Journal of Pharmaceutical Research International

25(6): 1-37, 2018; Article no.JPRI.47014
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparison and Evaluation of Seven Animal Models of Ischemic Skin Wound: A Review Article

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Authors' contributions

This work was carried out in collaboration between both authors. Author MB collected the papers and wrote the first draft of the manuscript. Author SC edited it scientifically. Author MB submitted it to the journal. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2018/v25i630119
Editor(s):
(1) Dr. R. DeveswaranM Associate Professor & Head, Drug Design and Development Centre,Faculty of Pharmacy, M.S.Ramaiah University of Applied Sciences, India.
Reviewers:
(1) Muhammad Shahzad Aslam, Pakistan International Human Right Organization, Pakistan.
(2) K. Ramesh Kumar, General Surgery,S. V. S. Medical College, India.
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Complete Peer review History: http://www.sdiarticle3.com/review-history/47014

Review Article

Received 10 December 2018
Accepted 09 February 2019
Published 13 March 2019

ABSTRACT

Focusing on pathophysiology, prevention, and treatment of ischemic wounds is apriority for medical and basic scientists in order to develop new clinical approaches. However it is not always easy for researchers to choose optimal animal models for their particular assessments. This review provides concise information on all currently available ischemic animal models, including rabbits' ear ischemic models, axial skin flaps (axial pattern flaps), burns, ischemic limbs, localized ischemic wounds, pressure ulcers, and skin flaps, along with their citations as a measure of their acceptance among other researchers. We searched the numerous databases consisting of PubMed, Scopus, Science Direct, and Google Scholar. Key words included ischemic wound, skin, and animals alone or in combination. Some important features of the seven types of ischemia as well as their results are presented in Tables 1 -7. Table eight presents the results of entire groups of ischemic animal models, with their number of papers, number of wounds, and total and average Google Scholar

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citations, and web of science citations. We found that rabbits' ear ischemic models, localized ischemic wounds, and pressure ulcers have the highest total and average citations amongst the studied groups. It was concluded that the rabbits' ear ischemic model, rat pressure ulcer models, and localized ischemic wound models, have made the greatest contribution to our understanding of the pathophysiology of the ischemic wounds and increased production of new therapeutic protocols based on the citations reported by Google scholar and the web of science databases between 1977 and 2017.

Keywords: Skin ulcer; wound healing; wound and injuries; pressure ulcer.

1. INTRODUCTION

1.1 Why are Tissue Ischemia and Skin Repairs Important?

When the normal repair is disrupted, chronic wounds develop. Ischemia is one of the most common causes of chronic wounds [1] which fail to heal in a ''normal'' period of time. Clinical observations suggest that persistent tissue ischemia in the vicinity of the wound is an important underlying feature of chronic wounds. Ischemia severely impairs the healing process by causing wound repair dysregulation, ultimately threatening limb and life [2]. Long term ischemia leaves wounds vulnerable to infection, inflammation, and necrosis and is an important factor in repair hindrance in many diseases [3]. Chronic wounds are heterogeneous, and are clinically challenging because they strictly damage tissue repair [4-7]. In the USA, 6.5 million people suffer from chronic wounds including ischemic wounds costing in excess of $25 billion each year in the management of chronic wounds [8].

1.2 Normal Skin Repair (Wound Healing Process)

Understanding normal skin repair is necessary for effective prevention and treatment. Skin repair happens on a time continuum with steps including hemostasis, inflammation, proliferation, and remodeling [9]. Each step is vital to achieve complete wound healing, and any alteration from the normal state can be associated with postponed or abnormal skin repair [9].

1.3 Ischemic Skin Repair

At first we should describe some important terms. Hypoxia refers to low organ oxygen tension, ischemia applied when blood flow to a tissue or organ is limited, leading to low oxygen and nutrition levels [10], and an ischemic ulcer (wound) is an ulcer caused by diminished blood flow through an artery [11].

Low oxygen levels reduce neutrophils' and fibroblasts' functions, decrease collagen synthesis, and increase wound infection [12-14].

1.4 The Need for Animal Models

Animal models are crucial to increase our knowledge [15], and serve as surrogates of the human condition in order to translate experimental findings into clinical use. The most critical factor is the requirement to mimic the clinical environment of the ischemic condition [16]. Previous studies have shown that although more than 100 factors could be involved in non-healing wounds, one critical pathophysiology is associated with a deficient blood supply. Ischemia may not be the initiating factor for many chronic wounds, as most ulcers start from a combination of neuropathy, pressure loading, infection, and/or trauma. Tissue ischemia is the main cause that hinders healing—wounds do not heal in tissue that does not bleed, whereas they always heal in tissue that bleeds extensively. Currently, the most common animal models of ischemia include: Rabbit ear ischemic model (REIM), axial skin flap (or axial pattern flaps) (ASF), burn, ischemic limb (IL), localized ischemic dermal repair (LIDR), pressure ulcer (PU), and different models of random patterns of blood vessels in skin flaps (SF).

1.5 Available Animal Models of Ischemic Wounds

1.5.1 Rabbits' ear ischemic model (REIM)

The REIM model was initially created using a microsurgical technique [17]. Recently an improved version of this ischemic wound model that does not require microsurgery instruments has been reported [18].

1.5.1.1 Technique

The technique creates incisions at the ear base, and the central and cranial arteries along with

their accompanying nerves are severed and ligated, leaving the central vein and the caudal bundle intact. The subcutaneous tissues and muscles are also cut to reduce collateral formation. For wound study, two to four circular full-thickness wounds are created on the ventral side of each ear [18].

1.5.2 Axial skin flap (axial pattern flaps) (ASF)

This model is based on a direct cutaneous artery and veins providing a piece of skin. They provide a versatile option for big injury closure [19,20]. This model requires good surgical technique and careful attention to detail when inducing the flap [19,20].

1.5.2.1 Technique

The technique creates anterior abdominal skin flaps, based solely on the epigastric artery and vein, in the rat model. A unilateral axial pattern skin flap is elevated under direct microscopic vision. The flap is re-sutured into place and observed for a period of 3 to 4 days [20].

1.5.3 Burn

Cutaneous burns are dynamic injuries with a central zone of necrosis surrounded by a zone of ischemia [21]. Acute tissue destruction occurs at the site of burn injuries by direct thermal energy. In addition, a delayed loss of tissue occurs in the surrounding, uninjured skin as a consequence of progressive ischemia [22].

1.5.3.1 Technique

One common technique is the induction of a full-thickness burn by hot metal. Two burns are created on each animal's dorsum using a brass comb with four bars preheated in boiling water and used for 30 seconds, resulting in 4 full-thickness burns separated by 3 unburned interspaces (zone of ischemia) [21].

1.5.4 Ischemic Limb (IL)

Critical IL refers to the clinical state of advanced arterial occlusive disease, placing an extremity at risk of gangrene and limb loss [23]. This is associated with significant morbidity including chronic wounds, infections, mortality, and health care resource utilization [24,25,1].

1.5.4.1 Technique

The technique involves a transient ligation of the femoral artery and vein, and collateral vessels in rabbits using a microvascular clip. After a 2-hour period of ischemia, the clips are removed to allow reperfusion for 4 hours [26].

1.5.5 LIDR

Localized tissue ischemia is a key factor in the development and poor prognosis of chronic wounds [27]. This ischemic wound model is reliable, relatively inexpensive, easy to perform, and reproducible [27].

1.5.5.1 Technique:

A dorsal, bipedicle skin flap was raised in the craniocaudal direction deep into the skin muscle (panniculus carnosus). Two adjacent excisional ischemic wounds were created in the center of the flap. Precut and sterilized non-reinforced medical grade sheeting is then placed underneath the flap. The skin flaps and silicone sheet are sutured to the adjacent skin edges. The silicone sheet inhibits wound contraction and internally controlled, non ischemic full-thickness wounds are created (Fig. 1) [27]. The excisional wounds provide sufficient tissue for laboratory tests, and are amenable to the evaluation of topical and systemic therapies that may induce angiogenesis or improve ischemic wound healing [27].

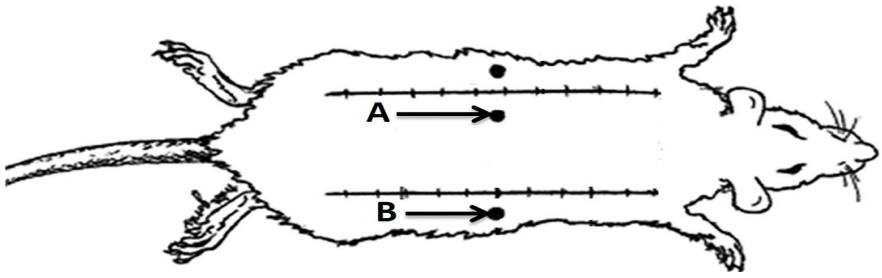

Fig. 1. A schematic localized ischemic wound model; A: ischemic wound; B: non ischemic control wound. Fig. was drawn by authors

1.5.6 PU

PUs develop as a result of a localized injury caused to the skin and/or underlying tissue, or both, resulting from prolonged pressure on the skin. The ulcers usually arise over a bony prominence, and are recognized as a common medical problem affecting people confined to a bed or wheelchair for long periods of time [28].

1.5.6.1 Technique

One approach is to gently pull up the dorsal skin of mice and trap it between two round ferrite magnetic plates for 12 hours. Once the plates are removed the mice develop two round ulcers separated by a bridge of normal skin [29].

1.5.7 Skin Flaps (SFs)

This technique has been considered an important procedure in plastic and reconstructive surgery in order to cover defects. Flap necrosis due to failure of blood circulation results in severe complications [30]. SFs provide cutaneous coverage, and may be local, pedicled, or free [31]. Nakajima and colleagues classified SFs into cutaneous, fasciocutaneous, adipofascial, septocutaneous, and musculocutaneous [32]. Random blood vessel pattern skin flaps (RSF) provide the greatest adaptability in reconstructive surgery [32].

1.5.7.1 Technique

In this technique, a random skin flap, including the entire thickness of the skin and panniculus carnosus is made. The base of the RSF is located on a horizontal line between the crest of the iliac bones. The dimensions of the flaps are 20×70 mm. After elevation, the flaps are immediately replaced. The surface area of the flap is measured immediately and seven days after surgery [33]. It is noted that all skin wounds in this review article were full thickness.

1.6 Necessity for the Current Review Study

A total of 6.5 million American patients suffer from chronic and ischemic wounds and would benefit from improvements in wound treatment. To achieve this goal, scientists and physicians would benefit from appropriate and accurate animal models to study ischemic wounds [1]. There are currently a limited number of review articles about animal models of chronic and ischemic wounds. Schäffer et al presented a limited review on SF, PU, and LIDR ischemic models in 2002, and concluded that animal model of ischemia are useful in developing information, although extending the application of these models into the human condition is an excessively lengthy and complex process [1]. Salcido et al provided an outline of techniques used to induce PU in animal models in 2007 [15]. They concluded that the mechanism of healthy tissue or organs progressing to PU remains unknown [15]. Nunan et al (2014) classified all chronic wounds into one of three major categories: leg ulcers, diabetic foot ulcers, and PU. Nunan et al concluded that it should be possible to optimize animal models so that they better recapitulate the medical hallmarks of this situation and permit researchers to better understand its pathological mechanisms [10]. McCafferty et al. described the development of ischemic conditioning strategies from lab to patient, and highlighted where transition into patient investigations has been less successful compared to animal models [16].

Studies focusing on pathophysiology, prevention, and treatment of ischemic wounds remain a priority for medical and basic scientists in order to develop new clinical approaches. However it is not always easy for researchers to choose the optimal animal models for their particular assessments.

The present review article provides concise information about all available studies on ischemic animal models using REIM, ASF, burn, IL, LIDR, PU, and SF, along with presenting their citations in order to determine their acceptance among other researchers, an area that has not been studied completely in the literature to date.

An exhaustive literature review was done on the articles available in the databases such as PubMed, Scopus, Science Direct, Google Scholar and other published manuscripts related to our study using the keywords “ischemic wounds, skin, and animals (Rat, Mice, Rabbit, Pig, Mini pig, Horse)” alone or together. Besides presenting technical notes of the studies, our results also indicate the reliability of these techniques among peer review panels, and editors of journals based on the number of published papers in each item, and their citations in Google scholar and web of sciences.

2. METHODS

2.1 Search Strategy

We first searched Pub Med, Medline, Scopus, Science Direct, Google Scholar and other published manuscripts related to our study using ischemic wound, skin and animals key words alone or together. Then, in order to prevent any probable bias, the titles and abstracts of all the selected studies (published in the English language) were evaluated by another scientist who was not the co-author of this work, and did not have any conflict of interest. He downloaded the full text of these papers and blocked authors' names and affiliations. After that we categorized entire animal models of ischemic wounds into REIM, ASF, burn, IL, LIDR, PU, and SF categories. Finally, article citations issued in Google Scholar and web of sciences were recorded and total citations were calculated. Since citations of papers were reported automatically by Google scholar, and web of sciences, there was no bias in this step.

2.2 Study Selection

All the full text published papers using the key words ischemic wound and skin and animals in their titles and abstracts were incorporated. We found and selected 240 published articles between 1977 and 2017. Next we considered some inclusion criteria for the selected papers in the review. Inclusion criteria prevented any further bias.

Inclusion criteria

1. The full text of the paper should be available.
2. The language of the paper should be English.
3 Ischemia should be noted in the abstract.
4. Ischemia should be evaluated in skin.
5. The research should be performed in an *in vivo* model.

Exclusion Criteria

1. Studies on ischemia involving human beings.
2. Study protocols, book chapters, supplements, or editor comments.
3. The papers on animals which full text were not available.
4. Language was not English.

We got the number of citations for each paper by reviewing the selected papers in Google Scholar and Web of Sciences websites.

3. RESULTS

Method and steps of the research was shown in flow chart no one.

Some important data of the seven types of animal ischemic models (REIM, ASF, Burns, ischemic limb, localized ischemic wound healing, PU, skin flaps) as well as their results are presented in Tables 1 -7. In table eight for each of animal ischemic models, the number of studies, number of wounds, and total and average Google Scholar citations, and Web of Science citations are included. Accordingly we have found 16 papers related to rabbits' ear ischemic models, 18 papers related to axial skin flaps, 18 papers related to burn models, 9 papers related to ischemic limb models, 16 papers related to localized ischemic wound healing, 11 papers related to pressure sores, and 29 papers related to skin flaps. In total, there were 107 papers.

Flow Chart 1. Flow chart of method and steps of the research

<table>
<tr><td>Files identified through PubMed, Medline, Scopus, Science Direct, and Google Scholar
(240)
↓</td><td>Additional files identified through other databases
(n = 0)
↓</td></tr>
<tr><td colspan="2">Files after duplicates deleted
(n = 140)</td></tr>
<tr><td>Files screened
(n = 107)
↓</td><td>Files excluded
(n = 0)
↓</td></tr>
<tr><td>Full-text papers assessed for eligibility
(n = 107)
↓</td><td>Full-text papers excluded, with reasons
(n = 0)
↓</td></tr>
<tr><td colspan="2">Studies included in qualitative synthesis
(n =107)</td></tr>
</table>

Table 1. Specifications of rabbits' ear ischemic model in the reviewed papers; abbreviations: Proadrenomedullin N- terminal 20 peptide (PAMP), stromal progenitor cell (SPC) , Platelet-derived growth factor(PDGF), high-performance liquid chromatography (HPLC), human telomerase reverse transcriptase (hTERT), Keratinocyte growth factor-2 (KGF-2), recombinant human Macrophage colony-stimulating factor (rh M-CSF), Reverse transcription - polymerase chain reaction (RT-PCR), rh basic fibroblast growth factor (bFGF)

Ref. no & 1st author's name & published year, animal	Target organ or tissue, technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
34. Reyes-ortega, 2015, Rabbit	Ear, One artery and vein were ligated	1circular excisional wound	A 2 layer dressing for repair of non healing wounds	Macroscopic & Microscopic tests	The dressing enhanced wound repair in both ischemic and non-ischemic injuries	20,12
35. García-Honduvilla, 2013, Rabbit	Ear, one artery and vein were ligated	A circular wound, 2 cm in diameter	Topical treatment with proadrenomedullin N- terminal 20 peptide (PAMP), Alone, or with stem cells	Macroscopic & Microscopic tests	The treatments improve healing both in normoxic and ischemic conditions.	8,5
36. Said, 2009, Rabbit	Ear, Division of the different arteries	7 wounds In each ear	They postulated that ischemic situation could ctivate hypoxic signalling paths	Luciferase assay	The biologic systems for hypoxic signalling could be applied to show local ischemia	2,0
37. Wang, 2009, Rabbit	Ear, The two arteries were ligated	Four round full-thickness wounds	ATP-vesicles was used	Histologic studies, Wound Tissue Angiogenesis	The treated-wounds exhibited extremely fast granular tissue growth.	16,9
38.Volk, 2007, Rabbit	Ear, One or more of the arteries or veins were ligated & circumferential incisions made.	Four 6mm diameter wounds	Stromal progenitor cell (SPC) therapy	4	Treated -wounds showed significantly accelerated wound healing	15,13
39. Kloeters 2007, Rabbit	Ear, Two arteries were dissected	Four 7 mm full-thickness punch wounds	Ad-Smad3 or Ad-LacZ was administrated.	-Histological analysis	Reepithelialisa-tion Was enhanced in an ischemic wound mode	14,7

Ref. no & 1st author's name & published year, animal	Target organ or tissue, technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
40. Chien, 2007, Aged Rabbit	Ear, Two arteries were ligated, & a circumferential tunnel was made.	2 to 4 circular 6-mm -full-thickness wounds	An occlusive Dressing with ATP	-Measurement of ATP by high-performance liquid chromatography (HPLC)	ATPs were higher in the normal ear than in the ischemic ear.	18,12
41.Sun, 2007, Rabbit	Ear, One or more of vessels were ligated& circumferential incisions	Two 8-mm excisional dermal ulcers	Collagen-based Platelet-Derived Growth Factor (PDGF) targeting delivery ystem	-Histological test for new collagen deposition,& capillary lumens	PDGF-BB could effectively promote ulcer healing	47,29
42. Mogford, 2006, elderly Rabbit	Ear, Division of 2 arteries, with preservation of the 3 veins	Three to five 6-mm full-thickness dermal punches	Treating wounds by gene delivery of human telomerase reverse transcript ase (hTERT)	4	hTERT significantly improved ischemic wound healing in old rabbits	23,18
43. Breitbart, 2001, Rabbit	Ear, Division of the two of 3arteries	3 Eight-millimeter-diameter excisional wounds	Treating by cultured fibroblasts enriched with growth factors	-Immuno histochemistry	Treatment modulates ischemic wound healing	46,27
44. Xia, 1999, Rabbit	Ear, Division of two arteries & circumferen-tial incisions	Three 6-mm full thickness dermal ulcers	Topically applied Keratinocyte growth factor-2 (KGF-2)on wound	-Histological analysis	KGF-2 is effective.	133,63
45. Liechty, 1999, Rabbit	Ear, One or more of three arteries or veins were divided and circumferential incisions.	6 mm wounds	Topical treatment by an adenovirus containing the PDGF-b	4	Platelet-derived growth factor-B overcame the ischemic defect in wound healing .	143,98

Ref. no & 1st author's name & published year, animal	Target organ or tissue, technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
46. Wu, 1997, Young rabbits	1,2, or 3 arteries or veins were divided and circumferential incisions.	Four 6 mm diameter full-thickness circular wounds	Treating by recombinant human Macrophage colony-stimulating factor (rh-M-CSF)	1.Histology, 2.Reverse transcription - polymerase chain reaction (RT-PCR)	M-CSF increases dermal ulcer ischemic wound healing	51,42
47.Uhl, 1993, Mice	Two of the three principal Neurovascu-lar bundles were ligated	A (6.6mm2) full-thickness dermal layer was excised	Treatment with hyperbaric oxygen	1.Measurement of wound surface area, 2.Laser Doppler imaging	Hyperbaric oxygen therapy improves reepithelializa-tion in normal and ischemic skin tissue	114, 76
48.Uhl, 1993, Mice	two of the three principal neurovascu-lar bundles were ligated	a (5 mm2) full-thickness dermal layer was excised	Injection of basic fibroblast growth factor (bFGF)	1.Measurement of wound surface area, 2.Morphological studies	bFGF decreas wound surface area of ischaemic tissue.	58,44
16. Ahn, 1990, Rabbit	1,2, or 3 arteries or veins were divided and circumferen-tial incisions.	Four 6-mm Surgical punch biopsies	To test effects of blood flow changes on dermal repair	4	This ischemic ulcer model is reliable & quantifiable.	140, 102

Table 2. Specifications of axial skin flaps in the reviewed papers; abbreviations, ischemia-reperfusion (I/R), platelet rich plasma (PRP), Axial skin flap (ASF), human umbilical cord matrix stem (HUCMS) cells, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-beta) and extracorporeal shock waves (ESW)

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
49. Leng, 2017, Rat	Skin , Abdominal perforator skin flaps	No wound	Treating by a new method of the "stem cells-gene" combination therapy.	1.Evaluation of flap surface, 2. Evaluation by HE staining 3. Evaluation of platelet endothelial cell adhesion molecule	This stem cells therapy can effectively improve the repair of ischemia-reperfusion(I/R) injury	0,0
50. Sönmez, 2013, Mice	Skin,A lateral thoracic artery pedicled island skin flap was made & arteries were occluded .	No wound	Treating by platelet rich plasma (PRP)	-In vivo bioluminescence imaging, - Histology and immunohistochemistry	This study shows the angiogenic effects of PRP	18,10
51.Leng, 2012, Mice	Skin, Axial skin flap (ASF), using clamp for epigastric artery for inducing ischemia	No wound	Treating by human umbilical cord matrix stem (HUCMS) cells	4	HUCMS cells could progress the viability of ASF by promoting vascularization	12,4
52. Mirabella, 2012, Rat	Skin, A ASF elevated in the Abdominal region & inferior epigastric vessels was ligated.	No wound	Amniotic fluid stem cells (AFSC) derived conditioned media (ACM) delivered topically into a ASF	-Histological analysis, - Recruitment studies and progenitors isolation	ACM is good for patients	31,19
53. Plock, 2008, Mice	Skin, Two flaps were made on both sides of mices, then the related arteries were ligated	Incision	To target healing and survival of flap by application of liposomal hemoglobin vesicles (HbVs).	-Histological examination, - Laboratory analysis	HbVs may improve the viability and wound healing in ASF	24,16

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
54. Schlaudraff, 2008, Rat	Skin, Random dorsal skin flaps were made, and related arteries were divided	No wound	To test the effects of leeches in mixed arterio-venous insufficiency	-Macroscopic and Planimetric Analysis, - Laser-Doppler Flowmetry	Application of leeches can be hazardous to flap viability	15,8
55. Fujihara, 2008, Rat	Skin, Dorsal island skin flap based on the related artery were made	No wound	Delivereing basic fibroblast growth factor (bFGF) to flap	4	Delivery of bFGF to the flap area enhances the viability of an ASF.	33,16
56. Michlits, 2007, Rat	Skin, A flap was made, and the related vessels were ligated.	No wound	To evaluate the effect of topical administration of a vascular endothelial growth factor (VEGF)-A plasmid to the flap bed	4	This protocol may also enhance wound healing in post trauma skin lacerations or in skin grafts	49,34
57. Giunta, 2005, Rat	Skin, A flap was made and inferior and superior epigastric arteries were dissected	No wound	To test the effect of preoperative injection of adenoviral vectors encoding (Ad)VEGF(165)	4	Results confirm the important role of VEGF(165) on angiogenesis in ASF	54,28
58. Huemer, 2005, Rat	Skin, An epigastric skin flap model were made, next the related vessels were ligated	No wound	To compare the effect of gene therapy with transforming growth factor-beta (TGF-beta) & extra-corporal shock waves (ESW) to treat ASF	- Evaluation of flap survival, - Microscopic flap analysis	Treatment with ESW enhances ASF viability significantly more than TGF-beta	60,27
59. Harder, 2004, Pig	Skin, skin flap was made on each side of the gluteals, next the related vessels were ligated	No wound	to test, if ASF survival may be improved by local heat preconditioning	- Histological examination, - Apoptosis	Necrosis and apoptosis rate of ASF could be reduced significantly in treatment group	44,27

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
60. Furuta, 2004, Mouse	Skin, The related artery was ligated, later the zoned skin was incised, and elevated	No wound	to test ASF viability, &angiogenesis whilst under pharmacological or genetic inhibition of nitric oxide synthase (NOS)	- Flap survival, -Histology, - immunoreactivity	NOS has a significant role in promoting wound healing/angiogenesis in its early stages	17,0
61. Mittermayr, 2003, Rat	Skin, Denervated epigastric island skin flaps were elevated, tolerated ischemic for 8 hours, then reperfused	No wound	to test whether S-nitroso human serum albumin(oxide-donor) improves ASF survival	4	Nitric oxide has as an key mediator in the defence against ASF I/R injury	31,17
62. Cottler, 1999, Rat	Skin, An ASF were made & the related artery was ligated temporarily	No wound	Two 18-gauge needle-puncture outlets , or two sessions of leech therapy	-Assessment of flap perfusion and viability	Two spatially separated outlets are as effective as one leech in improving flap viability	25,14
22. Taub, 1998, Rat	Skin,Unilateral axial pattern skin flaps (6×3cm) was made, based on the epigastric artery, & temporary occlusion	No wound	To test the effect treating with the gene for VEGF	1. Dye fluorescence, & 2. planimetry	Treatment can improve the survival of ASF	42,33
63. Taub, 1998, Rat	Skin,Unilateral ASF based on the related artery, & temporary occlusion	No wound	Treatment with the gene encoding of VEGF	1. Dye fluorescence, & 2. immunohistochemical analysis	The treatment improved flap viability	135,85
64. Ueda, 1998, Rat	Skin, the ASF were made, next the related vessels were ligated	No wound	To test the effect of sulfatide on I/R injury	4	The treatment has a significant defensive effect against I/R	17,12

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
65. Lees, 1991, Horse	Skin, An ASFflap in the horse were made. End-to-end anastomoses were used in some flaps	No wound	To review authors experimental work with the ASF flap in the horse	Follow-up	Horse must be highly susceptible to I/R injury	3,1

Table 3. Specifications of burn models in the reviewed papers; abbreviations: recombinant human erythropoietin (rhEPO), topical lidocaine/prilocaine cream (EMLA), D-myo-inositol-1,2,6-trisphosphate (IP3)

Ref. no& 1st author's name & published year, animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
66. Fourman, 2014, swine	Skin, 4 burns were made	Wound	To test the capability of two methods of angiography in the estimation of burn progression	-Perfusion analysis, - wound assessment	Indocyanine green dye angiography has markedly beneficial potential in the estimation of burn development	12,8
67. Soto-Pantoja, 2014, mice	Skin, Burns were induced by using a 95 °C heated brass rod	Wound	To test absence of CD47 on the rate of wound closure	4	Affecting CD47 may accelerate burn healing process	18,9
68. Tobalem, 2014, Rat	Skin, The burns were made using comb burn model	Wound	To evaluate the effect of local warming on burn progression	4	Treatment improved the microcirculatory perfusion	11,9
69. Hanjaya-Putra, 2013, mouse	Skin, Third degree burn was generated.	Wound	To test engineered human vasculatures when embedded in a burn model	Histology and Immunohistochemistry	Vasculature was improved in ischemic conditions	22,16

Ref. no& 1st author's name & published year, animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
70. Bader, 2012, Mice	Skin, A zone on the back of the mice was burned by hot water	Wound	To know the effect of nanosized re-combinant human erythropoietin (rhEPO) in burn healing	1.Histological analysis, 2.Gene expression Analysis, 3.Western blot analysis	rhEPO improved burns	21,10
71. Lanier, 2011, domestic pig	Skin, 4 full thickness burns were made using a comb model	Wound	To understand the rates of cellular death and apoptosis in the area of ischemia close to burn	5	It was demonstrated pathological signs of cell death	32,23
72. Singer, 2009, Rat	Skin, A brass comb burn makes3 burns	Wound	To test A brass comb burn model	- Photography -Histopathologic studies	the progression of most unburned ischemic zones to necrosis were happened	26,18
73. Singer, 2008, Rat	Skin, 4 burns were made by a brass comb model	Wound	To test the involvement of necrosis and apoptosis to cell death in the ischemic part.	Immunohistochemistry	Both apoptosis and necrosis are present in the ischemic part	50,29
74.Singer, 2007, Rat	Skin,4 burns were made with a brass comb	Wound	To test the effect of curcumin on the conversion of the ischemic zone to necrosis	-Photography, -Histopathologic studies	curcumin reduced the percentage of unburned skin that progressed to necrosis.	44,25
75. Penington, 2006, Rat	Skin, Two burns was made with a brass block, them a axial skin flap (ASF) was made	Wound	To define whether the area of stasis displays a clear phase of sensitivity to a sublethal exposure to ischemia	Histological examination	Area of stasis shows amplified sensitivity to ischemia one to two days after burning	3,2
76. Cassuto, 2005, Rat	Skin, Partial and full thickness burns were induced in the abdominal skin	Wound	To test the effect of alpha- and beta-adrenoceptors in blood circulation of normal and burned skins	-Blood pressure and heart rate, - Blood flow	Activation of alpha(2)-receptors meaningfully impair skin circulation	10,7

Ref. no& 1st author's name & published year, animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
77. Arslan, 2005, Rat	Skin, At first a dorsal skin flap was made, next 9cm2 of the flap was burned	Wound	To test the effects of mixture of L-carnitine and vitamin C on partially burned skin flap	- Macroscopic examination	The treatment decreased risk of ischemia-induced necrosis in flap.	15,6
78. Tan, 2002, Guinea pig	Skin, The skin of the guinea pigs were burned by hot water	Wound	To test the effect of Ibuprofen on inhibiting post burn ischemia	- Determination of depth of capillary stasis - Assessment of 6-keto-PGF1α and TxB2 in skin tissue	Ibuprofen did not inhibit progression of ischemia after burning	13,8
79. Lindblom, 2000, rat	Skin,A full-thickness burn was made in the abdominal skin	Wound	To test the effects of Vasoactive intestinal polypeptide (VIP)on post burn skin perfusion & progressive ischemia	- Laser Doppler measurements of skin blood flow	VIP application significantly impaired skin perfusion	7,3
80. Jönsson, 1999, Rat	Skin,A full-thickness burn was made in the abdominal skin	Wound	To test the effects of lidocaine on eicosanoid formation by normal and burned skins	-Eicosanoid analysis	The absence of effect of vascular route of lidocaine could relate to the severe burn trauma	19,12
81. Cetinkale, 1997, Rat	Skin, 4 burns were induced.	Wound	To examine the responses in the adjacent zone of burn damage that might cause to more necrosis	- Assessment of muscle perfusion, - Assessments of tissue oedema	Neutrophils might be contributed in the pathogenesis of local reaction to burn injury	38,23
83. Tarnow, 1996, Rat	Skin,A burn injury was induced in the abdominal skin	Wound	To test the effects of D-myo-inositol-1,2,6-trisphosphate (IP3), on the development of ischemia	- Skin blood flow	IP3 improved local dermal perfusion in burned skin	16,12
84. Battal, 1996, Rat	Skin,A combo brass burn model was made	Wound	To test the effects of a prostaglandin I2 analogue, on burn injury	4	Prostaglandin I2 plays an important role in burn injury	21,13

Table 4. Specifications of ischemic limb models in the reviewed papers; Abbreviations: remote ischemic preconditioning (RIPC) , the heme oxygenase-1 (HO-1), histone deacetylase inhibitors (DIs) , bone marrow platelet rich plasma (bm-PRP), peripheral blood platelet rich plasma (pb-PRP), E-twenty six (ETS) factor Ets variant 2 (ETV2), poly-D,L-lactide-co-glycolide (PLGA), nitric oxide (NO), thrombospondin 2 (TSP2), bone marrow-derived endothelial progenitor cells (BMD EPCs), Duchenne muscular dystrophy (DMD)

Ref no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
89. Cremers, 2017, Mice	Skin, 3 cycles hind limb ischemia was induced, next 2 full-thickness excisional wounds were made on the dorsal side of mice	Excision	To improve skin wound repair by remote ischemic preconditioning (RIPC) treatment via induction of the heme oxygenase-1 (HO-1).	-Immunohistochemical staining & test, - Real Time-Quantitative-PCR	RIPC did not accelerate wound closure.	0,0
26.Park, 2016, Rat	Skin, Hindlimb ischemia was induced by femoral artery ligation, then an excisional wound were made	Excision	To study the role of E-twenty six (ETS) factor Ets variant 2 (ETV2)on vascular egeneration	5	A novel obligatory role for the ETV2 was reported	15,12
90. Spallotta, 2013, Mice	Skin, Femoral artery was excised.	No wound	To test the effect of Histone deacetylase inhibitors (DIs) during tissue regeneration following acute peripheral ischemia	7	Class-selective DIs interfere with normal mouse ischemic hindlimb regeneration	18,13
91. Nishimoto, 2013, Rabbit	Skin, All related arteries were ligated.3 weeks later, a 2×2 skin defect created on both legs	Excision	To test effect of Platelet rich plasma (PRP) derived from bone marrow aspirate (bm-PRP) and from peripheral blood (pb-PRP) on wound healing of persistent ischaemic rabbits' limbs	-DiI staining, -wound observation	Injection of bm-PRP is good for treating wounds on ischaemic limbs.	4,2

Ref no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
92. Porporato, 2012, Mice	Skin, After resection of femoral vessels, a circular wound a 5- or an 8-mm diameter were made.	Excision	Whether the pro-angiogenic potential of lactate may be exploited therapeutically to accelerate wound healing	4	Poly-D,L-lactide-co-glycolide (PLGA) promoted angiogenesis & accelerated wound losure	52,40
93. MacLauchlan, 2011, Mice	Skin, Ischemia was induced in one leg of mice by ligation of both the femoral and saphenous arteries, next 2 full-thickness excisional wounds were made	Excision	Providing evidence that nitric oxide (NO) induces angiogenesis	6	Modulation of thrombospondin2 (TSP2) expression is a major function of NO	44,18
94. Alizadeh, 2007, Rat	Skin, After femoral arterial resection, a full-thickness skin area of 1.2×0.8 cm was removed from rats' foot	Wound	A new animal model designed to assess the impact of ischemia on wound healing	4	A significant delay in wound closure was observed	30,20
95. Bauer, 2006, Mice	Skin, The related vessels were ligated, next the mice received bilateral excisional wounds with a 3-mm punch biopsy on the hindlimb.	Excision	To test the relationship between bone marrow-derived endothelial progenitor cell s (BMD EPCs) and wound healing.	5	BMD EPCs were incorporated into the neovessels in the granulation tissue	74,50

Ref no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
96. Straino, 2004	Skin, In a model of hindlimb ischemia on femoral artery ligation, a full-thickness wound of 3.5 mm diameter was created	Wound	To test, whether new blood vessel development was altered in mdx mice. mdx mouse is a model for studying Duchenne muscular dystrophy (DMD)	-Histology, Immunohistochemistry, - Angiogenesis Assays	Arteriogenesis is enhanced in mdx mice both after ischemia and skin wounding and in response to growth factors	46,40

Table 5. Specifications of localized ischemic wound healing in the reviewed papers; abbreviations: mu opioid receptor (MOPr), kappa opioid receptor knockout (KO), hyperbaric oxygen (HBO), hypoxia-inducible factor-1alpha (HIF-1alpha), glycyl-L-histidyl-L-lysine tripeptide-copper complex (TCC), tumor necrosis factor alpha (TNF-alpha), matrix metalloproteinases (MMP), vascular endothelium growth factor (VEGF)

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
97.Wang , 2017, Mice	Skin,2 parallel incisions were made, next 2 full-thickness, 6 diameter wounds were made on the midline	Wound	To test the effect of mu opioid receptor (MOPr)-on healing of full thickness ischemic wounds using MOPr or kappa opioid receptor knockout (KO) mice	4	MOPr plays an important role in the proliferation phase with the formation of granulation tissue	0,0
98. Trujillo, 2015, Rat	Skin , A bipeicled flap were made, next two 6-mm-circular "ischemic" wounds were made, A silicone sheet were placed under flap.	Wound	To show an ischemic flap model that permits a prolonged reduction of blood flow resulting in wounds that resemble a ischemic&chronic wound model	4	This model presents a valuable alternative to previously developed ischemic skin flap models.	9,1

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
99. Moor, 2014, Rat	Skin, 2 full-thickness 6-mm excisional wounds were created in the center of a 10.5× 3.5-cm flap	Wound	To test the hypothesis that age and tissue ischemia alter the balance of endogenous antioxidant enzymes	6	Deficiencies in two antioxidant pathways in aged rats observed that become exaggerated in ischemic tissue	12,8
100. Zhang, 2014, Rat	Skin, A dorsal, bipedicle skin flap was raised , then two 6 mm full-thickness excision wounds were created in the center of the flap	Excision	To test whether hyperbaric oxygen treatment (HBOT) modulates reactive oxygen species (ROS) and matrix metalloproteinase (MMP) regulation in ischemic wound tissue	-Western blot, - Histology and immunohist ochemistry	HBOT acts via the ROS / mitogen-activated protein kinases (MAPKs)/ MMP signaling axis to improve ischemic wound repair	21,12
101. Ruedrich, 2013, Rat	Skin, At first a 3 × 11.5-cm dorsal pedicle flap were made, Next four, 6-mm wounds were created symmetrically	Wound	To determine the most stable reference gene for studying gene expression in a rat ischemic wound-healing model using reverse transcription-quantitative polymerase chain reaction 9RT-qPCR)	- Real-Time PCR	Results provide insight on dependence of reference-gene stability on experimental parameters	3,0
102. Howe, 2011, Rat	Skin, An ischemic tissue flap was created . Two ischemic wounds were created	Wound	A electrical stimulation bandage has been developed for use with an established rat ischemic wound model	Clinical observation	The device has been successfully demon-strated using the rat ischemic wound model for a period of seven days	1,0
103. Weinreich, 2010, Rat	Skin, A pedunculated ischemic skin flap (3 × 7 cm) was lifted, One 8-mm wound was made in the flap	Wound	To test the hypothesis that systemic administration of isoniazid or niacin can enhance ischemic wound healing in	- PCNA immunohist ochemistry, - Angiogenic assays,	Isoniazid stimulates wound-healing in ischemic tissue to the level of nonischemic wounds	2,1

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
104. Roy, 2009, Pig	Skin , 4 full-thickness bipedicle skin flaps (15 × 5 cm) were made, one 8-mm excisional wounds were made in the each flap	Excision	To develop and characterize the first porcine model of ischemic wound utilizing pig	8	This study serve as a base to develop hypotheses aiming to elucidate the biology of ischemic chronic wounds	82,45
105. Xue, 2009, Pig	Skin, An ischemic tissue flap is created. One ischemic wound was made	Wound	To develop a mathematical model of ischemic dermal wounds.	4	Ischemic conditions limit macrophage recruitment to the wound-site and impair wound closure	90,52
106. Zhang, 2008, Rat	Skin, A dorsal, bipedicle skin flap was raised , then two 6 mm full-thickness excisional wounds were created in the center of the flap	Wound	To test the effect of HBO on ischemic wound healing	6	HBO improves wound healing by downregulation of hypoxia-inducible factor-1alpha (HIF-1alpha)	115,71
107. Poonawala, 2005, Rat	Skin, 2 parallel incisions were made, then two 8-mm wounds were inflicted between incisions.	Wound	To test the effect of topically applied opioids on the healing of ischemic wounds in rats	1-istological evaluation, 2-Immuno-fluorescent staining, 3-Western blot analysis	Opioids accelerate wound healing	93,62
27. Gould, 2005, Rat,	Skin, Bipdicle skin flap were made, Two 6mm excisional wounds were created in the the flap, and a sheet was inserted into wound bed.	Excision	To develop a reproducible ischemic model for use in wound-healing studies	Wound-breaking strength, Lactate test, PDGF test	The excisional wounds provide sufficient tissue for biochemical and histologic analysis	40,28

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
108. Canapp, 2003, Rat	Skin, 6-mm-diameter, wounds were created within an ischemic bipedicle skin flap	Wound	To test the effects of topical glycyl-L-histidyl-L-lysine tripeptide-copper complex (TCC)2% gel on tumor necrosis factor alpha (TNF-alpha) , &matrix metalloproteinases (MMP) in a ischemic open wound	TNF-β Concentrations, MMP-2 and MMP-9 Concentrations	Topical TCC resulted in accelerated wound healing in ischemic open wounds.	59,29
109. Zhang, 2003, Rat	Skin, Normal incisional wound and H-shaped double flaps were made, The ischaemic test wound was the horizontal bar in the H-shaped double flap	Incision	To test the effect of exogenous vascular endothelium growth factor (VEGF) on wound healing in an ischaemic skin flap model	VEGF level determination, Tensile strength test, CD31 immunohistochemical staining	Treatment can increase early angiogenesis and tensile strength	90,45
110.Lee, 2000, Sheep	Skin, Bilateral 10 × 15 cm dermal flaps were reated, flap was then divided into 3 fields and Staphylococcus aureus was injected to each field	No wound	To study the effect of a noncontact radiant heat bandage in controlling an ischemic soft tissue infection	Bacterial quantification	Treatment controls ischemic soft tissue infections	16,6
111. Chen, 1999, Rat	Skin, Six wounds were made within a bipedicled dorsal flap	Wound	To provide molecular and mechanistic evaluation of an ischemic wound model	4	This model will likely prove to be useful in chronic wound research.	90,56

Table 6. Specifications of pressure ulcers in the reviewed papers; abbreviations: Cyclooxygenase-2 (COX-2), Ischemia-reperfusion (I/R), pressure ulcer (PU), laser speckle flowgraphy (LSFG), Erythropoietin (EPO)

Ref. no & 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
112.Romana-Souza, 2016, Mice	Skin, Dorsal skin was pulled up and placed between a pair of magnet for 2 periods	Wound	To test the effect of the administration of celecoxib [a selective Cyclooxygenase-2 (COX-2) inhibitor] in wound healing of pressure ulcers.	5	Celecoxib administration improves the wound healing of pressure ulcers	4,0
29.Uchiyama, 2015, Mice	Skin,The skin was pulled up and trapped between two round ferrite magnetic for 12 hours	Wound	To assess the role of MFG-E8 in the formation of skin ulcers	Real time -PCR	Exogenous application of MFG-E8 is good for I/R injuries	14,9
113. Assis de Brito, 2014, Mice	Skin,16-hour period of magnet placement, followed by a release period of 8 h for 2 cycles.	Wound	To test the effect of β1-/β2-adrenoceptor blockade in wound healing of pressure ulcers	6	β1-/β2-Adrenoceptor blockade delays wound healing	12,10
114. Jiang, 2011, Rat	Skin, One of four Ischemia-reperfusion (I/R) cycles [70 mm HG of pressure for 2 hours followed by 1, 2, 3, or 4 hours of reperfusion].	Wound	To explore the possible mechanism of I/R injury in begining of pressure ulcer(PU) development using clinically relevant amounts of pressure and pressure duration	-Biochemical test, -Histological test	a minimum of 4 hours pressure relief may be helpful for PU prevention	30,15

Ref. no & 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
115. Nakagami, 2010, Rat	Skin, Ischemic wounds were created between the 2 incisions by applying an indenter for 3 hours	Wound	To test the usefulness of laser speckle flowgraphy (LSFG) for assessing skin blood flow in PU	Skin Blood Flow Measurements, Light Microscopic Assessment	LSFG measurements were useful for assessing tissue circulation	11,8
116. Erbayraktar, 2009, Rat	Skin, 5 recurring 2-h ischemic episodes, each separated by 30 min of reperfusion (12 h total), were performed, followed by a period of 12 h of ischemia	Wound	To test the effect of receptor-selective derivatives of Erythropoietin (EPO) in an PU	Wound size measurement	Wound healing is mediated by the tissue protective receptor isoform	44,28
117. Tsuji, 2005, Mice	Skin, 4 cycles of compression release. One cycle consisted of 2 hours of compression and 1 hour of release.	Wound	To establish a PU model that visualizes the microcirculation	Intravital microscopic images	Significant contribution of I/R injury to the pathophysiology of PU observed.	118,74
118. Stadler, 2004, Mice	The skin was gently pulled up and placed between 2 magnetic plates that had 12 mm diameter for 3 cycles	Wound	This paper reports the development of a reliable mouse model of I/R injury by the external application of magnets.	Macroscopic evaluation, Recording skin temperature	This method will facilitate the development of new prevention and management strategies.	75,48
119. Peirce, 2000, Rat	Skin, I/R injury was induced by applying and removing a permanent magnet to a rat skin under which a ferromagnetic steel plate was implanted	Wound	To develop and characterize a reproducible model of cyclic I/R injury in the skin of small un-anesthetized animals	4	Using this model, the biological markers of I/R-induced wound development can be studied	265,121

Ref. no & 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision/ Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar & Web of sciences citations
120. Houwing, 2000, Pig	Skin, Pressure application was achieved with a newly developed computer-controlled pressure device	Wound	To investigate the role of I/R in pressure-induced tissue necrosis in the trochanteric region	Pathological examination, Biochemical analysis	Administration of vitamin E may prevents PU in humans undergoing elective surgery	103,?
121. Lauritzen, 1981, Rabbit	Skin folds were located in chambers with temperature of (36°C&10°C) during cuff compression (200 mmHg) for 4 h	Wound	To quantitate the skin injury caused by the pressure ischemia	-The breaking load of the wounds	Cooling may preserve the reparative capacity in skin subjected to pressure ischemia	1,1

Table 7. Specifications of flap skins in the reviewed papers; abbreviations: hepatocyte growth factor (HGF), random skin flaps (RSF), Propionyl-L-carnitine (PLC) , L-arginine (LA), Kaurenoic acid (KA), 17β-estradiol (E2), nitric oxide (NO), fibroblast growth factor-2 (FGF-2 or bFGF) and erythropoietin (EPO), polydeoxyribonucleotide (PDRN), plasmid DNA encoding VEGF(165) (pVEGF), pentoxifylline (PTX), cerebrospinal (CSF), erythropoietin(EPO) nuclear magnetic resonance (NMR), xanthine oxidase (XO)

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
122. Chenu, 2017, Mice	Skin, A U-shaped peninsular skin incision was made	No wound	To study the role of steroid hormones in male mice	4	Testosterone provides males with a strong protection against cutaneous necrosis	2,0
123. Seyed Jafari, 2017,	Skin, A random dorsal skin flaps (modified	No wound	To test effect of lectropora-tion mediated hepatocyte growth	4	Electroporation-mediated HGF gene delivery	3,0

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
Rat	McFarlane) were made		factor (HGF) gene delivery to random dorsal skin flaps		enhanced viability and vascularity of the ischemic skin flap	
124. Zellner, 2015, Pig	Skin, four random skin flaps(RSF) per animal were made	No wound	To determine if skin flap failure rates could be improved with the use of a dissolved oxygen wound dressing	Histology	Treated-flaps had fewer clinical failures and improved histological profiles	5,2
125. Scioli, 2015, Rat	Skin, A 10 × 3 cm l skin flap was elevated. An excisional wound in other rats were made.	Excision	To investigate the effects of Propionyl-L-carnitine (PLC) in rat skin flap and cutane-ous wound healing	6	PLC treatment improved rat skin flap viability, accelerated wound healing and dermal angiogenesis	13,6
126. Cao, 2015, Rat	Skin, A McFarlane flap model (9 × 3 cm) was designed	No wound	To investigate the effects of lidocaine on RSF survival in rats.	4	Lidocaine increased flap viability	7,7
127. Silva, 2015, Rat	Skin, A modified McFarlane flap model (2.5 ×8) cm was made	No wound	To investigate the protective effects of L-Arginine (LA) and Kaurenoic acid (KA), against ischemia reperfusion (I/R)injury	Biochemical Assays	KA may attenuate the oxidative stress and the inflammation	12,6
128. Harder, 2014, Mouse	Skin, A randomly perfused flap(11×15mm) Were made	No wound	To present a well-established model to directly visualize microvascular architecture	Intravital Epifluorescence Microscopy	The model has proven reliability in several published experimental studies	9,4
129. Khan, 2013, Mouse	Skin, A peninsular flap (3×1.5cm) by making three soft tissue incisions were made.	No wound	To study the significance of monocyte heterogeneity in physiologic neovascularisation and flap	4	Loss of function of chemokine ligand and receptor genes influenced the transcription of local genes involved in monocyte chemotaxis and wound angiogenesis	7,4

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
130. Shafighi, 2012, Rat	Skin, A caudally pedicled flap measuring 3 ×9 cm was made	No wound	To investigate the influence of of topical E2 on the survival of skin flap	Flap survival assessment, measuring distribution of blood flow	Treatment significantly increase survival of ischemically challenged skin flaps	11,6
131. Fayazzadeh, 2012, Rat	Skin, Full-thickness rectangular skin incisions (2×8) were made	No wound	To investigate the effects of fibroblast growth factor-2 (FGF-2 or bFGF) and erythropoietin (EPO) in prevention of skin flap necrosis	-Measuring survival rate, -Histology	Treatment of skin flaps could remarkably increase tissue viability and accelerate the wound healing process	6,4
132. Polito, 2012, Rat	Skin, H-shaped flap(2×4cm) were used	No wound	To assess the ability of polydeoxyribonucleotide (PDRN) to restore blood flow & improve wound healing	4	PDRN restores blood flow and tissue architecture	19,14
133. Milch, 2010, Rat	Skin, A modification of the single pedicle dorsal skin flap were made.	No wound	To determine if monocytes activated toward an angiogenic phenotype can be used to improve ischemic tissue healing	Macroscopic Evaluation, Histology	Delivery of activated pro-angiogenic monocytes enhance histologic evidence of vascularity	5,5
134. Ferraro, 2009, Rat	Skin, The RSF was elevated and sutured back to its bed	No wound	Plasmid DNA encoding VEGF(165) (pVEGF) was delivered to the ischemic skin	5	pVEGFE+ increase perfusion and healing of skin flaps and ischemic wounds	69,39
135. Kuo, 2009, Rat,	Skin, A random-pattern extended dorsal-skin-flap (10 × 3 cm)	No wound	To assess whether extracorporeal shock wave (ESW) treatment rescues the compromised flap tissue	5	ESW treatment exerts a positive effect of rescuing ischemic extended skin flaps	60,42
136. Uema, 2008, Rat,	Skin, A RSF (10×4)were made.	No wound	To evaluate the possible benefits of eletroacupuncture stimulation of the points over the skin flap	Macroscopic appearances	Treatment preserved vitality and decrease RSF necrosis	8,6

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
137. Liapakis, 2008, Rat	Skin, A full thickness dorsal flap (10 × 2 cm) was designed	No wound	To determine the effect of local application of exogenous leptin on the survival of full thickness skin flaps	Histological and immunohistochemical evaluations	Treatment increases early skin flap angiogenesis	13,0
138. Liebano, 2008, Rat	Skin, The random skin Flap(10×4 cm) was raised and a plastic barrier was placed between the flap and its bed	No wound	To determine the effect of low-frequency (2 Hz) transcutaneous electrical nerve stimulation (TENS) on the viability of ischemic skin flaps	Estimating the percentage of necrotic area	Treatment was effective in improving the viability of skin flap.	39,22
33. Bayat, 2006, Rat	Skin, A RSF(20×70)were made	Incision	To clarify the histological, & ultrastructural effects of pentoxifylline (PTX) on the survival of RSF	4	Thirty days of pretreatment of RSFs with PTX significantly increased the survival of RSF	19,8
139. Park 2004, Rat	Skin,A flap (1.25× 2.5-cm) was elevated in the athymic nude mice,then a silicone sheet was separated the flap from the bed	No wound	To determine whether circulating endothelial stem cells might selectively traffic to regions of tissue ischemia	- Assessment of the Flap, -Histologic Assessment,	Systemic delivery of endothelial progenitor cells increased neovascularization	94,58
140. Babuccu, 2004, Rat	Skin, a 3 × 3 cm skin flap was elevated	No wound	To find out the effect of cerebrospinal(CSF) fluid leakage on wound healing after flap surgery	-Radioactivity in the CSF collection -Macroscopy, -Histology	CSF leakage itself has effects on wound healing.	14,4
141. Buemi, 2002, Rat	Skin, The RSF (3×9) were cut on the skin of the rat.	No wound	To ascertain whether erythropoietin(EPO) plays a role in repair processes following ischaemic skin flap injury	5	Treatment improve the wound healing process	78,50

Ref. no& 1st Author's Name & Published year, Animal	Target organ or Tissue, Technique	Incision /Excision (wound) /Nothing	Intervention	No of evaluating methods	Main results/ Conclusions	Number of Google scholar& Web of sciences citations
142. Quirinia, 1997, Rat	Skin, The horizontal wound joining the two single flaps of a(2×8 cm)H-shaped double flap were made,	Incision	The influence of diclofenac and indomethacin on the healing of normal and ischemic incisional wounds using a flap model were studied.	-Biomechanical test, -Measurement of surface necroses	The treatments may be used for reducing superficial necroses of skin flaps.	26,19
143. Quirinia, 1996, Rat	Skin, H-shaped double flaps (2×8 cm), as well as suture sites were made on the skin each animal	Incision	The effect of buflomedil and isoxsuprine on the healing of ischaemic wounds was investigated	- Measurement of surface necrosis, -biomechanical test	The treatments were not effective in the treatment of ischaemic wounds or flaps	13,10
144. Quirinia, 1995, Rat,	Skin, H-shaped double flaps (2×8cm) were created.	Incision	To test the effect of 100% oxygen (2.4 ATA) on different phases of healing ischaemic and normal incisional wounds	- Biomechanical testing, - Measurement of length of surface necrosis	When hyperbaric oxygen was given on days 4-9 there was a tendency towards a decrease in the biomechanical parameters	30,27
145. Cheung, 1994, Rat	Skin, A McFarlane skin flap (3 × 9 cm) was raised	No wound	A localized 31P nuclear magnetic resonance (NMR) spectroscopy were examined	-NMR Coil Design and Construction, -Phantom Studies, - Flap Spectroscopy	This technique may facilitate a better understanding of cutaneous metabolic derangements	5,3
146. Rees, 1994, Rat	Skin, A McFarlane flap model (10 ×4cm) was made	No wound	To test the hypothesis that xanthine oxidase (XO) activity was increased along an ischemic gradient of a skin flap	-Xanthine oxidase and dehydrogenase assay,- Myeloperoxidase assay	XO activity as source of free radical injury in skin necrosis seen in RSF.	45,21

4. DISCUSSION

We found that the ischemic wound in the rabbits' ear ischemic, PU, and localized ischemic wound models have obtained the highest Google Scholar and Web of Science citations among the seven animal models of ischemia. Additionally we should note that pressure sore models as well as burn models are not quite the same thing as excisional wounds in ischemic tissues, as the former are surrounded by well visualized healthy tissue.

Finding an appropriate animal model for ischemic wound study has been a major challenge to scientists as well as clinicians [15,18,40]. The choice of animal models to mimic the human condition is based on a compromise of cost, ease of use, reproducibility, and reliability of the data [25].

The ischemic wound in the rabbits' ear ischemic model has many characteristics of the ideal ulcer model: ischemic enough to affect wound healing significantly, reproducible, quantifiable both in term of epithelialization and granulation tissue formation, associated with minimal contraction, viable without necrosis, comparable to reliable control, and analogous to clinical situations [18,40]. This model is potentially useful to evaluate new therapeutic agents to promote healing such as growth factors [37,39,18,40,41,42,44], and stem cell therapy [31,32,34].

A McFarlane - or bipedicled - skin flap on the dorsum of mice or rats is frequently used as an ischemic cutaneous wound model [126,131]. However, the amount of ischemia to each model differs with the extent and length of the flap, with new blood vessel progression occurring rapidly within a short time, and blood perfusion proceeding to normal within nearly 14 days [3,147]. The ischemic rabbit ear wound model is a better but not a perfect model, because in three weeks even the healthy control wounds are healed [18,40]. However dermal repair times in old and diabetic animals were extended, particularly when diabetic time was more than one year [18,40].

The modified minimally invasive procedure of rabbits' ear ischemic model [17,33,36,18,40] which was recently reported by Chien et al has several advantages, such as less skin damage, simpler procedure, a higher success rate, and more flexibility [40]. Salcido et al at 2007 found that murine models were relevant models for understanding the causal factors as well as the wound healing elements of PUs. However Salcido et al concluded that no single method of induction and exploring PU in animals can address all the aspects of the pathology of PUs. Each model has its particular strengths and weaknesses [15]. In the current review, animal models of PUs have gained a second score in Google Scholar and Web of Science citations among seven animal models of ischemic wound tissue. It shows the importance of PU morbidity and mortality among basic scientists. Animal models that allow wounded tissue to be reperfused with blood following hypoxia might better recapitulate human PUs in which perfusion has been restored [15]. Although the reperfusion of ischemic tissue is crucial for survival, is known to cause secondary tissue damage through inflammatory mediators and the release of free oxygen radicals [15]. Hypoxic-ischemic injury with I/R is an important mechanism in PU development that epidermal, dermal, and muscle damage occurs within several hours. However, the mechanisms of I/R injury are probably multifactorial and the actions of free radicals may be more complicated in the early stages of PU development in humans as compared to the rat model [15,113].

In the current review, localized ischemic wound healing has gained a third score in Google Scholar and Web of Science citations among seven animal models of ischemic wound tissue. However there are few differences with PU ischemic wound models. Both the PU ischemic wounds and localized ischemic wound models achieved equal scoring in Web of Science citations.

The localized ischemic wound model is easy to perform, reliable to reproduce tissue ischemia, and is amenable to study therapeutic modalities. The ischemic rabbit ear dermal ulcer model, while elegant in design, requires use of an operating microscope in some models [32,43,44]. This model depends on the large rabbit ear and has not been successfully adapted to either rats or mice [43,44]. Furthermore, rabbits impose more housing and handling difficulties than small animals such as rats and mice, and are consequently more expensive. The localized ischemic wound model is a longitudinally oriented, dorsal, bipedicle flap model that addresses these criteria and will prove to be a valuable model for studying tissue ischemia [35,148]. The rat model has the advantages of

ease of use, low cost, small size, and easy attainability [148]. However, wound healing in rats has been subjected to scrutiny because of their ability to heal infected wounds and the high rate of inter animal variability [25]. This rat skin wound model has a molecular profile similar to that of chronic human wounds [109]. It has been reported that the 2.5 cm flap without silicone is not ischemic compared with controls, but does have a slower rate of healing. The addition of an intervening silicone sheet decreases tissue oxygen slightly, but does not impact upon other parameters of wound healing. By further narrowing the flap to 2.0 cm, Gould et al have provided some biochemical and mechanical evidence that correlates with tissue ischemia [25]. Recently Gould et al have made some changes in their procedure to make 10.5×3-3.5 cm ischemic wounds in F344 rats [97,96].The laboratory ASF model was reported in 1965 by McFarlane et al. [149].

The most popular is an H-shaped cutaneous flap model developed by Quirinia et al [150]. The technique has been modified numerous times since then and is still commonly used for ischemic wound studies not only in rats but also in other animals [151,152,153]. Several problems have been reported for this model. McFarlane et al. pointed out in their original study that the occurrence of skin-flap necrosis was unpredictable and might occur in more than 90% of rats [154]. Schaffer et al. [1] and Martson et al. [155] pointed out the existence of natural cranio-caudal differences in granulation tissue formation in small animals like mice or rats, which added to the complexity in making comparisons. Dunn and Mancoll pointed out that there are major differences in skin blood flow patterns between "loose-skin" and "tight-skin" species such as the rat and human, respectively [154], and this difference also contributes to higher skin contractions in small animals. Gould et al. also pointed out that rats have a higher ability to heal infected wounds and a higher rate of inter animal variability [27]. The major problem is the short period that the flap can maintain ischemic. Studies by Nakajima indicated that although perfusion to the flap was immediately reduced, new vascular channels were present around the entire wound margin and also developed from the recipient bed within 2-3 days [156]. Blood perfusion increases in a linear fashion to normal at postoperative days 14-16 [2]. The rapidity of perfusion recovery precludes extended testing of potential vulnerary agents [157].

Finally we should note that pressure sore models as well as burn models are not quite the same thing as excisional wounds in ischemic tissues, as the former are surrounded by well visualized healthy tissue.

In order to prevent any probable biases we did consider and obey three rules in the method section: 1, the titles and abstracts of all selected studies (published in English) were evaluated by another scientist who was not a co-author of this work and did not have any conflicts of interest; he downloaded the full text of papers and blocked authors' names and affiliations. 2, We Considered inclusion and exclusion criteria for selecting papers that prevented any further bias. 3, Since citations of papers were reported automatically by Google scholar, and web of sciences, there were no bias existing in this step.

Table 8. Number of papers, number of wounds, and total and average Google scholar citations, and web of sciences citations of studied groups

Groups	Number of papers	Number of samples with wounds	Google scholar citations		Web of sciences citations	
			Total	Average	Total	Average
1. Rabbits' ear ischemic model	16	16	848	53	557	34.8
2. Axial skin flaps	18	1	610	33.8	351	19.5
3. Burn models	18	18	378	21	233	12.9
4.ischemic limb models	9	8	282	31.3	195	21.7
5. Localized ischemic wound healing	16	16	633	39.6	371	23.2
6. Pressure ulcers	11	11	677	61.5	371	28.5
7.skin flaps	29	5	612	23.5	367	14.1

5. CONCLUSION

It was concluded that the rabbits' ear ischemic model and rat PU models, and localized ischemic wound models, have made the greatest contribution to our enhanced understanding of the pathophysiology of the ischemic wounds and increased production of new therapeutic protocols based on the citations reported by Google scholar and the web of science database between 1977 and 2017. Authors believe that the information presented here will help researchers in selecting the right animal model in order to study ischemic wound healing.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGMENT

The Authors acknowledge that there was no financial support for this paper. The Authors thanks Ms Mahsa Kazemi for her final proof reading.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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