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CASE REPORT

To study references and analysis of an experimental model for skin burns in rats

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Abstract

The purpose of the work: Review and systematization of scientific knowledge about the experimental model for skin burns in rats. *Research methods:* From 2018 to January 2022, a bibliographic analysis was conducted in a database that included international journals. *Keywords used:* A total of 289 studies on rat burn models were identified and 137 were selected. *Results:* Findings: 54/86 (62.7%) were third-degree burns; 55/103 (75.3%) were secondary; 45/78 (57.6%) were caused by boiling water and 27/78 (35.9%) by incandescent tools and 39/78 (50%) by systemic exposure. 42/116 (36.2%) received postoperative fluid therapy, and the time interval after the burn until the start of the analysis of the results was found to vary from 7 seconds to four weeks. Some issues of burning experiments were discussed. *Conclusions:* Hot water is the primary method of inducing third-degree burns with anesthesia using ketamine and xylazine after depilation. They were evaluated microscopically in the postoperative period without the use of analgesia or antibiotics. The studies were not very reproducible.

Keywords: Models, Animals. Burns, Skin rats.

Introduction

Burn mortality has been decreasing in recent decades due to advances in the clinical management of this serious injury (Brigham PA, McLoughlin E. 1996). However, in the United States of America (US), there are still more than a million cases of burns per year, resulting in more than half a million cases being treated in the emergency room (McCaig LF, Burt CW. 2004). According to the World Health Organization (WHO), there are approximately 300,000 deaths due to burns worldwide each year. Burns cause many pathophysiological changes in the body (Geneva 2008, Rosenkranz KM, Sheridan R. 2002) and a severe form of injury can lead to the following complications: increased infection, increased hospital stay, prolonged immobility, and increased mortality (Summer GJ, Puntillo KA, Miaskowski C, Green PG, Levine JD. 2007, Hawkins A, Maclennan PA, McGwin Jr G, Cross JM, Rue LW, 2005). Psychological changes such as post-traumatic stress syndrome are also observed in victims of extensive burns (Corry NH, Klick B, Fauerbach JA. 2010, Taal LA, Faber AW 1997). Although there have been many advances in the treatment of burns, treatment is still far from ideal due to the lack of evidence-based burn medicine (Iurk LK, Oliveira AF, Gragnani A, Ferreira LM 2010). Burn injuries are a major public health issue in both LDCs and developing countries. Many lack adequate infrastructure and research centers to provide adequate burn care (Gragnani A, Ferreira LM. 2009, Holmes JHT. 2008). Large surface area burns can become a systemic problem, affecting various organs and causing high morbidity and mortality (Horton JW. 2004). A hypercatabolic state increases the risk of infection (Longarela A, Olarra J, Suarez L, Garcia de Lorenzo A. 2000, Herndon DN, Tompkins RG. 2004). Also, intensive and continuous inflammatory processes can last for a long time (Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M. 2001). A variety of experimental models can be used to expand knowledge of burn pathophysiology and to explore possible therapeutic agents, including a) cell and tissue culture studies on the mechanisms of action of therapeutic agents, as well as burn

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research on tissue substitutes; b) consists of studying animals of different sizes, shapes and body masses to evaluate the effectiveness of therapeutic agents, as well as to allow in vivo studies of the biological phenomena associated with burns. After these steps, the feasibility of conducting clinical trials in humans can be evaluated (Ferreira LM, Hochman B, Barbosa MV. (2005). Of course, this is done taking into account the safety aspects that have been proven in pre-clinical experiments in animals (Hillmer MP, MacLeod SM. 2002).

Laboratory rats are used because many systems, organs, physiological and pathological processes are similar between rats and humans (Rosenthal N, Brown S. 2007). In addition, rats are small in size, easy to keep and breed quickly. These characteristics make rats an ideal animal as a model for experimentation.

Research methods

The study was approved by the Research Committee of the Scientific Laboratory of the Institute of Pharmaceutical Education and Research with protocol 1556/10. From January 2018 to January 2022, scientific articles on our model and methodological approach were studied. The research was carried out using Scopus, Web of Science and PubMed international databases. The main keywords used were "animal models, burns and rats."

By applying such criteria and procedures, 289 documents were identified. There were 182 articles on the parameters listed in Scopus. At the same time, the following were excluded: a) 19 articles on esophageal burns, b) 17 articles on eye burns, c) 9 articles on inhalation burns, d) 11 articles on hemorrhagic shock, e) one article used a pig as an experimental animal, f) 51 non-experimental studies - 74 articles were selected for the study.

About 60 studies found in Web of Science. However, one was excluded due to esophageal burns, 15 were eye burns, one was due to inhalation burns, and five were excluded because they were non-experimental, resulting in a total of 38 cases. Finally, 116 research studies were found through the PubMed platform and all of them were found to be related to rats as a skin burn model.

The methods used in these studies varied. As a result, not all data could be identified for each study. This was due to the lack of detail in the methodology or other sections of the text. Therefore, it was not possible to perform a complete statistical analysis of the data, and the presented results were given relative numbers.

The study was organized in accordance with the methodology of rat skin burns, taking into account the extent and depth of burns, the trigger of burns, the time of exposure to temperature, the parts of the body where the burns are located. Burns are carried out using specific local effects or systemic effects. Anaesthetics used, including body site preparation, laboratory analysis and experimental techniques, postoperative analgesia and fluid therapy, antibiotic use, and time period were reviewed to determine study outcomes.

Some articles evaluated the biological processes associated with burns by a) histological, b) protein c) genetic analysis by light microscopy, immunohistochemistry, Western-Blot, electrophoresis and PSR.

Research results

The technique of forming a burning surface

Methods used to create burn surfaces for the experimental model include heated water, incandescent devices, and electricity.

Of the 137 selected studies, 92/137 (67.24%) described a burn model. Studies with hot water were presented in 79/137 (57.6%). Accent instruments were recorded in 47/137 (34.6%). Electricity and Kerosene are listed in 9/137 (6.4%), and Cobalt is in 2/78 (1.2%). The hot water model has its liquid heated to the temperature specified by the author.

The size and thickness of the burn

102/137 of 137 studies (74.1%) described the occurrence of superficial and deep ulcers. In 3/137 (2.3%) first and second-degree burns were detected; 48/137 (34.9%) had second-degree burns; Third-degree burns were described in 86/137 (62.8%). The remaining 35/137 (25.8%) did not provide any information on burn severity. Burn size relative to total body surface area showed wide variability, with values ranging from 1 to 60% of body surface area. The area of burn produced by the use of instruments was affected by the size of the tip of the instrument and the time the instrument was in contact with the anatomical area of the animal.

Second-degree burns were distributed as follows: the area defined in the six studies was 1, 3, 10, 20, 30, and 60%, respectively. In the other three studies, the areas were the same size as the tip of the instrument (200, 225, and 500 mm2). The tooltip size was 2.5 and 20 mm in the other four cases. The formula was used to calculate the areas: [TBSA (cm2) = 9.1BW2/3], where 9.1 is a fixed value and "BW" represents the animal's weight in grams. The area was calculated in only one article and was not described in the other articles.

Third-degree burns were reported in 40 studies and regions

Varies from 2 to 60%; five studies described area as tooltip size (6, 150, 225, 800, and 1000 mm2); two articles specify tooltip diameters (6 and 15 mm).

Temperature and duration of exposure

The temperatures reported in the studies showed changes from 52.5°C, when the material has a red color, to the incandescent state.

The duration of exposure to the heat source varies from touching with an incandescent tool to 15 minutes. As for

the use of hot water, the temperature is from 60 to 100°C, measured with a thermometer. Using incandescent devices, the temperature varied from 70°C to incandescent and the exposure length from touch to 45 s.

Burning place

Of the 137 studies, 86/137 (63%) described a burn site or anatomical region. Thus, 55/73 (75.3%) used only the back as the chosen burn site; 18/73 (24.6%) used another site or a combination of sites, including the back: scapula, temporalis, extremities, back, and abdomen. In other studies, 59/137 (37%) did not mention the location of the injury.

The effect

Of a total of 137 studies, 92 (67.24%) described the effects of burns. Therefore, local effects related to 39/78 (50%); and systemic effects were also described in 39/78 (50%); in the remaining cases, 45/137 (32.76%) had no indication of the effect.

Anesthetics

Of the 137 studies, 84/137 (61.2%) mentioned the use of anesthetics. Ketamine and xylazine were used in 22/71 (31%) of the studies; pentobarbital in 16/71 (22.5%); isoflurane in 10/71 (14.1%); Ketamine 5/71 (7.1%); Thiopental was used in 3/71 (4.2%); Ether 2/71 (2.8%); Halothane 2/71 (2.8%); Urethane with chloralose 2/71 (2.8%); Urethane 2/71 (2.8%); Barbitone 1/71 (1.4%); Ethylcarbamate with Alphaxylorosa 1/71 (1.4%); Halothane with isoflurane 1/71 (1.4%); Ketamine with pentobarbital 1/71 (1.4%); Ketamine with xylazine added to thiopental 1/71 (1.4%); Ketamine with xylocaine 1/71 (1.4%); Ketamine with thiopental 1/71 (1.4%). The remaining 45/116 (38.8%) did not mention the type of anesthetic used in the study.

Depilation

Of the 137 studies, 75/137 (55.1%) involved depilation of the burn site. Animals that had their hair removed by shaving accounted for 61/64 (95.3%) of the study. One study noted that 1/64 (1.5%) used sodium sulfite as a depilatory. No depilation was reported in two or 2/64 (3.1%) cases, and in the remaining 61/116 (44.8%) cases, there was no information on whether depilation had occurred.

Laboratory methods used to study burn samples

In the burn area analysis, some options such as microscopy, immunohistochemistry, Western-Blot, PCR and electrophoresis were identified. Of the 137 studies, 85/137 (62%) reported using at least one form of the above options. Microscopy was found to be the most widely used form.

Analgesia in the postoperative period

Of the 137 studies, 20/137 (14.6%) mentioned the use of analgesia in the postoperative period. Animals receiving analgesia in the postoperative period were 13/17 (76.4%); 4/17 (23.5%) did not use any analgesics in the postoperative period. The remaining 117/137 (85.3%) did not mention the use of analgesics. Of the group using analgesics, 10/13 (76.9%) used buprenorphine; 1/13 (7.6%) used Dolantin; 1/13 (7.6%) used Dimenhydrinate; And 1/13 (7.6%) used Tenoxicam.

Fluid therapy in the postoperative period

Of 137 studies, 51/137 (37%) mentioned postoperative fluid therapy. Animals that underwent postoperative fluid therapy comprised 42/43 (97.7%). In such cases, the infusion formula presented a big change. Only 1/43 (2.3%) did not use postoperative fluid therapy. The remaining 62/137 (45.3%) did not provide information on the use of fluid therapy after surgery.

Local antimicrobial

Of the 137 studies, 10/137 (7.7%) reported a topical antimicrobial and 127/137 (92.3%) did not report a topical antimicrobial. It was found that 7/9 (77.7%), 2/9 (22.3%) did not use topical antimicrobials. Three of 7/9 (77.7%) used 1% silver sulfadiazine; the time of use and variable period are not described. One case used nonspecific antimicrobial ointment and isotonic saline, another used 1% silver sulfadiazine with xytosan gel, and another used mupirocin.

Time interval after burning

Of the 137 studies, 110/137 (81%) identified a postburn condition. The time interval to start the laboratory analysis varied from 7 seconds to four weeks. 26/137 (19%) of the articles did not mention the time period.

Discussion

Advances in the treatment of burns occurred mainly after World War II, and included advances in fluid therapy, antibiotic therapy, strict nutritional control, new types of dressings, bioengineering, and early surgical treatment. These were all significant changes, but much more needs to be done. Burn research can be done through cell culture, animal, or human clinical studies.

It addresses aspects of cellular and molecular biology in a variety of conditions, providing an effective model for studying pathophysiology. It is possible to develop tissue bioengineering and burn research on them, including developing new materials for treating various skin burns (Mesquita CJG et al 2010, Supp DM, Boyce ST 2005). Improving bio-molecular understanding and speeding up the development of new therapies are also advantages of this process. A disadvantage is that cell properties may change after a period of continuous growth and there is a lack of neuroendocrine signaling compared to experimental animals (Sobral CS et al. 2007, Gragnani A, Morgan JR, Ferreira LM. 2004, Gragnani A, Morgan JR, Ferreira LM. 2003).

As for clinical research with humans, the focus is on ethical issues and bioethics, respectively. When humans

are used as experimental models, the advantages and disadvantages are more obvious than in other studies. Another consideration is the need to have a significant number of patients with many differences between patient types and injuries to obtain meaningful results.

Procedures, anesthetics, and controls have improved animal studies during animal production (Schanaider A, Silva PC. (2004). Various educational institutions have established Ethics Committees and animal research must meet ethical and scientific standards to move forward in research.

In animal experiments, choosing appropriate methods for anesthesia and pain control is important, especially in the postoperative period. Burns are intense, physically and emotionally distressing experiences. Experiments that may cause pain should be performed using analgesics or anesthetics to inhibit neuromuscular transmission (Ramos M, Gragnani A, Ferreira LM. 2008).

Animal studies enable research in pathophysiology, histology, and molecular biology over time; Testing preventive and therapeutic treatments in burns is important, including making this knowledge available for further clinical research. Certain animals such as rats, mice, rabbits, pigs, sheep and dogs have been used as study models to understand the stages of healing. However, the use of these animals is not universal. Such studies have the advantage of providing physiological and pathological characteristics similar to those of humans, taking into account stimulation of the nervous, cardiovascular, endocrine and immunological systems.

The rat has many advantages, as it is small and provides ease of handling. They are also cheap and have a high reproductive rate. However, their disadvantages include differences compared to human size, metabolic characteristics, and anatomy (Gould LJ, Leong M, Sonstein J, Wilson S 2005).

The pig is the closest animal to humans in some characteristics, such as metabolism and skin structure; however, the cost-benefit perspective shows that they are more demanding in terms of investment and more complicated to use, in addition, they require more attention and costs (Santos Heredero FX et al 1996).

The aim of this study was to review the literature on experimental models using rats, burns and its properties. During the study, we tried to provide more detailed information about the main aspects and specific characteristics of many variables that are considered the main indicators of the health-disease-recovery process. After selecting the cases and reviewing the literature, we can observe that there is no standardization in the studied articles. These specialized journals and their editorial boards have published many articles that are incomplete and lack valuable information on many aspects of burn research.

As for the technique of producing burns, the hot water model was most often used. Hot liquids are one of the most common causes of burns in children, mostly under the age of five. Hot water is also easy to use for animal experiments. When working with animals, dousing hot water is not enough to cause a burn because it limits control of the burn site. Adherence to specific steps and proper use of equipment should be designed to allow full control of burn production according to research needs.

Although hot liquid is the most commonly used source in animal research, the most common agent for creating burns in Brazil is liquid alcohol, with an average of 30% for different burn centers. The reviewed articles did not use alcohol as a model for burns in rats (Lacerda L, Oliveira AF, Gragnani A, Ferreira LM. 2010).

As for the size and thickness of the burn, many researchers have studied these issues. Most of the studies examined second and third-degree burns. The size of the burns is very different, and each differs according to the study's main goals. However, a 60% burn area represents a significant mortality risk for animals, and these conditions are not studied enough to evaluate immediate postburn outcomes. In instrument burns, the area varied depending on the shape and size of the tooltip.

When it comes to the location of the wound, in most cases the back was the choice, probably due to its size and the difficulty of the animal to cause additional damage to the wound. Due to the risk of the animal rubbing against the cage wall and causing damage to the resulting burn, primary and secondary dressings with an antibacterial agent should be applied to the wound. The abdomen of the animal should be avoided, as it is easy for the animal to lick this area and even cause damage to the affected area.

Anesthetics were widely used in experiments. Regarding the use of analgesia in the postoperative period, more than half of the articles did not mention the use of any type of analgesic. The postoperative period is a key stage in the clinical treatment of burns, where pain management plays an important role in the overall clinical evolution. It is therefore surprising that more detailed information about analgesia is not available. As for the use of nonsteroidal analgesics in patients with burns, they are not used because of possible kidney complications and gastrointestinal bleeding. Steroids are not used because they lower burn patients' immune system and increase the risk of gastrointestinal bleeding.

In the postoperative period, fluid treatment of animals is carried out as a routine treatment. More than half of the studies used this therapy, which shows the importance of these processes for experiments with subsequent evaluation - it is associated with third-degree burns and burns of large surface areas, especially when 60% of the burn area is formed. As in clinical conditions, hemodynamic instability is observed (Oliveira HM.et al 2009, Jeschke MG, et al 2009, Barber RC, Maass DL, White DJ, Horton JW. 2008).

Regarding the use of topical antimicrobials, most studies do not mention their use. However, the use of an antimicrobial agent containing silver has been described.

It is currently considered the best option for wound care to reduce microbial growth and infection (Wasiak J, Cleland H, Campbell F. 2008).

Our findings suggest that most studies do not describe the entire normal burn sequence from burn to postoperative clinical management.

Research methods are important in conducting experimental research. The authors present the main processes involved in conducting the research. Experiments are repeated only when strict rules are followed and detailed information is provided. This characterizes high research quality and ethics. Journal editors must be prepared to review many relevant details for burn research. This is the only way to make research more applicable to real-life situations and improve future research.

Conclusion

Hot water is the main method of producing third-degree burns on the back, using ketamine bound with xylazine as anesthesia after depilation with appropriate equipment. The results are evaluated under a microscope, and painkillers or antimicrobial agents are recommended in the postoperative period. Incomplete information on the methods used was found in the selected articles, which leads us to conclude that studies on skin burns in rats are not easy to replicate.

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