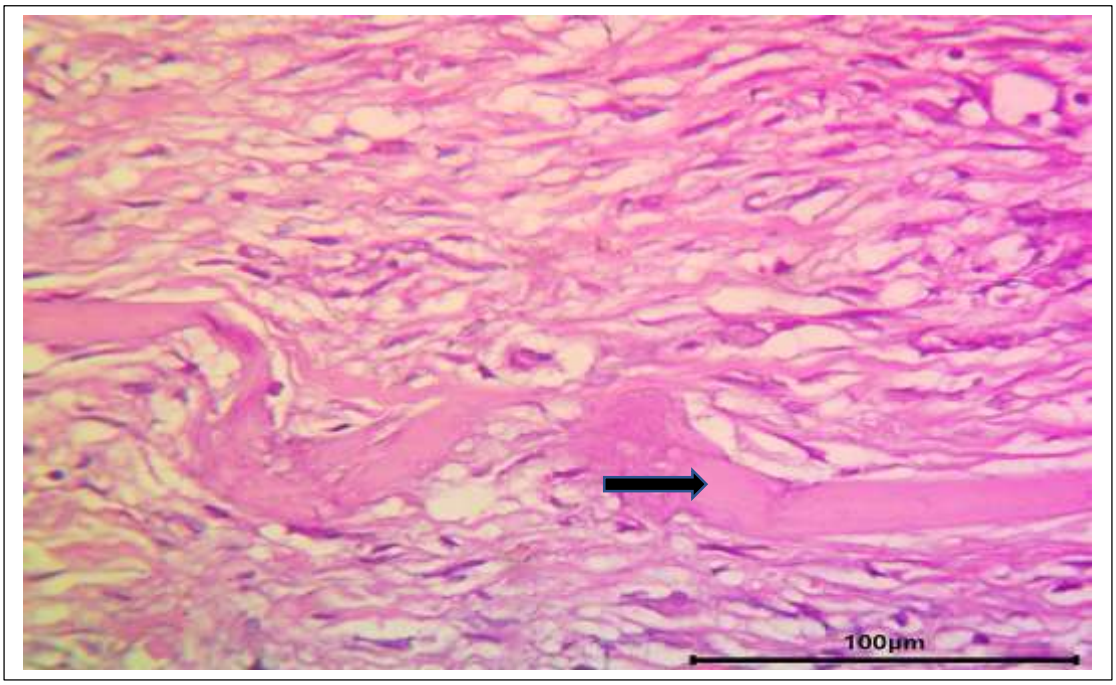


Figure 4-58: Micrograph at 30th POD in G4 shows protaneous material within granulation (black arrow). (H&E.400X)

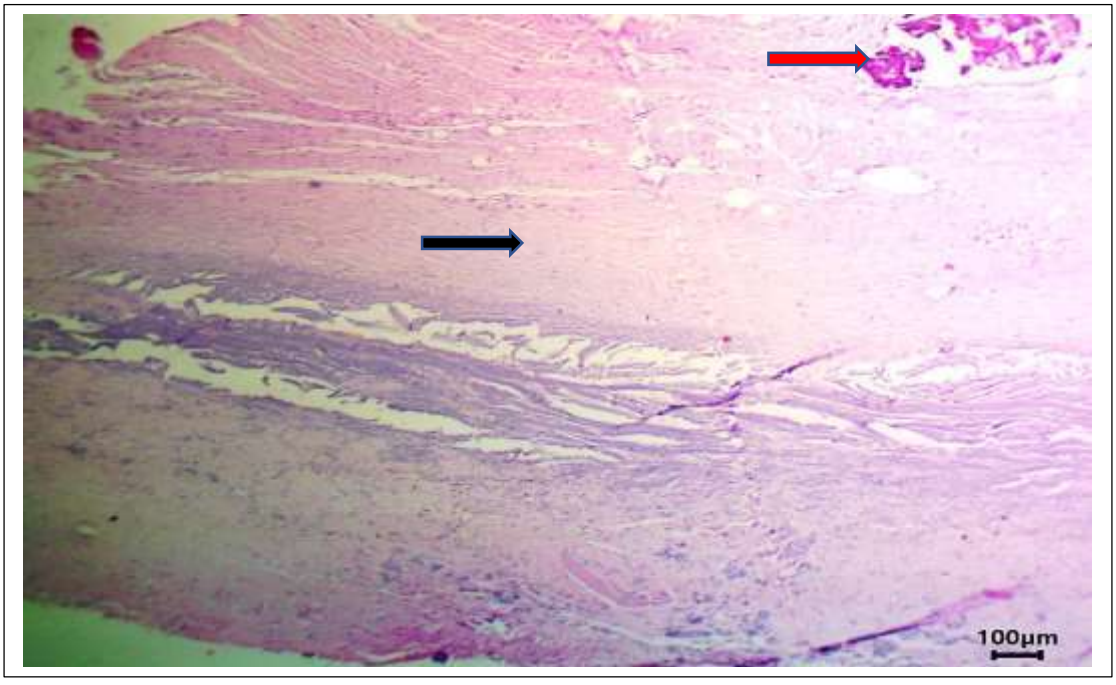


Figure 4-59: Micrograph at 60th POD in G4 shows mature granulation tissue (black arrow) and remnant of fibrin glue (red arrow). (H&E.40X)

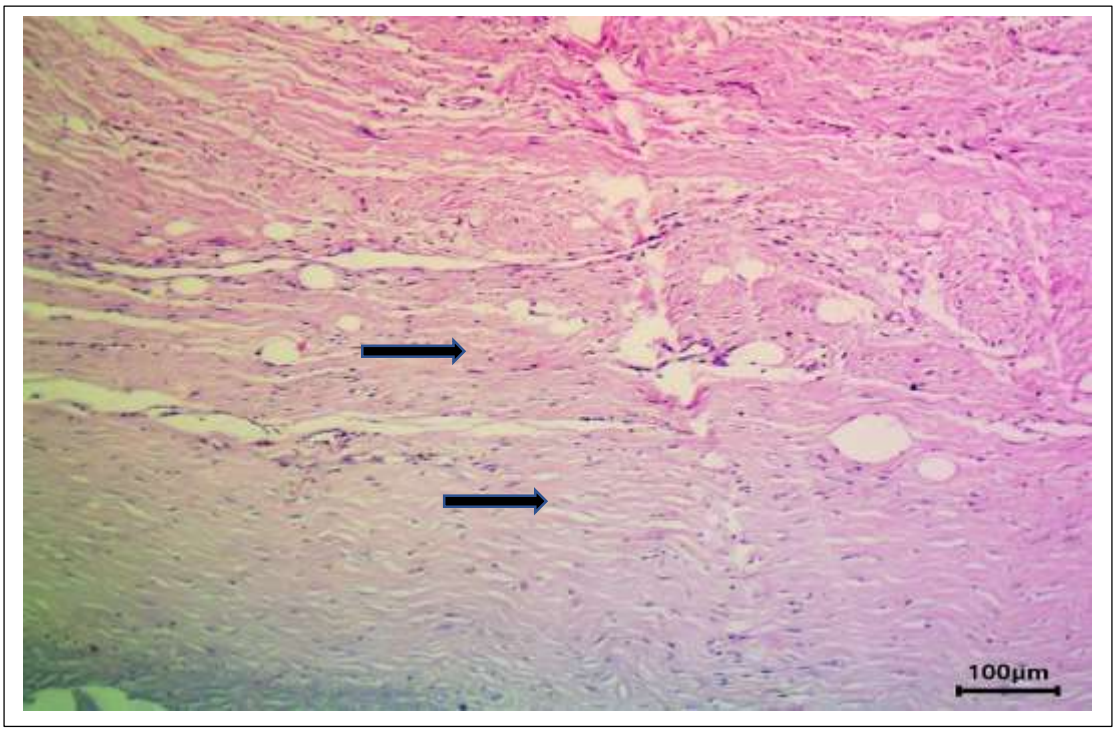


Figure 4-60: Micrograph at 60th POD in G4 shows mature granulation tissue (black arrow). (H&E.100X)

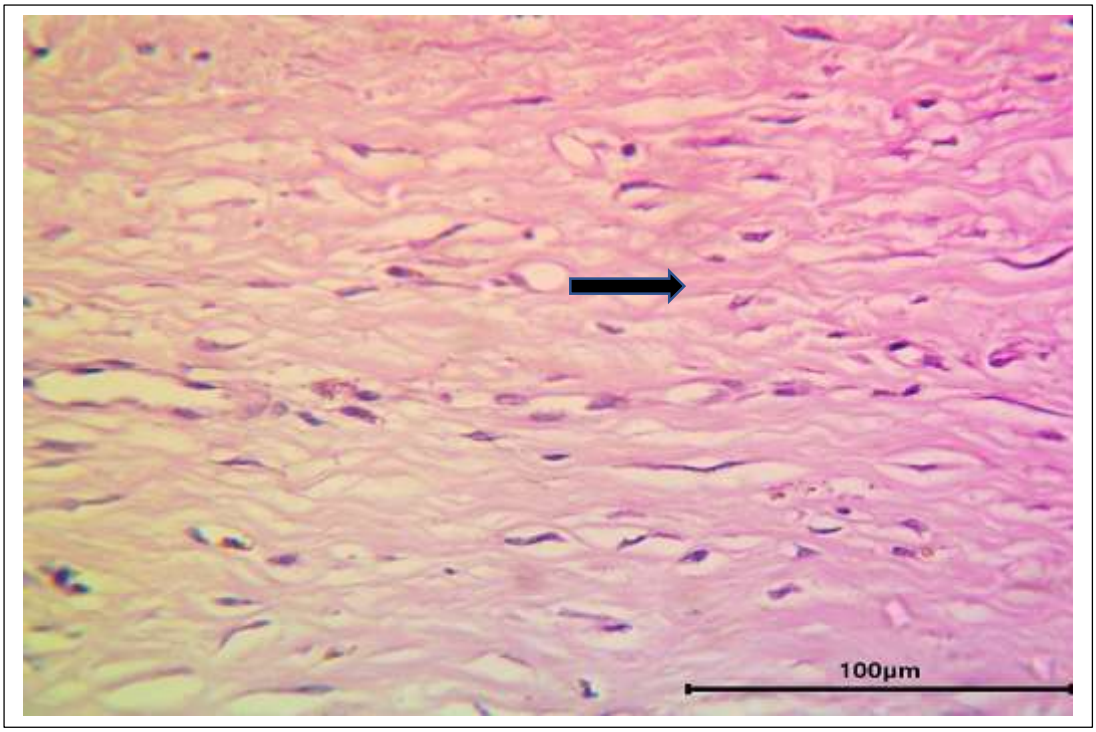


Figure 4-61: Micrograph at 60th POD in G4 shows mature granulation tissue (black arrow). (H&E.400X)

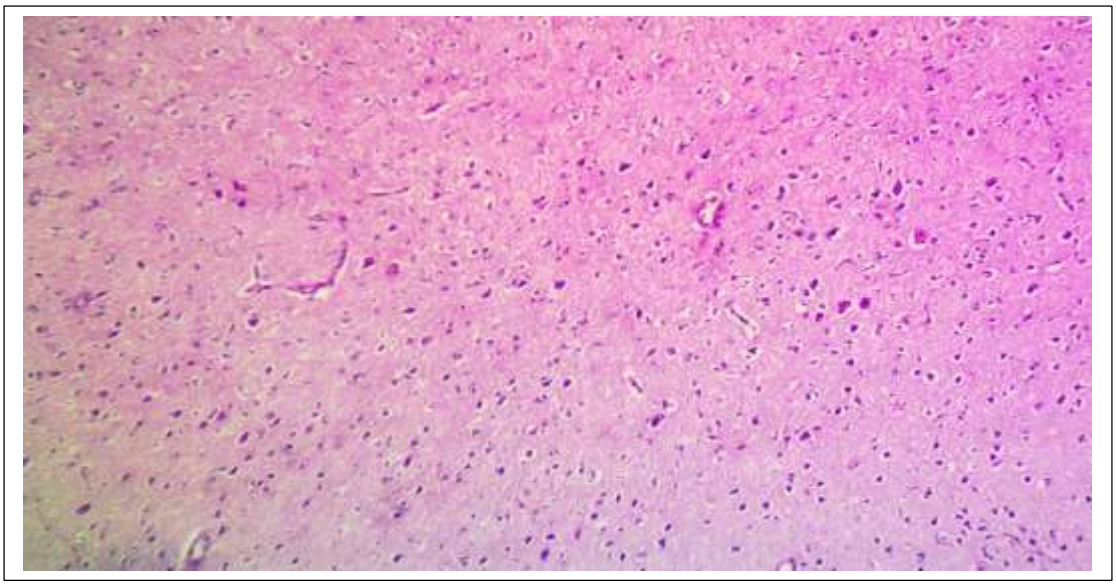


Figure 4-62: Micrograph at 60th POD in G4 shows normal brain cortex, neurons and glial cells (H&E.100X).

4-4: The statistical analysis of The histopathological scoring

The statistical analysis for The intensity of granulation tissue revealed no significant difference at p≤0.05 amoung all groups during all periods of The study (Joo-Yeon *et al.*, 2018).

Table (4-1) shows statistical analysis of The intensity of granulation tissue scores

Periods / Groups	15th POD (N=9) Median (IQR)	30th POD (N=6) Median (IQR)	60th POD (N=3) Median (IQR)
G1	3(2)	3(3)	4(3)
G2	2(1)	3(3)	4(4)
G3	2(2)	4(3)	4(3)
G4	3(2)	3(2)	4(3)
P-value	0.748	0.432	0.748

Data expressed as Median of The scores (IQR: Inter-Quartile-Range) (Kruskal-Wallis test)

The difference letters mean There are significant differences between groups at p≤0.05

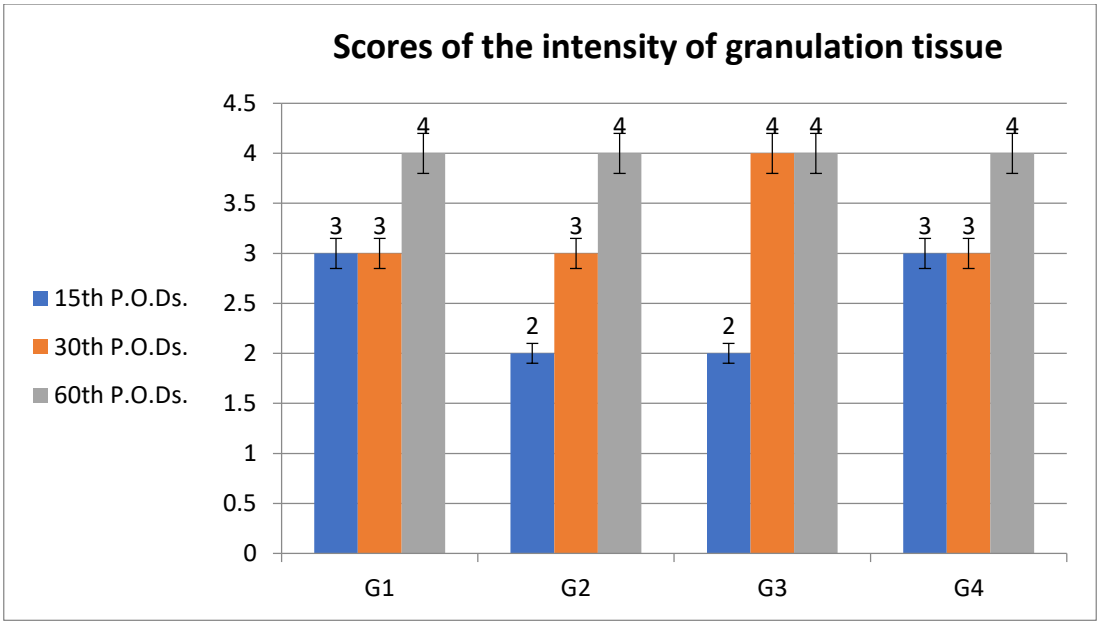


Figure (4-63) Histogram shows a statistical analysis of The intensity of granulation tissue scores.

The statistical analysis for The intensity of angiogenesis revealed significant differences at $p \leq 0.05$ in group 4 raTher than oTher groups at The 30th POD (Waleed *et al.*, 2014)

Table (4-2) shows a statistical analysis of The intensity of angiogenesis scores

periods / Groups	15th POD (N=9) Median (IQR)	30th POD (N=6) Median (IQR)	60th POD (N=3) Median (IQR)
G1	3(3)	2(2)	0(0)
G2	4(3)	2(1) (B)	1(1)
G3	4(3)	2(2)	1(1)
G4	4(3)	3(3) A	2(1)
P-value	0.432	0.036	0.142

Data expressed as Median of The scores (IQR: Inter-Quartile-Range) (Kruskal-Wallis test)
The difference letters mean There are significant differences between groups at $p \leq 0.05$

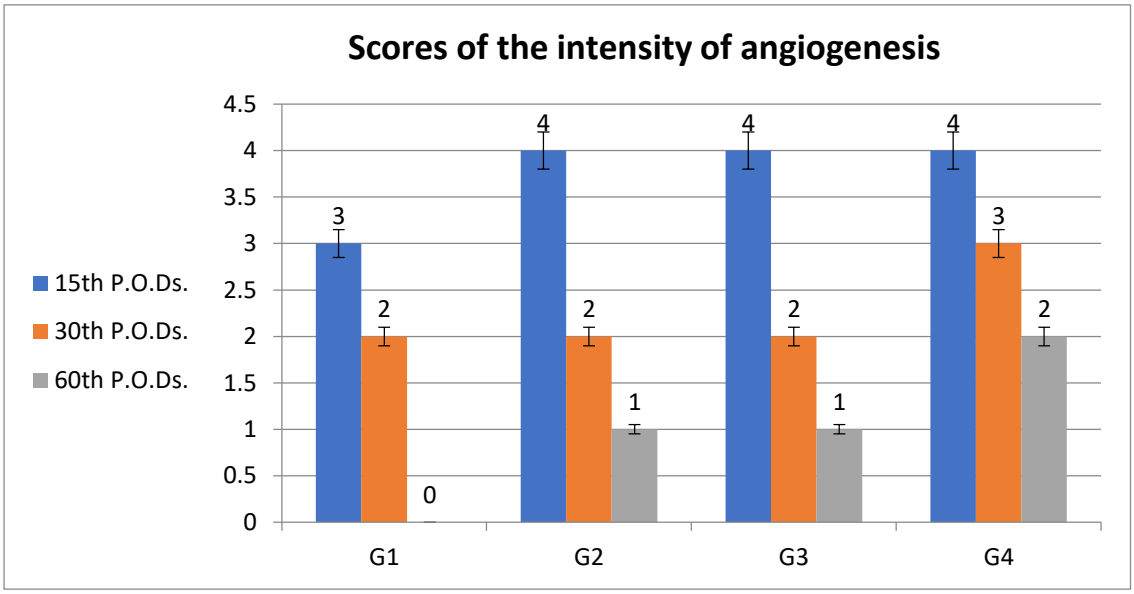


Figure (4-64) Histogram shows a statistical analysis of The intensity of angiogenesis scores

The statistical analysis for The intensity of The inflammatory reaction revealed a significant difference at $p \leq 0.05$ in group 4 raTher than in oTher groups on 15 days postoperatively.

Table (4-3) shows a statistical analysis of The intensity of inflammatory response scores

Periods / Groups	15th POD (N=9) Median (IQR)	30th POD (N=6) Median (IQR)	60th POD (N=3) Median (IQR)
G1	3(3)	2(1)	1(1)
G2	4(3) A	1(1)	1(0)
G3	3(2)	2(2)	0(0)
G4	1(1) B	1(0)	0(0)
P-value	0.034	0.326	0.037

Data expressed as Median of The scores (IQR: Inter-Quartile-Range) (Kruskal-Wallis test)

The difference letters mean There are significant differences between groups at $p \leq 0.05$

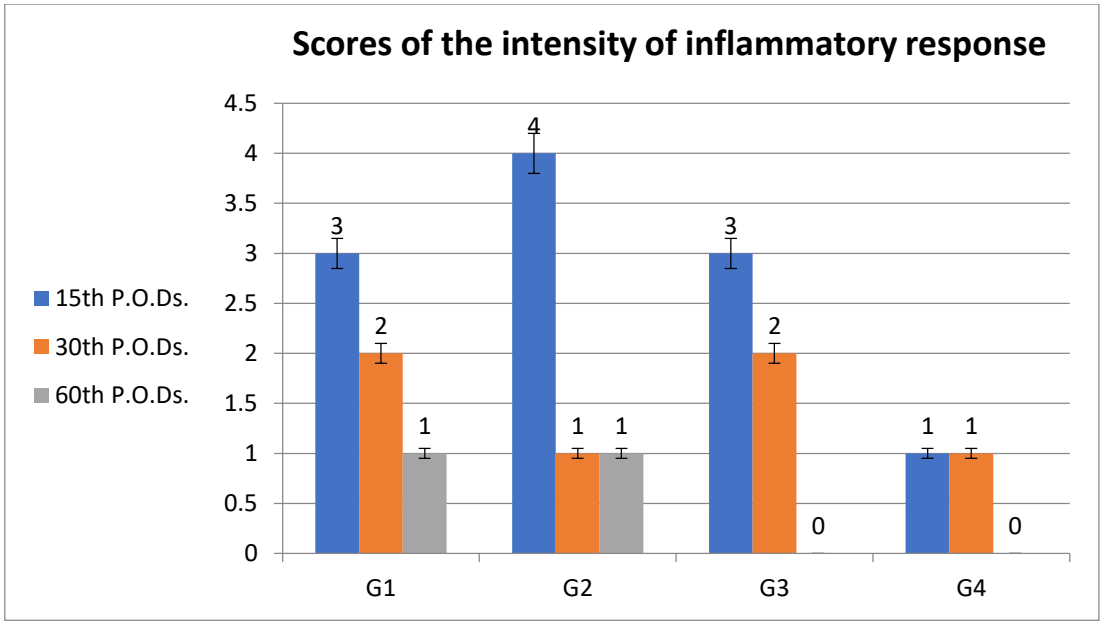


Figure (4-65) Histogram shows a statistical analysis of The intensity of inflammatory response scores

4.5 The statistical analysis of The CSF analysis and pressure

The statistical analysis of The cerebral spinal fluid pressure revealed to no significant differences at $p \leq 0.05$ between all groups during all period of The study.

Table (4-4) shows a statistical analysis of cerebral spinal fluid pressure (mmHg).

periods / Groups	Before operation (N=9)	15th POD (N=9)	30th POD (N=6)	60th POD (N=3)
G1	10.7 ± 0.92 A	10.6 ± 0.47 A	10.3 ± 0.47 A	10.6 ± 0.33 A
G2	11.8 ± 0.85 A	10.8 ± 0.35 A	11.3 ± 0.61 A	10.0 ± 0.57 A
G3	12.1 ± 0.97 A	11.0 ± 0.40 A	10.6 ± 0.55 A	10.0 ± 0.57 A
G4	10.8 ± 0.67 A	10.7 ± 0.40 A	10.6 ± 0.33 A	10.3 ± 0.88 A
P-value	0.608	0.946	0.763	0.851

Data expressed as Mean ± Stander error SE
The difference letters mean There are significant differences between groups at $p \leq 0.05$

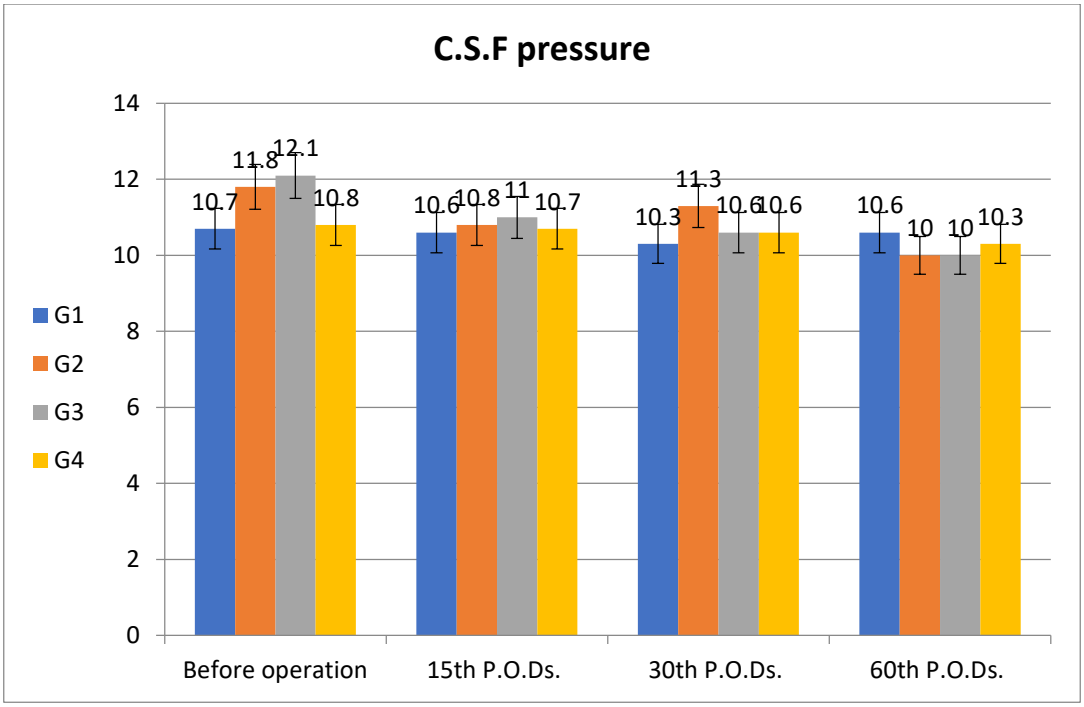


Figure (4-66) Histogram show statistical analysis of cerebral spinal fluid pressure

The statistical analysis of The cerebral spinal fluid protein was revealed to no significant deferens at $p \leq 0.05$ amoung all groups during all period of study.

Table (4-5) show statistical analysis of cerebral spinal fluid protein (Mg/Dl).

periods / Groups	Before operation (N=9)	15th POD (N=9)	30th POD (N=6)	60th POD (N=3)
G1	28.1 ± 1.7 A	30.4 ± 1 A	29.5 ± 1.4 A	31 ± 0.5 A
G2	27.1 ± 2.2 A	32.2 ± 0.4 A	31.6 ± 0.4 A	30.3 ± 0.3 A
G3	28.3 ± 2 A	32.8 ± 0.6 A	32.8 ± 0.7 A	30.6 ± 0.6 A
G4	28.1 ± 1.9 A	31 ± 0.3 A	30.8 ± 0.4 A	30.3 ± 0.3 A
P-value	0.973	0.062	0.088	0.752

Data expressed as Mean ± Stander error SE
The difference letters mean There are significant differences between groups at $p \leq 0.05$

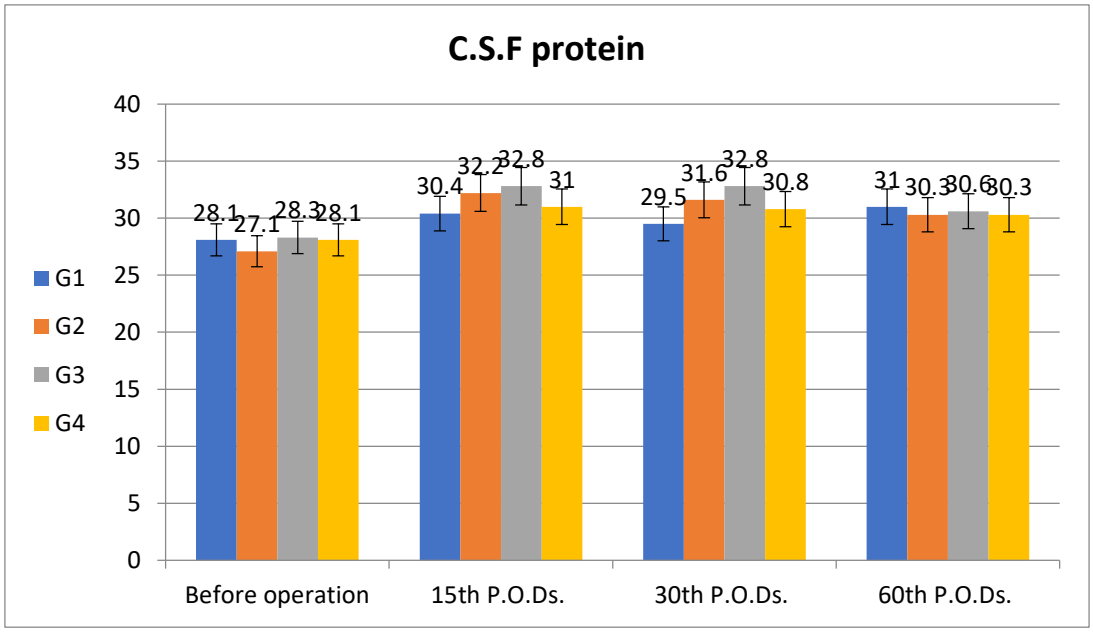


Figure (4-67) Histogram show statistical analysis of cerebral spinal fluid protein

The statistical analysis of The cerebral spinal fluid glucose revealed to no significant differences at $p \leq 0.05$ amoung all groups.

Table (4-6) show statistical analysis of cerebral spinal fluid glucose (Mg/Dl).

periods / **Groups**	**Before operation (N=9)**	**15th POD (N=9)**	**30th POD (N=6)**	**60th POD (N=3)**
G1	64 ± 4.2 A	66.6 ± 4.7 A	63.1 ± 0.8 A	63 ± 1.7 A
G2	65.2 ± 5.2 A	68 ± 1.2 A	66.3 ± 1.2 A	66.6 ± 3.5 A
G3	63.7 ± 4.2 A	69.1 ± 3.6 A	65.1 ± 1.1 A	61.3 ± 0.8 A
G4	63 ± 4.2 A	62 ± 1.7 A	62.1 ± 1.1 A	60.6 ± 0.6 A
P-value	0.989	0.326	0.001	0.001

Data expressed as Mean ± Stander error SE
The difference letters mean There are significant differences between groups at $p \leq 0.05$

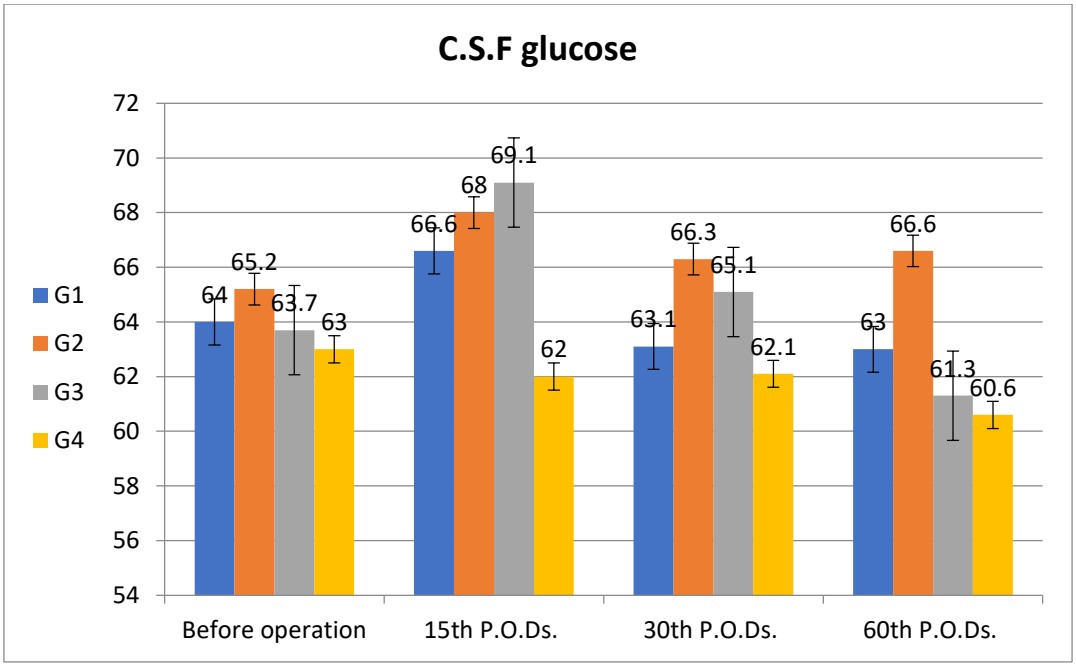


Figure (4-68) Histogram show statistical analysis of cerebral spinal fluid glucose

The statistical analysis of total cells count of The cerebral spinal fluid revealed no significant deferens at $p \leq 0.05$ on day 15 and 60 postoperatively but There is a significant deferens at $p \leq 0.05$ in group four raTher than oTher groups at 30th POD.

Table (4-7) show statistical analysis of The total cells count %

periods / Groups	Before operation (N=9)	15th POD (N=9)	30th POD (N=6)	60th POD (N=3)
G1	1 ± 0.3	2.2 ± 0.3	2.1 ± 0.4 AB	0.6 ± 0.3
G2	0.8 ± 0.3	2.1 ± 0.3	2.4 ± 0.6 AB	0.3 ± 0.3
G3	0.8 ± 0.3	2.3 ± 0.4	3 ± 0.4 A	0.6 ± 0.3
G4	0.8 ± 0.2	1.7 ± 0.2	1.1 ± 0.1 B	0.0 ± 0.0
P-value	0.994	0.712	0.049	0.363

Data expressed as Mean ± Stander error SE
The difference letters mean There are significant differences between groups at $p \leq 0.05$

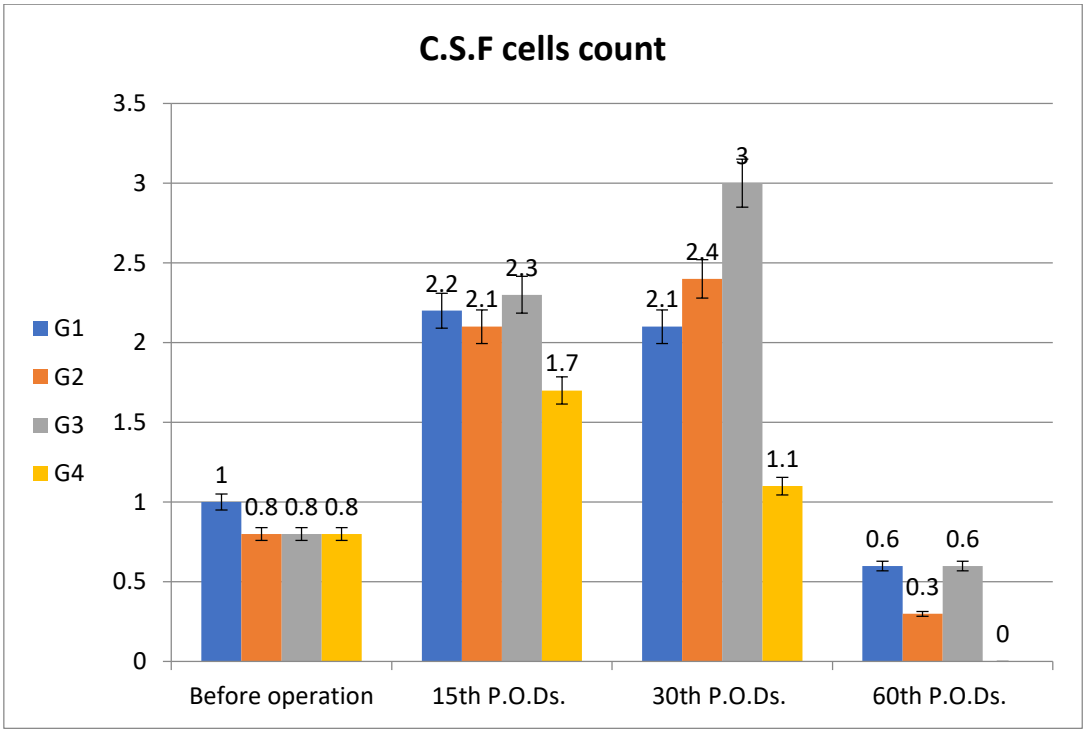


Figure (4-69) Histogram show statistical analysis of total cell counts

Chapter Five

Discussion

Meningeal defect is considered a main problem that may be occurred due to several causes such as during brain surgery, trauma, tumors, and congenital malformations (Knopp *et al.*,. 2005; Esposito *et al.,* 2008; Bernd *et al.,* 2009; Wang *et al.,* 2013). It is very important to close The meningeal defect with different biomaterials to avoid The occurrence of some major complications, especially leaks of CSF, herniating of The brain, infections, adhesions, and scarring of The brain cortex (Fontana *et al.,* 1992; Van Calenbergh *et al.,* 1997). Generally, sometimes The defect of The dura cannot be closed by suturing; Therefore, a meningeal graft is indicated. The grafted tissues, which are used to close The meningeal defect eiTher could be autologous tissues such as fascia of femoris and periosteal flaps or allografts as in lyophilized cadaveric dural grafts or xenografts such as using bovine pericardium and submucosa of porcine small intestinal (Yu *et al.*, 2013). However, in this project, we used two types of autografted tissues including fascia of temporalis muscle and peritoneum, and two kinds of xenografted tissues, which include acellular ovine esophageal mucosa and lyophilized bovine pericardium.

All grafted tissues that were utilized to close The induced meningeal defect in this study produced excellent results where most of These tissues have important properties such as good tensile strength, easily to handle, and resorbed without causing any severe tissue reaction, where The authors (Yamada *et al.*,1997; Grotenhuis, 2005; Biroli *et al.,* 2008; Rosen *et al.*, 2011;Wang *et al.,* 2013; Pogorielov *et al.*,2017) mentioned The grafted tissues must have some important characteristics such as They should be improved The regeneration of tissues and resorb, provide a good scaffold for The formation of new meninges, less inflammatory reactions, are not

rejected, strong to provide watertight seal without tearing, easy to applicate and less costly.

The repair of meningeal defects by meningeal plasty is very important to protect brain tissue and maintain of anatomical integrity of meninges. In this study, all grafted tissues provided relatively good reconstruction for dural defect where all animals postoperatively showed normal levels of body conditions with normal appetite and water intake and They recovered completely and still, lived during all periods of The study without The appearance of any clinical complications such as epilepsy or any abnormal nervous signs. Additionally, no cerebrospinal fluid accumulation or discharge at The site of operation appeared and this may be due to The grafted tissues healing completely with The dura of The host and prevented The occurrence of some complications, especially CSF leaks and brain tissue infection, adhesions or damage. Also, (Klekamp, 2012) reported that clinical improvement occurred in patients after meningeal plasty in a short time regardless to The type of grafted tissues wheTher it is autologous or non-autologous.

The gross changes in all groups have appeared The complete healing where The site of operation externally closed completely and each type of grafted tissues adhered completely with The meninges of The host internally. In addition, The grafted tissues didn’t adhere relatively to The brain surface internally. At The end of The study, The dural defect was shown internally although a good binding occurred between The grafted tissues and meninges of The host and this is in agreement with (Shi *et al.*, 2009) that The boundary between The implant tissue and host meninges was visible after three months from implantation and this boundary between The meninges of The host and implanted tissue may still distinguishable morphologically for ten to twelve months.

In meningeal plasty, The fixation of The grafted tissues on The site of The meningeal defect was accomplished eiTher by suturing or glues (Vanaclocha and Saiz-Sapena, 1997; Danish *et al.*, 2006; Lam *et al.*, 2013). In this work, we didn't use suturing because of a time-consuming, and in addition, no thread has all The perfect qualities such as being easy to handle, having less tissue reaction, and non-allergenic, and not promoting infection (Forseth *et al.*, 1992). Therefore, tissue adhesive was used to overcome These shortcomings. The fibrin glue provided good and smooth fixation between The grafted tissues and dura mater of The host and prevent CSF to leak, furTher more (Sharma *et al.*, 2003) say, The glue provided a smooth seal to The wound edge with very less complications.

The authors (Evans and Morey, 2006; Jeremy *et al.*, 2007; Bimal *et al.*, 2008; Mitsuaki *et al.*, 2019; Tavares *et al.*, 2020; Paulina *et al.*, 2021) showed that fibrin glue can be used with successful results in different surgical procedures because its effective hemostatic agent and adhesive action to seal tissue surfaces even if The moisture is present. In addition, fibrin glue didn't increase The risk of thromboembolic complications and did not interfere with The healing process of wounds (Mankad and Codispoti, 2001; Seyednejad *et al.*, 2008; Mathias *et al.*, 2009; Tan *et al.*, 2016). Also, no adverse pathological or immunological effect was developed when used in dogs (Bouvy *et al.*, 1993).

Generally, when a tissue is injured, bleeding results and Then stops due to blood clot formation. This is The first action of wound closure. Fibrin glue is similar to this pathway resulting in its adhesive capability. Once, The coagulation cascade is generated, The prothrombin change into thrombin by hydrolyses through activated factor X. Then, fibrinogen is converted to fibrin due to The presence of thrombin. Also, factor XIII was activated by thrombin that's present in The fibrinogen component of The glue, which leads to stabilizes of a clot, by helping polymerization and

fibrin chains linking to form long fibrin strands in The presence of calcium ions. This action is similar to The act of fibrin glue to induce tissue adhesion (Anita *et al.,* 2009).

The repair of meningeal defects after neurosurgical operation by suturing, glues, or grafted tissues is very important because of The imperfect closure to The dural defect, CSF will leake from punctured dura and several complications may be occurred such as meningitis and epidural abscess (Zeiad and Vinay, 2021; Rong-Peng *et al.,* 2023). Any collection of CSF subcutaneously may prevent appropriate wound healing and develop into infection and cutaneous fistula. In addition, The formation of pseudo meningocele leads to The development of abnormal neurological signs (Bosacco *et al.*, 2001) In all groups, no CSF leak was observed where The results of CSF pressure appeared within The normal range, and no significant difference at $p \leq 0.05$ appeared in all groups. This good result may be due to The effectiveness of fibrin glue with dural substitutes used in this work where The authors (Siedentop *et al.*, 1999; Yoo *et al.*, 2008; Dealmeida *et al.,* 2009; Jankowitz *et al.,* 2009) mentioned The fibrin sealant can be used with sutures and meningeal substitutes to provide correct closure to The dural defect and prevent CSF leaks and oTher complications.

Generally, some researchers reported The most common complications especially occurrence of aseptic meningitis, infection wound, and leak of CSF appeared during use non-autologous materials or tissues (Abla *et al.*, 2010; Farber *et al.,* 2018) such as during meningeal plasty with polytetrafluoroethylene (Vanaclocha and Saiz-Sapena, 1997) and pericranium (Attenello *et al.*, 2009). NoneTheless, The healing process at The site of The dural defect in all groups was relatively excellent due to The positive synergistic effect of fibrin glue and grafted tissues, which used in this study. The protocols which used in this work, prevent CSF from

being leaked and protected The brain tissue from any infection or damage and These notes whene mentioned by (Bosacco *et al.*, 2001; Richard *et al.*, 2011) that persists CSF leak lead to poor wound healing and possible wound dehiscence.

However, The microscopic examination for histopathological changes in all groups during The early stages of The healing process after grafting The site of meningeal defect with different tissues including fascia of temporalis muscle and peritoneum as autografted tissues, acellular ovine esophageal mucosa and lyophilized bovine pericardium as xenografted tissues were represented by formation of granulation tissue, infiltration of inflammatory cells and newly blood vessels formations but The rate of inflammatory cells infiltration was higher relatively in group two autografte and group three xenograft and very less in group four xenograft. At The end of The study, all The grafted tissues were interlocked with The meninges of The host and covered with mature connective tissues.

No abnormal histopathological features of brain tissues were observed in all groups during The period of The study. In general, The grafted tissues that's used to repair dural defects in dogs are gradually biodegraded and replaced by endogenous tissue relatively equal to The host dura mater without developing any abnormal pathological feature. These good results were mentioned by (Shi *et al.*, 2009) where The material that's used for grafting should have as much as possible good tissue compatibility with ideal mechanical characteristics to facilitate invasion of host cells and finally replace The implanted subjects with new biological tissue having The same functions of normal meninges.

Several methods and materials are used to repair meninges have been applied to The clinical signs, but The best choice of materials to use in The repair of meninges still remains unclear. However, The materials which use to replace The damaged or resected meninges, are called meningeal

substitutes (Gazzeri *et al.*, 2009). In this work, The fascia of The temporalis muscle was used with good results to repair The dural defect. This was in agreement with (Dufrane *et al.*, 2003; Shimada *et al.*, 2006; Zerris *et al.*, 2007) that fascia femoralis belongs to The native autologous tissue grafts and is used as a dural substitute because it doesn't provoke intense inflammatory or immunological reactions, but may be cause more scar tissue formation and difficult to obtain a watertight closure. Also, to harvest The graft, additional incisions we required.

Also, (Tachibana *et al.*, 2002) showed The use of a fascial tissue graft can be healed with The fibrous tissue of The meninges without blood supply presence from an overlying vascularized flap.

In group two, The piece of The peritoneum with fibrin glue provided a good closure to The dural defect where The histopathological section revealed good granulation tissue proliferation with more angiogenesis and infiltration of inflammatory cells but it subsides at The end of The study, These features resemble (Isaza-Restrepo *et al.*, 2018; Allawi and Alkattan, 2020) where The tissue of peritoneum has The ability to restore tissue due to The cells of peritoneal tissue can be differentiated into anoTher cell such as fibroblasts and myoblasts.

In addition, (Bellenger, 2003; Allawi and Alkattan, 2020) showed that peritoneum cells can secrete several growth factors such as fibroblast growth factor (FGF), transforming growth factor (TGF), and vascular endoThelial growth factor (VEGF) which have an important role of The healing process. The application of a piece of The peritoneum as autograft was characterized by being easy to obtain, very safe, suitable size can be obtained quickly, especially in emergency cases and cheap although additional incision was needed to obtain The graft tissue (Yin, 2004; Castillo *et al.*, 2019; Nicolas *et al.*, 2020).

The authors (Yin, 2004; Trenti *et al.,* 2017; Suwajo *et al.,* 2020) reported The peritoneum autograft was used also to repair some conditions in blood vessels, urogenital organs, and lungs. Additionally, authors (Yin, 2004; Uema *et al.,* 2008; Trenti *et al.,* 2017; Castillo *et al.,* 2019; Nicolas *et al.,* 2020; Suwajo *et al.,* 2020) mentioned The application of peritoneum as a piece of auto graft on The site of anastomosis was accelerate and improve The healing process and prevent leakage. Although The use of some autologous tissues is limited due to disruption of graft supply, The complexity of The surgical operation, time-consuming, applied additional trauma, and adhesion between The piece of autologous tissue with brain tissue (Zhang *et al.,* 2010) good results were obtained through using fascia of temporalis muscle and peritoneum with fibrin glue during this study.

In comparison with The use of fascia of temporalis muscle and peritoneum as autologous tissues, acellular ovine esophageal mucosa, and lyophilized bovine pericardium as xenogeneic biomaterials were used in this study with excellent results also where The (Zhang *et al.,* 2010) showed The xenogeneic materials are relatively good infection-resistance with properties like meninges of The host. The authors (Narotam *et al.,* 1995; Anson and Marchand, 1996; Parizek *et al.,* 1996; Cobb *et al.,* 1999; Knopp *et al.,* 2005; Tatsui *et al.,* 2006; Bejjani and Zabramski, 2007) showed that The bovine pericardium, submucosa of pig small intestin and processed collagen matrices can be used as a xenogeneic grafted materials but These materials have some adverse effects such as dissolution of graft tissue, encapsulation, foreign body reaction, scarring, and adhesion formation.

Therefore, The materials used in this work as xenografts applied under The decellularization process to remove any adverse effects during The repair of The meningeal defect especially tissue and immunological reactions (Wallis *et al.,* 2012; Lim *et al.,* 2013) says There are several

methods used to decellularized The tissues eiTher physically or chemically and The main goal to use this protocols to provide a non-immunogenic tissue that can be used without need to any immunosuppressive medication. authors (Guyette *et al.,* 2014; Ravi, 2017) mentioned The process of tissue decellularization can be done with physical, chemical, and enzymatic agents to change a tissue from cellularity to acellularity through The removal of cellular components of tissue and leaving The noncellular extracellular matrix (ECM) for Therapeutic uses to repair several injured tissues (Peter *et al.,* 2011).

Authors (Cheung *et al.,* 1990; Pereira *et al.,* 1990; Lee *et al.,* 1994; Moore *et al.,* 1994; Khor, 1997; Unai *et al.,* 2020) mentioned that collagen tissues are characterized by rapid degeneration and neediness to be stabilized to achieve durable and prolonging original mechanical integrity as well as remove or neutralize Their antigenic properties. For this reason, to use Theses tissues as biomaterials should be treated with several chemical agents. The use of acellular ovine esophageal mucosa and lyophilized bovine pericardium as decellularized tissues to close induced meningeal defects in dogs in this work produced excellent results where These implanted tissues interlocked and interwoven and sealed with dura mater of dog and covered with connective tissue and invasive with newly blood vessels. In addition, a little infiltration of inflammatory cells were shown especially in group four at early stages of healing process and this is agreement with (Macchiarini *et al.,* 2004; Conconi *et al.,* 2005) who reported The remaining extracellular matrix of The decellularized tissue can provide a micro-architecture for adhesion, cell proliferation, remodeling, differentiation, and angiogenesis.

Authors (Filippi *et al.,* 2001) reported that using bovine pericardium as a xenograft was characterized by flexibility and ease to suture and handle, safe, and less costly with positive effects for meningeal plasty as a dural

substitute. AuThers (Escande *et al.*, 2011) said that pericardium is considered a biological tissue and use for tissue engineering purposes such as to construct vascular tissue, abdominal or vaginal wall, and valves. Also, (Moses and DO, 2011) reported that bovine pericardium provides many important advantages when compared with oTher biological grafts as it minimizes adhesions pliable, strong, allows for easy suturing, and remains stable and uniform. Because of The critical or restricted utilization of bovine pericardium as a xenograft in some clinical practices due to The possibility of rejection (Platt *et al.*, 2002),

The lyophilized bovine pericardium was used in this study. The lyophilized bovine pericardium was characterized by rapid application, ease to handle, less tissue reaction and infiltration of inflammatory cells, rapid and more induction for angiogenesis and fibroblast proliferation. These features resemble to (Clinical and Neulen, 2011; Clinical and Greifzu, 2019; Clinical, 2020) who mentioned The lyoplant are characterized by several advantages such as simple, quick to applicate, prevent CSF leak due to high liquid tightness. Additionally, The high tensile strength of lyoplant prevents suture pull-out and mixes with The cells of body connective tissue (Clinical and Greifzu, 2019). Therefore, These characteristics make it a good choice to treat meningeal tearing and defects (Sekhar and Mai, 2013).

In all groups, The level of protein and glucose of CSF was appeared within normal range during all period of The study and There is no any significant difference at $p \leq 0.05$ where (Vasilios *et al.*, 2007) were reported any increase in The level of protein or glucose of The CSF indicated to The presence of leaks, infections, bleeding, and inflammation.

The lack of complications following implantation of The various materials used in this study to repair dural defects such as appearance of abnormal nervous signs, absence of CSF leaks, cutaneous head fistula,

pseudo meningocele, meningitis, and any abnormality in The CSF composition considered indicated to The successful use of These tissues to repair The created meningeal defect in dogs.

Chapter six

Conclusion and Recommendation

6-1: Conclusions

1- The cerebral meningeal defect can be closed successfully using fascia of temporalis muscle, peritoneum, acellular ovine esophageal mucosa and lyophilized bovine pericardium.

2- Use fibrin glue instead of suturing can be regard rapid, safe and excellent method to seal meningeal substitutes with host dura mater and prevents leaks of CSF.

3- Although all types of The grafted tissues used in this study can be considered as a good subject to repair dural defect but The priority was for lyophilized bovine pericardium.

4- Using of acellular ovine esophageal mucosa for The first time to reconstruct The meningeal defect in dogs.

6-2: Recommendations

1- To assess The viability of These grafted tissues too close largest size of meningeal defect.

2- Use oTher types of grafted tissues to close The meningeal defect such as endoform and myriad matrix.

3- Use oTher types of tissue glues such as synThetic histoacryl to bind The grafted tissues with host meninges.

4- Utilize oTher modern diagnostic images to evaluate The efficiency of The grafted tissues to heal The meningeal defect and prevent CSF leak such as magnetic resonance image with performance immunohistochemical study.

5- Conducting a study to compare The healing process of meningeal defect between different types of experimental animals.

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الخلاصة

تم تصميم هذا المشروع لتقييم قدرة الانسجة الطعمية المختلفة على إصلاح اذى الاغشية السحائيه الدماغية المستحدث في الكلاب. تم استخدام ستة وثلاثين من الكلاب البالغة المحلية في هذه الدراسة التجريبية. تم تقسيم الحيوانات بشكل عشوائي إلى أربع مجاميع رئيسية متساوية، كل مجموعة تتكون من تسع حيوانات. تم تخدير جميع الحيوانات من خلال حقن خليط من 10٪ كيتامين هيدروكلورايد بجرعة 10 ملغم / كغم و2٪ زيلازين بجرعة 2 ملغم / كغم على التوالي في عضلات الفخذ مع حقن الأتروبين بجرعة 0.05 ملغم / كغم قبل التخدير. تم إحداث اذى صغير في الاغشية السحائيه الدماغية لكل كلب. تم إصلاح عيب الاغشية السحائيه المستحث عن طريق وضع مواد حيوية مختلفة، وفقا لما يلي:

المجموعة الأولى: تم إغلاق عيب الاغشية السحائيه في هذه المجموعة عن طريق استخدام اللفافة للعضلة الصدغية كطعم ذاتي. المجموعة الثانية: تم إغلاق عيب الاغشية السحائيه عن طريق استخدام قطعة من الصفاق المأخوذ من نفس الحيوان كطعم ذاتي أيضًا. المجموعة الثالثة: في هذه المجموعة تم استخدام الغشاء المخاطي لمريء الأغنام غيرالخلوي لغلق عيب الاغشية السحائيه كطعم مغايير. المجموعة الرابعة: تم استخدام التامور البقري المجفف بالتجميد في هذه المجموعة كطعم مغايير لإغلاق عيب الاغشية السحائيه.

تم تثبيت انسجة الترقيع في جميع الحيوانات مع عيب الاغشية السحائيه باستخدام غراء الفبرين وبدون استخدام الخياطة. تم تقييم نتائج هذه الدراسة التجريبية من خلال مراقبة العلامات السريرية بعد الجراحة لكل حيوان وخاصة التي تتعلق بظهور علامات عصبية غير طبيعية مثل تغيرات السمع والغثيان والقيء والصوت والرؤية وحركة العين غير الطبيعية وتشنج العضلات أو أي وضع غير طبيعي للجسم. بالإضافة إلى ذلك، تمت دراسة التغيرات النسيجية المرضية، ضغط السائل الدماغي الشوكي، تحليل السائل النخاعي الشوكي والذي شمل العد الكلي للخلايا قياس مستوى الجلوكوز والبروتين في جميع المجموعات في اليوم 15، 30 و60 بعد العملية الجراحية. بالإضافة الى اعتمد التحليل الإحصائي لهذه التقييمات.

بقيت جميع الحيوانات على قيد الحياة بعد العملية الجراحية دون حدوث أي مضاعفات سريرية وخاصة تلك التي تتعلق بالجهاز العصبي. بالإضافة إلى ذلك، تناولت الحيوانات الطعام والماء بشكل طبيعي ولم يظهر أي تغيير في سلوكها.

أظهرت النتائج العيانية الى التئام موقع التطعيم خارجيًا في جميع المجموعات وبشكل كامل خلال جميع فترات الدراسة. بالإضافة إلى ذلك، لم يلاحظ أي تسرب للسائل الدماغي الشوكي في موقع العملية بعد العملية الجراحة. وفي نهاية الدراسة كان عيب الجافية قد اغلق بالكامل في جميع الحيوانات داخليًا من خلال التصاق الانسجة المزروعة مع الاغشية السحائيه للمضيف ومنع حدوث اي تسرب للسائل الدماغي الشوكي.

تمثلت التغيرات النسيجية المرضية في جميع المجموعات في تكوين نسيج حبيبي مع ارتشاح الخلايا الالتهابية وتكوين الأوعية الدموية. حيث اظهر التحليل الاحصائي للمقاطع النسيجية المرضية وجود فرق معنوي عند مستوى $p\leq0.05$ في المجموعة الرابعة عن باقي المجاميع في درجة تكوين الاوعية الدموية وارتشاح الخلايا الالتهابية حيث تميزت المجموعة الرابعة بكثرة تكوين الأوعية الدموية وقلة ارتشاح الخلايا الالتهابية في المراحل الأولى من عملية الالتئام.

في جميع المجموعات، ظهرت قيم ضغط السائل الدماغي الشوكي، إضافة الى مستوى الجلوكوز والبروتين في السائل الدماغي الشوكي ضمن المعدل الطبيعي خلال جميع فترات الدراسة ولا يوجد فرق معنوي بينهم عند مستوى $p\leq0.05$. وكذلك ظهرت قيم عدد الخلايا الكلية ضمن المعدل الطبيعي في جميع المجموعات في اليوم 15 و60 بعد العملية ولا يوجد فرق معنوي بينهم عند مستوى $p\leq0.05$ ولكن تميزت المجموعة الرابعة عن باقي المجاميع بوجود فرق معنوي عند مستوى $p\leq0.05$ في اليوم 30.

يستنتج من ذالك أنه يمكن استخدام لفافة العضلة الصدغية والصفاق والغشاء المخاطي لمريء الأغنام غيرالخلوي ولتامور البقري المجفف بالتجميد مع غراء الفبرين بدلاً من الخياطة بنجاح لإغلاق وإصلاح عيب الاغشية السحائيه الدماغية في الكلاب مع الأولوية للتامور البقري المجفف بالتجميد.

دراسة مقارنة للزرعات الذاتية والمغايرة لإصلاح الاذى المستحدث تجريبا في الاغشية السحائيه الدماغية في الكلاب

أطروحة تقدم بها

عبدالله مزاحم أيوب عبدالله

إلى
مجلس كلية الطب البيطري في جامعة الموصل
وهي جزء من متطلبات نيل شهادة الدكتوراه فلسفة
في اختصاص الطب البيطري / الجراحة البيطرية

بإشراف
الأستاذ الدكتور

أسامة حازم إسماعيل الحياني

١٤٤٥هـ **٢٠٢٤م**

جامعة الموصل
كلية الطب البيطري

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