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Review

Experimental burn models for evaluating wound healing agents and its current situation and existing disadvantages: a literature review

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ABSTRACT

BACKGROUND: Burns remain a crucial part of the structure of injuries in Russia and abroad. Therefore, providing high-quality medical care to burn victims is relevant. Despite the large number of proposed solutions to this condition, developments in the field of tissue engineering and medical materials science still lack standardization and consideration of specific features of animal burn models for their testing. Many studies showed minor and major disadvantages from a technical and descriptive point of view.

AIM: To analyze and identify the main disadvantages of existing burn models to assess the effect of wound healing agents.

MATERIALS AND METHODS: This article examines the search results in the databases Google Scholar and PubMed using the keywords "burns," "rats," "animal model," and "wound healing." Sixty publications were analyzed.

RESULTS: Seven quality criteria for the animal burn model have been determined, which allow obtaining reliable results and reproducing the described experiment: indication of the terms of quarantine and conditions of keeping laboratory animals, detailed description of the technique of applying burn injury, presence of one burn on a laboratory animal, presence of a control biopsy, indication of the absolute value of the initial burn area, presence of surgical treatment of burn wounds, and correct use of formulas for the planimetric assessment of wound healing.

CONCLUSIONS: A solution to the problem of creating a standardized model may be a more detailed description of techniques and following the proposed quality criteria.

Keywords: burns; rats; animal model; wound healing.

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Научный обзор

Экспериментальные модели ожоговых повреждений при оценке ранозаживляющих средств: актуальная проблема и недостатки (обзор литературы)

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АННОТАЦИЯ

Обоснование. Ожоговые травмы составляют значительную часть в структуре травматизма как в России, так и за ее пределами, поэтому вопрос оказания качественной медицинской помощи пострадавшим от ожогов сохраняет свою актуальность. Несмотря на большое количество предлагаемых решений данного вопроса, разработки в области тканевой инженерии и медицинского материаловедения все еще испытывают нехватку в стандартизации и учете видовых особенностей животных моделей ожогов для их апробации. Во многих исследованиях можно встретить как незначительные, так и грубые ошибки с технической и описательной точек зрения.

Цель — на основе анализа основных недостатков моделей ожоговых поражений для оценки действия ранозаживляющих средств выявить критерии качества и воспроизводимости подобных экспериментов.

Материалы и методы. В статье рассмотрены результаты поиска в электронных базах данных Google Scholar и PubMed с использованием ключевых слов «ожог», «крысы», «животная модель», «лечение ран». Проанализировано 60 публикаций.

Результаты. Мы выделили семь критериев качества животной модели ожоговой травмы, позволяющих получать достоверные результаты, а также воспроизводить описанный эксперимент: сроки карантина и условия содержания лабораторных животных, детальное описание техники нанесения ожоговой травмы, один ожог на лабораторном животном, контрольная биопсия, абсолютное значение начальной площади ожога, хирургическая обработка ожоговой раны, корректное использование формул для планиметрической оценки ранозаживления.

Заключение. Созданию стандартизированной модели может способствовать детальное описание техник и методик моделирования ожогового повреждения, а также следование предлагаемым критериям качества.

Ключевые слова: ожог; крысы; животная модель; лечение ран.

Как цитировать

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ЭКО•ВЕКТОР

BACKGROUND

Skin burns are one of the leading causes of injury in Russia. More than 600,000 cases of burns of various etiologies are reported annually, with a mortality rate of 8.6% [1]. Burn injuries account for approximately 25% of all emergency hospitalizations in children, and the incidence of burns in children is four times higher than in adults [2]. By etiology, thermal burns account for more than 90% of all burns [3] and include contact burns, flame burns, and scalds. The latter is the most common cause of household burns. Despite the fact that up to 80% of all burns are superficial in nature, the issue of providing quality care to patients with borderline and deep thermal trauma is particularly urgent due to the frequent long-term course, potential complications, and disability.

Currently, a wide range of treatment options for burn injuries have been proposed in the scientific literature: from the simplest single-layer polymer coatings that provide only mechanical protection of the wound [4, 5] to complex full-thickness skin equivalents [6, 7] that are designed to restore both anatomical integrity and lost function of the replaced tissue. In evaluating medical device efficacy, *in vitro* testing is limited in modeling the full pathophysiology of burn injury. For this reason, *in vivo* studies are the only way to evaluate a particular treatment option for burn injury [8]. However, there is currently a lack of standardization and consideration of species-specific pathophysiology. The burn injury model should reflect the molecular, cellular, and pathophysiological changes in the tissues as closely as possible to those that occur in the human body. Despite this requirement, many studies lack both technical aspects of burn modeling, which affect standardization and reliability of results, and descriptive aspects, which make it difficult to reproduce a similar experiment.

This review highlights the key criteria of all *in vivo* experiments that should be considered during a study. The strategy of such studies includes selection of the target biological species, preparation of experimental animals, infliction of a burn wound, determination of the target area of a burn lesion, postoperative management and use of adjuvants, and assessment of changes in wound healing.

The study aimed to identify criteria for quality and reproducibility of such experiments based on an analysis of the major limitations of burn injury models for evaluating the effects of wound healing agents.

MATERIALS AND METHODS

A literature search was conducted using Google Scholar and PubMed databases with “burn,” “rat,” “animal model,” and “wound care” keywords. Inclusion criteria were as follows: original article, published within the last 30 years, rat burn model, third-degree burn. Exclusion criteria were as follows: other animal models of burns, first-, second- and fourth-degree burns, diabetic and degloving wound models, review articles, other biological species as model object.

RESULTS AND DISCUSSION

Burn wound model in rats

Despite the active use of animal models in burn care [8], the choice of a particular model is rarely well justified. The positive and negative aspects for selecting the optimal burn injury model should be discussed in order to maximize the anatomic and physiologic similarity to the human body and to avoid excessive material costs, which is particularly important in the context of the exceptionally high costs of high-quality *in vivo* testing.

Burn severity is determined by the lesion depth and the layers of skin involved. First-, second-, and third-degree burns involve the epidermis, upper dermis (superficial burn), and almost full dermis with destruction of pain receptors, respectively. Third- and fourth-degree burns are full-thickness, deep burns; the first involves full dermis and the second involves deeper tissues such as muscle and bone. The majority of published studies use models of deep burns because their treatment is of greatest interest in burn care. Therefore, a comparative analysis of the structure and functions of skin (epidermis and dermis) damaged by deep burns in humans and animal models is required to select an optimal focus for *in vivo* experiments.

In the vast majority of publications, rats are used as model animals because of their small size, low maintenance costs, ease of breeding, and short reproductive cycle [9]. Despite the obvious scientific and technical advantages of using small rodents, this model has some limitations regarding wound healing pathophysiology due to differences in human and rat skin morphology [10]. The most important difference is related to the mechanism of wound closure; in humans, the skin is denser and less displaceable, so that healing occurs mainly by re-epithelialization, whereas in rats, the skin structure is looser, so that their wounds heal mainly by contraction [9]. Unlike re-epithelialization, this is a shorter process, which complicates comparisons between rat and human wound healing. The sharp constriction of the wound in rats is caused by the presence of the subcutaneous *Panniculus carnosus* muscle, which is absent in humans. Less important differences between rat skin and human skin include the absence of apocrine and eccrine glands, the possibility of endogenous production of vitamin C, and increased sensitivity to hypothermia in rats. It should be noted that the porcine model of burn injury is the closest to the human model in terms of wound progression [11]. Scarring in Red Duroc pigs is anatomically and biologically

similar to hypertrophic scarring in humans [12]. However, experiments are hampered by the complexity and high cost of maintaining these animals in the laboratory. Due to poor experimental design, the model is not widely used by research teams.

In the vast majority of cases, the use of a specific burn model involves testing different agents that stimulate damaged tissue to regenerate. Thermal burns are associated with the formation of necrotic masses in the wound bed, which should be removed in a timely manner according to current principles of burn wound care. After a thermal burn, necrotic tissue should be removed within 1 to 7 days. This essentially reproduces the model of an excisional wound [13]. The full-thickness excisional wound model, which removes the epidermis and dermis down to the fascia, may bring rat wound closure closer to that in humans. Although wound edge contraction still occurs, wound closure is achieved primarily by granulation tissue formation and subsequent re-epithelialization, as observed in typical cases of secondary wound intention [14]. Suturing the wound edges to the underlying muscle tissue may make the rat burn wound model even more similar to the human model, but this technique is poorly discussed in literature [15, 16]. However, suturing the wound prevents wound edge contraction and increases scar formation.

Animal preparation for burn simulation

After selection of a model animal, proper care and maintenance are required. In a housing room, all animals are subject to mandatory isolation for a quarantine period of 5–15 days for small rodents and 20 days for other animals. In most cases, this is sufficient to detect latent diseases that were not detected during the initial examination of the animals. The final outcome of wound healing depends on many factors, including stress. To minimize this factor, it is necessary to separate predatory and herbivorous species, maintain a 12-hour day/night cycle, and ensure free access to food and water [17, 18]. In order to avoid mistakes in handling laboratory animals, it is necessary to comply with such standards as GOST R 53434-2009, GOST 33044-2014, GOST 33215-2014, GOST 33216-2014, GOST 34088-2017.

Thermal burn simulation

The choice of wound modeling technique is one of the most important steps in the study because the type of material used, the duration of its exposure, and the related pressure affect severity of the burn. If the description of the chosen technique is not detailed enough for other researchers, the model will not be reproducible.

Several methods are used to model burn injuries in animals.

1. *Contact burn.* A metal object of various shapes and sizes is heated to a certain temperature to cause a burn. This is the most commonly used rat burn wound model, with 72% of studies using the contact burn technique [19–22]. Advantages include the consistent wound area and depth and ease of use. Contact burn techniques described in the literature include burning with a constant temperature heating element [23, 24], burning with a metal object preheated in boiling water [25] or over an open flame [26]. Both techniques ensure that the burn area remains constant. The obvious advantages of the first technique are constant wound depth and ease of use, which allows standardization of experimental conditions. The second technique has a significant limitation; if the element, preheated in hot water, is used for a long time, a partial loss of the heat emitted by it is possible, which affects the severity of the burn injury. To minimize the difference in heat loss when using metal elements of different composition, it is necessary to specify the composition of the device used. In this case, the choice of the same material by other researchers will lead to the same effect, making the model reproducible [27, 28].

Several of the studies [29–32] (14% of the papers on a contact model) reported critical omissions in the description of the burning technique: no mention of the duration of exposure of the heating element to the skin and no indication of its temperature. These errors are considered critical because they lead to the irreproducibility of the burn model.

2. *Scalds*. A burn wound is simulated by exposing the skin to boiling water. In this case, although the temperature is maintained at a constant level throughout the exposure period, the final area of the resulting burn is difficult to control due to both the instability of the effect of boiling water and the individual anatomy of each animal, which does not allow provide a burn of the same size in each animal [33, 34]. Another model of scalding was described: a rod was placed on the animal's back, and boiling water was poured into the rod's cavity. This technique avoids differences in burn size in animals [35].

3. *Steam burn.* Several papers described a technique to produce a burn by steam generated by a heating element when applied to gauze soaked in isotonic sodium chloride solution and placed on the animal's skin. A standardized burn size can be obtained by using a heat-resistant mat with a hole cut according to the labeled boundaries [36]. Another study described a steam delivery system with computerized control of temperature, pressure, and duration of steam exposure to minimize human error [37]. Other studies suggest a model for supplying steam generated by boiling water [38].

4. *CO_2-laser.* This refers to non-contact methods of burn simulation [39, 40]. The main advantages include the ability to precisely control time, size of the exposure area, effective temperature maintenance, and absence of any pressure

on skin. Together, these factors ensure high accuracy and reproducibility of the depth of the burn wound [40]. According to the data found, different laser exposure intervals can simulate burns of different depths, expanding the potential use of this technique [40]. Currently, one of the major limitations of the CO_2-laser is that only a small laser diameter (3.5 mm) can effectively and accurately simulate a burn wound [40]. This size is not sufficient for long-term observations because the short wound healing time does not allow evaluation of the difference between different treatment options. When exposed to a 1 cm diameter laser, the burn wound increases to 2.5–3.0 cm^2 by Day 2 as a result of disrupted microcirculation in adjacent tissues [39]. The data obtained increases the unpredictability of attempts to achieve a specific final burn size.

5. *Exposure to open flame.* This technique is as close as possible to emergency burn conditions. With certain parameters, a constant flame intensity can be achieved. However, it is quite difficult to maintain a uniform effect on the skin when using special stencils for the same wound area. In terms of limitations, increased fire safety measures should be noted, so it is important to remove the animal's fur more extensively and thoroughly to avoid ignition. The description of models found in literature is rather poor [41], so it is impossible to reproduce a burn wound using this technique because different materials, such as alcohol in an alcohol lamp, gas in a burner, or gasoline in a lighter, release different amounts of heat.

Other requirements

It should be noted that only one burn should be produced in each animal to avoid the cumulative effect of release of cytokines and other inflammatory mediators. Even in the case of many small area wounds simulated in an animal [42], their combined effect may influence the final overall systemic response, leading to unpredictable experimental results. In most cases, several burns are performed simultaneously to reduce the number of animals used, which is encouraged from the ethical point of view of the experimental activity. However, the systemic effect of the burn undoubtedly justifies the strategy of performing only one burn per animal. The exception is studies of the ischemic area between burns [43]. In one of the studies [44], different degrees of burns were simulated in one animal, which is unacceptable for the reasons described above.

In *in vivo* studies, it is necessary to verify the depth of tissue damage after a burn [17]. The most accurate and informative method is to take biopsy samples of damaged tissue to perform histomorphology. It is better to take the biopsy on Day 2 after producing a burn, since the damaging effect of edema on Day 1 can increase the severity of the lesion [45]. If biopsies are not evaluated in a study, but histomorphology was performed previously and the burn model was not changed, the authors should indicate this by referring to previous studies [46].

Burn area

In our literature search, we found no data on the selection of a minimum burn area for animal models that would ensure the objectivity of the study. In addition, none of the publications supported the choice of one size over another. However, the burn area in different studies varied from very small (<2 cm^2, which is <1% of the rat's body surface area) [47–49] to significant one (>10 cm^2) [50]. If the lesion is too small, the defect may close quickly as the wound heals by primary intention rather than by granulation tissue formation. Therefore, the relatively large lesion provides significant objectivity to the study and minimizes the contribution of contraction to wound healing.

When searching the literature for data on the reproducible area of a burn, it is common to find publications that have omissions in the description of the size of the defect. Papers with an incorrect or unspecified lesion area require special consideration. Although some studies refer to known burn techniques, such as producing a burn representing 15% [51] or 30% [52] of a rat's body, absolute values of burn size are critical for reproducing the model both within the study and by other research teams.

Similar errors in the description of the burn area are found in the study [50], where the percentage of damage to the total body surface (TBSA) of the animal was calculated using the formula $TBSA = k \cdot W^{\frac{2}{3}}$ (TBSA is expressed in cm^2; k is the empirical coefficient; W is the weight of the animal in grams), but the absolute values of the burn size were never given; and in the study [53], where, unlike in the previous case, the method for calculating the size of the lesion was not even provided.

The problem of miscalculation of the relative size of a burn wound can be found in other studies [54, 55]. Based on the proposed formula [56], the body surface area of a rat weighing between 180 and 320 g in the cited studies should be in the range of 320–470 cm^2. Therefore, burns of 1.3 cm^2 [55], 8 cm^2 [50] and 2.25 cm^2 [41] should in any case represent less than 2% of the TBSA of the rat. However, in the studies cited, the reported rate of skin lesions sometimes reached 20%, which is a gross error.

Therefore, the literature often lacks transparency regarding burn area data. There is also a tendency to artificially inflate the relative size of lesions.

Surgical debridement

Clinical guidelines for the treatment of deep grade IIIb burns (according to the 1960 National Classification of Burns) recommend excision because complete skin regeneration

is impossible when the reticular layer of the dermis is damaged, and debris remaining in the wound stimulates the inflammatory process. Because of the greater blood loss during scab removal after Day 16 [57], it is recommended that this procedure be performed earlier. In the event of burn shock, the continued spasm of the capillaries prevents massive blood loss, making it easier to perform a necrectomy. Based on the above, it is recommended to perform the necrectomy within 7 days from the injury, but not earlier than the first 24 hours, as evidenced by the experience in burn treatment and literature data [57, 58].

Damage occurs not only at the moment of injury, but also in the early post-burn period due to the development of tissue edema in the border area of the burn (necrosis is not directly caused by the damaging factor in this area, but the cells are ischemic due to spasm of the capillary bed). The lack of active action at this stage of treatment leads to the expansion of inflammation, resulting in tissue death and deepening of burn lesion. As a consequence, in the case of deep burns, necrectomy should be performed in the early stages of the post-burn period [45].

Evaluation of rates and quality of wound healing

Planimetry is one of the key approaches to macroscopically and quantitatively assess changes in wound healing by measuring the wound at specific time intervals. Wound areas can be evaluated at different follow-up days either by plotting a curve of wound area versus time, or by converting absolute values to relative values compared to the initial defect size, or by determining the defect area reduction (in percent) per unit of time.

The first is the simplest and only shows a decrease or increase in wound size over time in a particular group of animals, but does not allow comparison of healing rates across groups. This may be the reason for the relatively low use of this technique [59, 60].

Because of the common need to compare the effects of different wound enhancers, analysis of relative wound area values is increasingly used. The obvious advantage of the latter technique over absolute parameters is the ability to consider the human factor at the burn modeling stage, which often results in some initial defect size differences. Relative values are most often calculated using the formula $\frac{(S_0 - S_n)}{S_0} \cdot 100\%$, where S_0 is the wound area at the first measurement; S_n is the wound area at the current measurement. The closer the calculated value is to 100%, the greater the wound healing effect of the study treatment. Another way to evaluate the relative wound area is to calculate the ratio of the current defect size to the baseline one using the formula $\frac{S_n}{S_0} \cdot 100\%$.

The third way is to sequentially calculate the percentage reduction in wound size per unit of time using the formula $\frac{(S_m - S_n)}{S_m \cdot t} \cdot 100\%$, where S_m is the wound area at the previous measurement; S_n is the wound area at the current measurement; t is the interval between measurements of S_m and S_n [53]. This approach also allows assessment of the rate of wound contraction.

CONCLUSION

In vivo studies have long been an integral part of research to evaluate efficacy of wound healing agents. By meeting the requirements for standardization and reproducibility of burn injury modeling experiments, valuable and reliable results can be obtained to compare different medical devices.

As shown in the literature review, the situation remains complex due to the lack of standardized animal models of burn injury. Even the most commonly used burn simulation techniques have limitations, both minor (e.g., lack of some details in the description of laboratory animal preparation) and major (lack of data on the burn area), that make it impossible for other research teams to reproduce the experiment. This issue may be addressed by a more detailed description of burn injury simulation techniques.

We proposed seven recommendations to improve quality of burn experiments by addressing the descriptive limitations of existing models.

- Specify quarantine periods and animal housing conditions before and during the experiment.
- Describe in detail the techniques used to simulate burn injuries.
- Produce only one burn per animal (except for evaluation of ischemic area between burns).
- Perform a control biopsy (or refer to a previous biopsy, if available) to confirm the depth of the burn.
- Specify the absolute value of the initial burn area.
- Perform surgical debridement of the wound.
- Correctly use formulas for planimetric assessment of wound healing.

ADDITIONAL INFORMATION

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