Research article

Application of recombinant human basic fibroblast growth factor in repair of the aged dog bite wound

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ABSTRACT

Background: Dog bite wounds usually have severe local soft tissue damage and the wounds are likely to be contaminated by a large number of bacteria or even a series of rare pathogenic bacteria, leading to repeated infection and delayed wound healing. Recombinant human basic fibroblast growth factor (rh-bFGF) has excellent ability to promote wound repair and widely used in various complicated wounds.

Objective: Observe the clinical efficacy of Recombinant human basic Fibroblast growth factor (rh-bFGF) applied in the treatment of dog bite wounds.

Methods: A total of 31 patients (16 adult and 15 aged) with rabies exposure grade III dog bite wounds treated in the department of emergency surgery in our hospital from February 2020 to February 2022 were reviewed. Rh-bFGF was applied in the wounds after debridement and the patients were treated with preventive anti-inflammatory therapy. Observe the wound healing rules, infection rate, related complications and application time of antibiotics.

Results: Eventually, all the wound were well healed and the healing time needed for most patients were about 2–3 weeks. The wound infection rate of aged patients was much higher, therefore application time of intravenous antibiotics injection in the aged patients was significantly higher than it in the adults (P < 0.05), but the difference of the time reach the intermittent wound dressing change was not statistically significant (P > 0.05).

Conclusion: Rh-bFGF is safe and reliable for severe dog bite wounds in both the elderly and adults, it may help improve the early stage healing speed of aged patients, but the specific treatment needs to be individualized and accurate depends on different personal physique and wound conditions.

1. Introduction

Animal bites and related infections have been the focus of many emergency and clinical research work due to the high incidence rate. Farms, parks, city roads and homes, etc., human and animal contact could happen in various environments. Therefore, it is not surprising that animal bite wound, especially dog bite injury has a high incidence rate. According to the epidemiological analysis of dog bite in China between 2016–2018, it was found that animal bites mainly occurred in summer and autumn, yet dog bites consist 91.46% in total. Among the exposure, most wound (about 71.88%) reach the rabies exposure grade III level (Table 1), and the incidence rate of middle-aged and elderly people was higher than that of young people [1]. Animal bites are usually deep, polluted by large amounts of bacteria and may contain a variety of rare bacteria. Bruce Meyers [2] once conducted bacterial culture analysis on 104 dog bite wounds caused by 50 dogs, finally, Only 16 percent of the wounds ended up free of any bacterial growth, the other 16% were aerobic infection, 1% were anaerobic infection, and the remaining 67% were mixed infection of aerobic and anaerobic bacteria, even pasteurella canis, streptococcus pyogenes, bacillus, actinomycetes and oral Streptococcus can be isolated from the wound. Therefore, if the injury was not treated in time, the probability of local infection and wound nonunion will be high, which may even induce serious complications such as limb necrosis, systemic malignant infection and sepsis [3, 4].

For the treatment of wounds with serious pollution or severe local tissue damage, wound debridement was crucial, yet it can only achieve relative sterility, so the probability of wound infection and subcutaneous abscess formation is relatively high, which may even lead a improved risk

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of bacteremia. Therefore, it is recommended to only conduct primary debridement treatment for animal bites. If the wound was large and indeed needs to be sutured, loose suture with large needle pitch was usually preferred, which may facilitate pus drainage after abscess formation. What if the wound was facial laceration requires high aesthetics after healing, or the wound was a clean laceration, early wound debridement and suturing was recommended. Meanwhile, it is necessary to take appropriate anti-inflammatory treatment according to the specific situation of the wound to prevent related complications and infection [5].

Due to the complexity of the dog bite wounds, it was usually considered as contaminated wounds, and the clinical work faces many challenges. Since contaminated wounds usually have a high probability of subsequent bacterial infection, it is usually necessary to place wound drainage to facilitate pus discharge. Traditional drainage materials usually include latex drainage pieces, plastic drainage tube and VSD negative pressure drainage, etc. These materials usually don't have biological activity, some patient's immune system may even reject the drainage material as a foreign object. Moreover, some drainage materials are expensive and pose a great pressure on the economic burden of patients.

Based on pathological changes, the wound healing process can be divided into inflammatory reaction stage, wound contraction stage, granulation tissue hyperplasia stage and plastic stage of scar tissue formation. rh-bFGF can induce inflammatory cells, fibroblasts and vascular endothelial cells gather to the injury site and activate the phagocytosis of macrophages; promote neovascularization, accelerate nerve regeneration and promote fibroblast proliferation; it also promotes the proliferation of epithelial cells and regulates the synthesis and secretion of collagen. Since rh-bFGF can activate chemotactic migration of inflammatory cells (macrophages, neutrophils, monocytes, mast cells, etc.) and tissue repair cells gather to the wound, eliminate pathogenic microorganisms of the wound through phagocytosis and enzymatic degradation of inflammatory cells, it also has a certain anti-infection effect [6,7]. According to the characteristics of animal bite wounds, we plan to infiltrate the sterilized dressing with rh-bFGF solution to make a short-acting drug sustained-release carrier, cut into a suitable size drainage strip and put it into the wound, observe the wound healing rules and verify the feasibility of the treatment scheme.

2. Patients and methods

2.1. Inclusion and exclusion criteria

Inclusion criteria: (1) Clear history of dog bite, and the debridement time after injury was within 8 h; (2) Ages from 14 to 80 years old; (3) The wound conforms to class III classification of animal bite wound (Table 1); (4) No allergic history of rh-bFGF. Exclusion criteria: (1) Large skin defect with a defect area of more than 1.5 cm × 1.5 cm; (2) Severe tissue laceration with important vascular or nerve injury in the wound; (3) Large amount of scar tissue left by old trauma at the bite position; (4) patients with severe cardiovascular and cerebrovascular diseases, diabetes and coagulation disorders (5) Lactating and pregnant female (6) Patients who did not finish the complete treatment in our hospital (7) Mental patients who cannot cooperate with the treatment.

2.2. General data

A total of 31 cases of grade III dog bite wounds in the emergency surgery department from February 2020 to February 2022 met the above criteria, 16 patients aged 18–60 years old divided into the adult group, while the other 15 old patients from 60 years old to 80 years old were included in the aged group. All patients were voluntarily choose to use rh-bFGF, we didn't interfere the willingness of patients. The study was approved by Beijing Geriatric Hospital Ethics Committee, and informed consent was obtained from all patients in this research.

2.3. Primary therapy

The wound repeatedly washed with soap water(20%, W/W)and flowing water for 20 min, then flushed with hydrogen peroxide and iodophor, syringe with normal saline inside was used for flushing deep wounds when needed. After the debridement, antiseptic dressing loaded with rh-bFGF cut into appropriate size, placed in the wound as drainage, initially, wound dressing change once a day with rh-bFGF antiseptic dressing placed inside always after debridement. At the late stage of wound healing, the wound usually shrunk significantly and rh-bFGF loaded drainage strip can't put inside. Therefore, we pour rh-bFGF solution on the innermost wound dressing as wound external cover. Meanwhile, clindamycin intravenously injected twice a day as anti-inflammatory treatment. For the following progress of the wound, If there was a large amount of purulent exudation or deep abscess formation in the wound, wound expansion and drainage was performed according to the situation.

2.4. Indicator for observation and wound healing standard

At the early stage after debridement, all patients wound dressing change once a day. While most of the redness and swelling around the wound subsided, the exudation was not much, stop clindamycin injection. If the intravenous anti-biotic therapy proceed for more than 3 days, we usually consider the wound was infected. At the time when the wound is basically no secretions, redness and swelling around the wound basically subside, body temperature is normal, dressing change switched to once for every two days until the wound healed. Wound healing standard: the wound has no obvious redness, swelling and exudation, no obvious pain on local tissue, covered with complete scab, as shown in Figure 1. Record

Figure 1. General view of healed dog bite wound. Note:A 69 years old dog bite female patient, wound debridement was conducted 2 h after injury, the wound was basically healed after continued dressing change until the 20th day.
the time point of stop intravenous antibiotics, intermittent wound dressing, complete wound healing.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 26.0. Chi square test was used for enumeration data, ANOVA analysis was used for measurement data, and the measurement data were expressed in (x ±S), P < 0.05 has statistical significance.

3. Results

3.1. General information

All patients were treated within 8 hours after injury. There was no significant difference in gender, treatment time after bite between the two groups (Table 2). Among all patients, the most common injury site was the hand, followed by the upper limb, and the highest incidence season of dog bites was autumn, followed by summer (Figures 2 and 3). After the application of rh-bFGF, all the cases didn’t experienced local allergic reaction or fever during the treatment. In the adult group, a 52 year old male with hand bite patient suffered thenar abscess formation 3 days after the debridement, the wound healed gradually after wound expansion and drainage until 14th day.

3.2. Wound healing process

Most patients have different degrees of inflammatory reaction in the early stage of the wound, especially the narrow and deep wound or the wound with serious local tissue damage. Some severe cases suffered soft tissue necrosis within 3–7 days after injury. The maintenance time of continuous redness, swelling and exudation caused by inflammatory reaction varies greatly from different patients. The longest period of inflammatory reaction would last for more than 20 days, while those rapid healing wounds could observe the regression of inflammatory reaction within 1 week after injury. After the inflammatory reaction basically subsides, usually the wound will healed around 1 week (Figure 4a, b, c, d, e, f).

3.3. Time of intravenous anti-inflammatory treatment and wound healing

The intravenous anti-inflammatory time in the aged group was significantly higher than that in the adult group (P < 0.05). While the average time required for the aged group to reach the wound intermittent dressing standard was slightly higher than it in the adult group, but the difference was not statistically significant. The complete healing time of the wound was about 20.7 days in the aged group and 16.1 days in the adult group, which was statistically significant (Table 3).

3.4. Evaluation of overall treatment effect

Overall infection rate was 65%, aged group was 80%, while the adults group was 50%, which indicate the high infection probability of the dog bites, especially the aged patients suffered a higher infection risk (Figure 5). The wounds of all patients finally healed well, the shortest healing time was one week after debridement (2 cases in adult patients), and the longest healing time was the 29th day after debridement (a 44 year old female patient), while the average healing time was about 18.3 days. For the intermittent dressing change time point, shortest time was 1 day (a 25-year-old male patient) and the maximum time was 20 days (a 50-year-old male patient), with an average of about 9.1 days. The shortest time of intravenous anti-inflammation was 1 day (a 25-year-old male patient), and the longest was 12 days (2 patients in aged group), with an average of about 5.5 days. A 69 year old male patient’s wound intermittent dressing change time point was smaller than the intravenous anti-inflammatory time, at the 5th day of anti-inflammatory treatment after debridement, the wound secretion basically disappeared and switched to intermittent dressing change, but the redness and swelling around the wound remain obvious, so we continued the anti-inflammatory treatment until the wound redness and swelling basically disappeared on the 8th day, while other patients usually switched to intermittent dressing change when stop intravenous anti-inflammatory or a few days later, the overall treatment effect was satisfactory.

4. Discussion

Nearly 100 million people around the world are bitten by dogs every year, China has the largest number of dogs in the world, almost 130 million dogs in 2012, with more than 12 million bites per year. Globally, about 59000 people dead of rabies every year. 99% of human rabies cases
Figure 4. Macroscopic view of wound healing process after dog bite. Note: The figure shows a 38 year old female patient visited doctor within 1 h after the injury. The wound was a typical grade III animal bite wound, depth could reach forearm muscle layer, with adipose tissue laceration, local tissue was heavily polluted. After wound debridement, sterile dressing loaded with rh-bFGF was infiltrated inside the wound as drainage. For the 4th day, small amount of purulent exudation remain visible, and local tissue was red and slightly swollen, therefore, Intravenous anti-inflammatory treatment was stopped on the 5th day after injury. At the 8th day, the wound secretion was significantly reduced, but the redness and swelling around the wound was still obvious. When it was the 12th day, the wound basically had no exudation, local tissue was slightly red, so wound dressing change switched to once for 2 days. On the 16th day, the inflammatory reaction of the wound was significantly subsided, until the 20th day, the wound basically healed.
are transmitted by dogs, and a small part are transmitted through wild animals (such as foxes, wolves, jackals, bats, raccoons, skunks or mongooses). Due to the potential high risk of infection and the randomness of injury, dog bite wounds may produce various complex wounds such as crush injury, avulsion, tear and puncture injury [9]. In this study, the dog bite wounds we faced were deep and complex which cause a high risk of anaerobic infection, so we have a lot of controversy about whether to perform primary wound suture after debridement. Nikolaos and others [10,11,12] believe that animal bite wounds are usually contaminated wounds, and the treatment principle of the wounds should not be sutured in early stage except debridement. In this study, a patient with hand bite suffered abscess formation 3 days after wound debridement and nearly 65% cases spend more than 3 days for anti-biotic treatment, which indicate relatively high risk of infection of the dog bites. Since the proportion of elderly patients with animal bite in our hospital was relatively high, their trauma recovery ability were relatively poor, therefore the probability of infection was higher. Once the deep tissue abscess was formed after the primary suture of the wound, the pus cannot be drawn out in time, the inflammation may gradually spread to the subcutaneous tissue or even the blood circulation, which can induce bacteremia or even sepsis in some severe cases [3]. Therefore, according to the situation and experience here in our hospital, we leave the wound open after the debridement.

Rh-bFGF is a multifunctional cell growth factor, which was initially isolated and purified from bovine pituitary gland. Many subsequent studies have confirmed that rh-bFGF can stimulate the differentiation and proliferation of vascular endothelial cells and other cells from mesoderm and neuroectoderm, which can play an important role in tissue healing [15,16]. In addition, rh-bFGF can induce inflammatory cells accelerate move to the trauma site, thereby it would have a certain degree of anti-inflammatory effect [17]. Based on the mechanism of the rh-bFGF in vivo, it is especially suitable for high infection risk wound like diabetic wound, skin burn and even gastrointestinal ulcer, etc [15,18–20].

Usually, it was considered the aged patients have a lower wound healing speed. However, in this study, the difference of intermittent dressing time point change between the elderly and adults was not significant, which may indicate that rh-bFGF can help facilitate the early stage of wound healing with a certain grade for the aged. Yet for the late stage, wound complete healing time of the adults was significantly lower than it in the aged patients, we suggest it may because the wound was not able to fully absorb the rh-bFGF since the drug loaded antiseptic dressing was externally covered instead of placed inside the wound. Both the elderly and adult patients have some cases suffered Intravenous anti-inflammatory treatment for more than a week, some patients even experienced abscess formation, we consider it possibly because of the wound was excessive deep or with serious tissue damage, even repeated wound debridement was hard to eliminate all the bacteria inside.
5. Conclusion

The dog bite wounds in aged patients needs a longer time of antibiotic treatment for the higher risk of wound infection. Rh-bGFG applied in dog bite wounds was safe, it may help improve the healing speed of the aged patients, but the sufficient anti-biotic therapy should not ignored while using. Due to the high infection rate (Figure 5), the specific treatment of dog bite wound needs to be individualized and accurate, and the wound should perform a thoroughly debridement as much as possible.

Declarations

Author contribution statement

Chaoxi Zhou: Conceived and designed the experiments;Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Hongming Wang, Hongju Jin and Wei Zhang: Performed the experiments.
Jianhua Ma: Analyzed and interpreted the data.
Qinglei Wang: Contributed reagents, materials, analysis tools or data.
Yongzhen Zhao: Wrote the paper.

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Data availability statement

Data included in article/ supp. material/referenced in article.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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