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Review

Research status of facial nerve repair☆

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ABSTRACT

The facial nerve, also known as the seventh cranial nerve, is critical in controlling the movement of the facial muscles. It is responsible for all facial expressions, such as smiling, frowning, and moving the eyebrows. However, damage to this nerve can occur for a variety of reasons, including maxillofacial surgery, trauma, tumors, and infections. Facial nerve injuries can cause severe functional impairment and can lead to different degrees of facial paralysis, significantly affecting the quality of life of patients. Over the past ten years, significant progress has been made in the field of facial nerve repair. Different approaches, including direct suture, autologous nerve grafts, and tissue engineering, have been utilized for the repair of facial nerve injury. This article mainly summarizes the clinical methods and basic research progress of facial nerve repair in the past ten years.

Contents

☆ **Scientific field of dental Science:** Maxillofacial surgery and facial nerve regeneration.

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1. The concept of the facial nerve

The facial nerve is an important cranial nerve that contains mixed nerves composed of motor fibers, sensory fibers and parasympathetic fibers [1–3]. Motor fibers originate from the facial nerve nucleus located ventrolaterally at the caudal end of the pons, and they innervate facial muscles other than the masticatory muscles and levator palpebrae, as well as the ear muscles, occipital muscles, and platysma muscles. The gustatory fibers originate from the geniculate ganglion in the facial nerve canal. They, which called the chorda tympani, branch off from the main trunk of the facial nerve near the stylomastoid foramen, pass through the tympanic cavity, and attach to the lingual nerve of the mandibular nerve. In this way, they innervate the taste buds of the anterior two-thirds of the tongue. In addition to these functions, the facial nerve is responsible for conveying some sensorial information. A small number of sensory fibers offer general sensation to parts of the skin of the tympanic membrane, the lacrimal glands, salivary glands, the pinna, and some of the mucous membranes of the oral cavity [4]. The parasympathetic nerve fibers of the facial nerve originate from the superior salivary nucleus and regulate the secretion of the sublingual and submandibular glands. Significantly, the facial nerve is mainly composed of motor fibers, sensory fibers (including gustatory fibers) and parasympathetic nerve fibers pertain to intermedius nerve (Wrisberg's nerve). Altogether, the facial nerve plays an integral role in the functioning of numerous structures within the human body [5] (See Fig. 1).

2. Clinical manifestations of facial nerve injury

Facial nerve injury can have a range of clinical manifestations that vary depending on the location of the injury. Local symptoms can occur in the frontal, periorbital, mid-face, and perioral areas. In addition, all facial muscles on the same side can become paralyzed, resulting in a range of symptoms. Paralysis of the frontalis muscle is noticeable. This can cause the inability to frown, as well as a lower position of the eyebrows compared to the healthy side. As the frontalis muscle is responsible for creating wrinkles in the forehead, its paralysis can make the forehead lines shallow or completely disappear [6]. When the orbicularis muscle is affected, this can lead to weak closure of the eyelids. Even with forceful closure, the eye may turn outward and upward, exposing the sclera. Paralysis of the buccal muscles can cause the corners of the mouth to droop when closed, resulting in a bulging appearance of the cheeks and the leaking of air. Whistling may be impossible, and food may become trapped between the cheeks and gums while eating [7,8]. During the recovery period, there may be joint movement or excessive movement of the affected side. The symptoms of facial paralysis can not only affect physical health but can also lead to significant mental health issues. Patients may experience a decrease in self-confidence and difficulty engaging in social activities due to visible physical changes [9]. It is essential that facial nerve injuries receive prompt treatment to minimize the risk of long-term complications.

3. Classification of facial nerve injury

The facial nerve is an important component of the peripheral nervous system. It is important to accurately evaluate the extent of nerve damage to determine the best course of treatment. Commonly used evaluations for facial nerve damage include the Seddon classification [10], Sunderland classification [11], House-Brackmann grading system [12], and more. Among them, the House-Brackmann (HB) grading system is specifically used for assessing facial nerve injuries, while Seddon's classification system and Sunderland's classification system are more commonly used for evaluating peripheral nerve injuries. When studying nerve damage in basic experiments, a range of models may be used to simulate different types of injuries. Such models often include compression injuries, traction injuries, shear injuries, amputation

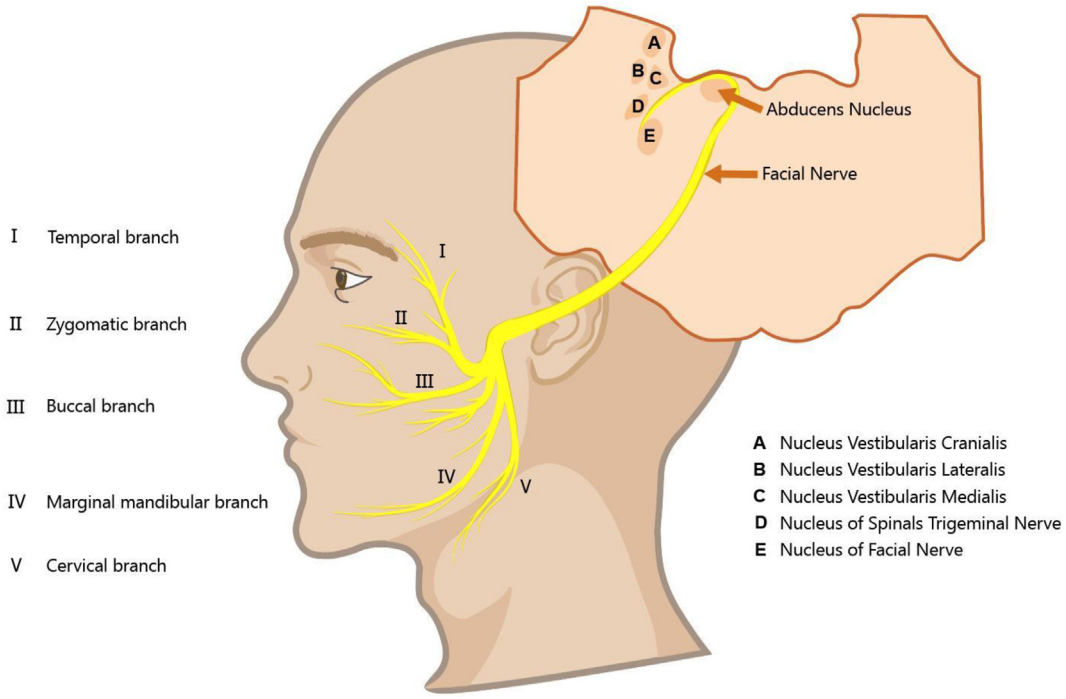

Fig. 1. The distribution of facial nerves on the face after being emitted from the facial nerve nucleus located in the brainstem.

Table 1
Seddon's classification.

I	Neurotmesis (Division of a nerve)	The nerve bundle or nerve trunk is completely severed or separated by scar tissue, and requires surgical nerve suturing. Functional recovery may be achieved or incomplete functional recovery may occur after nerve suturing.
II	Axonotmesis (lesion in continuity)	The axon is severed within the myelin sheath, while the nerve sheath remains intact. Retrograde changes occur in the distal nerve fibers, and after a period of time, the nerve can recover on its own.
III	Neurapraxia (transient block)	Neurotransmission dysfunction is a temporary physiological blockage in which there are no apparent anatomical or morphological changes in nerve fibers, and there is no degeneration of distal nerve fibers. Neurotransmission function will recover on its own within several days to weeks.

injuries, ischemic necrosis injuries, transection injuries, etc. [13,14]. By understanding how these different injuries affect the peripheral nerves and the body as a whole, researchers can develop new treatments and rehabilitation strategies to help patients recover from nerve damage (See Tables 1–3).

4. Causes of facial nerve injury

Nerve damage can be divided into iatrogenic trauma and non-iatrogenic trauma based on its cause [15–17]. Iatrogenic trauma, as the name suggests, is damage caused during treatment, most of which occurs during surgery performed on areas adjacent to the facial nerve. Noniatrogenic trauma includes physical injuries such as impact, stabbing, cutting, explosion, burn, and electric shock. According to the mode of external force, such trauma can be divided into exposure, traction, compression, squeezing, sharp cutting and friction injuries caused by blunt instruments.

In Odebode's report, the incidence of traumatic facial nerve injury in craniocerebral injury combined with facial nerve injury was 5.04%, and the incidence of facial paralysis caused by the latter was 3%. Fractures of the petrous part of the temporal bone and mastoid are common causes, and 30%–50% of longitudinal fractures of the petrous bone and 10%–30% of transverse fractures may be accompanied by facial nerve palsy. In addition, extensive soft tissue contusions on the face and penetrating injuries to the head and face (especially bullet wounds) can also result. Among these injuries, more than 70% of facial paralysis cases involve the lower motor neurons, which results from a lesion in the facial nerve or its nucleus and is characterized by total paralysis of the ipsilateral hemifacial muscles, and the frequency of traumatic facial nerve injury combined with hearing impairment is also high, at more than 70% [18]. It has been reported that temporary facial nerve dysfunction occurs in 20–65% of patients who have undergone parotidectomy, while permanent facial nerve dysfunction occurs in only 0%–7% of patients [19–22].

Craniocerebral surgery (such as acoustic neuroma and other cerebellar pontine angle tumor resection), parotid gland resection, submandibular gland resection, and temporomandibular joint-related operations can all cause facial nerve injury [16,23–25], mainly due to excessive stretching, pinching or accidental cutting of the nerve during the operation, electric knife injury, etc., and postoperative tissue edema and compression. Thus, in the process of treating tumors within the inner ear, it is important to take precautions to protect the blood vessels. Surgeons should also be well-versed in the anatomical layers and know the path of the facial nerves, striving to dissect them under direct visualization with gentle movements while avoiding direct, prolonged tension on them. The use of electrocautery should be minimized, and suction devices should be positioned as far away from the facial nerves as possible to avoid excessive negative pressure. In the event of accidental nerve transection, immediate nerve repair surgery should be carried out (See Fig. 2).

Table 2
Sunderland classification.

Grade I	Focal segmental demyelination
Grade II	Axon damaged with intact endoneurium
Grade III	Axon and endoneurium damaged with an intact perineurium
Grade IV	Axon, endoneurium, and perineurium damaged with an intact epineurium
Grade V	Complete nerve transection

Table 3
House-Brackmann grading system.

Grade	Description	Characteristics
1	Normal	Normal facial function in all areas
2	Mild dysfunction	Gross: slight weakness noticeable on close inspection; may have very slight synkinesis At rest: normal symmetry and tone motion Forehead: moderate to good function Eye: complete closure with minimum effort Mouth: slight asymmetry
3	Moderate dysfunction	Gross: obvious but not disfiguring difference between the two sides; noticeable but not severe synkinesis, contracture and/or hemifacial spasm At rest: normal symmetry and tone motion Forehead: slight to moderate movement Eye: complete closure with effort Mouth: slightly weak with maximum effort
4	Moderately severe dysfunction	Gross: obvious weakness and/or disfiguring asymmetry At rest: normal symmetry and tone motion Forehead: none Eye: incomplete closure Mouth: asymmetric with maximum effort
5	Severe dysfunction	Gross: only barely perceptible motion At rest: asymmetry motion Forehead: none Eye: incomplete closure Mouth: slight movement
6	Total paralysis	No movement

5. Treatments for facial nerve injuries

5.1. Direct suture

For relatively small peripheral nerve gaps (<5 mm), direct use of 9-0 or 1 0-0 sutures to suture the epineurium at both ends can achieve better results. Smetana said that if the nerve defect gap is relatively large, when end-to-end suturing is performed directly, the suture will bear too much tension, and it will be difficult to obtain an ideal prognosis [26]. However, related studies show that

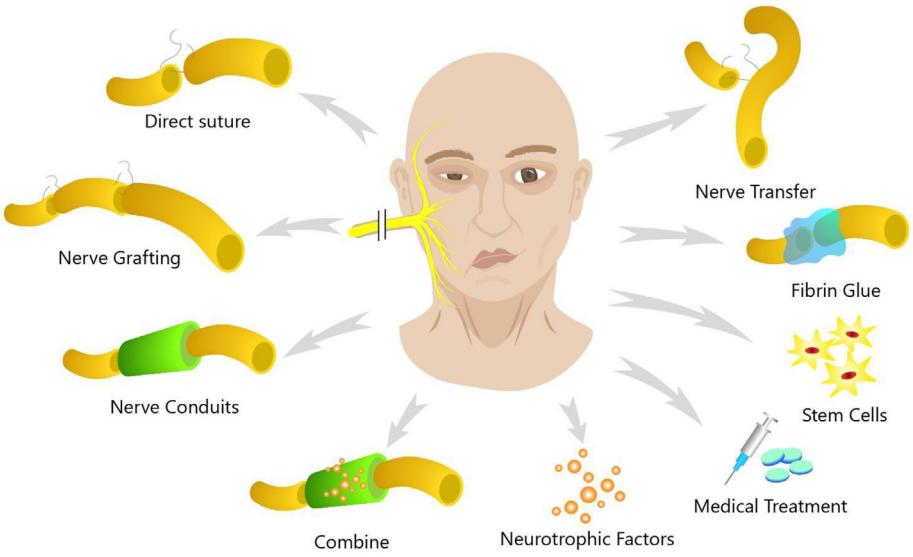

Fig. 2. Various treatment methods are mainly applied to facial nerve injury repair, including clinical treatment methods and related basic research.

direct suturing sometimes causes excessive manipulation, which leads to excessive damage to some nerves and degenerative changes during the inflammatory response. However, it must be admitted that this method is still the most frequently used clinically and has the best effect [27]. For large defects that are difficult to suture in place, end-to-side nerve anastomosis can also be used to anastomose the broken nerve with its adjacent nerve. The principle is to let the nerve ending on the normal side send out new nerve fibers so that damaged nerves can regenerate and reinnervate the corresponding target organs. As early as 1903, Ballance [28] applied this technology to the repair of facial nerve damage; however, the clinical effect was not satisfactory, so even after a century, it was not widely used in the end [29]. Several studies have proposed ways to improve the efficacy of this technique, such as removing the external nerve sheath of normal nerves at the end and reducing the angle of suturing nerves, which can indeed achieve better repair results than traditional end-to-end anastomosis [30–32].

5.2. Nerve grafting

In fact, nerve grafting is more suitable for large nerve gaps than direct suturing. Nerve transplantation includes autologous nerve transplantation, allogeneic nerve transplantation, and nerve graft transplantation. Autologous nerve transplantation is more commonly used. The method is to obtain a section of healthy and normal nerve fibers from the body itself (except the damaged area) and transplant this graft to the damaged area to repair the gap at the site of damaged nerve rupture [33,34]. However, the disadvantage of this method is that a second surgery area needs to be opened up, and there are considerable requirements for the donor. When autologous nerve transplantation is performed, sensory nerves such as the greater auricular nerve, sural nerve, and lateral femoral cutaneous nerve are often selected clinically [35–38]. The great auricular nerve and the sural nerve are most commonly used. The former has the advantage of being close to the facial nerve, and its shape is similar to that of the facial nerve. The latter has the advantage of sufficient length and many nerve bundles. However, since the facial nerve innervates the facial muscles mainly via motor nerves, when sensory nerve transplantation is used, the original nerve impulse may not be restored due to blood supply problems and other reasons, resulting in continued facial paralysis symptoms. Moreover, the direction of stimulus conduction of motor nerves and sensory nerves is opposite, so during the transplantation, the proximal end of the sensory nerve and the distal end of the facial nerve are sutured, hoping to obtain a better repair effect [39].

In addition to autologous transplantation, allogeneic transplantation is also an effective treatment method. This operation requires patients to undergo long-term immunosuppressive treatment with a large number of various drugs to prevent the rejection of the graft in the body [40]. Inhibition may in turn lead to an increased incidence of infection to some extent. Therefore, at present, more decellularized nerve grafts are used [41,42]—these grafts have had the Schwann cell nuclei and myelin sheaths that cause immune reactions removed and only retain the basic structure and extracellular matrix of the nerves, which can greatly reduce the occurrence of rejection [43,44]. After the operation, the patient does not need to receive immunosuppressive treatment, which reduces the risk of infection [45]. Hu found that the postoperative follow-up of patients showed a significant recovery of facial paralysis and no obvious rejection reaction [46]. The disadvantage of decellularized nerve grafts is that the lack of Schwann cells limits their regeneration effect, especially when they are longer in length. Related studies have shown that adding growth factors to decellularized nerve grafts can improve this effect [47,48].

In addition to decellularized grafts, various types of nerve conduits are suitable for this procedure. Due to the characteristics of the peripheral nerve structure, when there is enough space between the nerve stumps not occupied by other tissues, the nerve fibers can also slowly regenerate along the canal. There are many kinds of materials for making catheters, which are mainly divided into nonabsorbable materials and absorbable materials. The most researched materials are polylactic acid (PLA), polycaprolactone (PCL) and polyglycolic acid (PGA), polyphosphoester (PPE), PGA, poly-L-lactic acid (PLLA) and poly-DL-lactide-co-glycolide (PLGA) [49–51]. The use of this type of catheter can obtain an effect similar to allogeneic nerve transplantation, and catheters loaded with related growth factors or drugs can achieve better repair results than acellular grafts [52,53]. However, catheters made of nonabsorbable materials pose the problem of rejection, and some patients need a second operation to remove the catheter after surgery, which aggravates the degree of nerve damage to a certain extent.

Additionally, the catheter may degrade before the nerve stump is healed, causing the surrounding connective tissue to invade the nerve defect, and eventually, the nerve healing effect cannot meet expectations. Aside from artificial catheters, natural materials derived from the body itself can also be made into nerve catheters. The tissues and structures existing in the body, such as skeletal muscle tissue and blood vessels, are more compatible with the body than other materials. Stronger, better effect of guiding axon growth, and more parts and greater quantities can be obtained. Many studies have shown that catheters or blood vessels made of skeletal muscle tissue can effectively repair peripheral nerves in experimental animals [54–56].

In general, nerve transplantation is suitable for nerve injuries with high tension between stumps and wide nerve gaps, but its repair effect is poorer than that of direct suturing. The reason may be that nerve stumps need to span a long distance The distance to be repaired is greater, and more cross-sections have been passed; these reasons lead to the limited final repair effect of nerve grafting [57,58].

5.3. Nerve transfer

If the motor nerve adjacent to the facial nerve is transferred, part of the facial expression muscle function, such as the contralateral nerve, masseter nerve [59], and hypoglossal nerve, can be restored [60]. This method is suitable for situations where it is difficult for the stump of the facial nerve to regain the nerve impulse corresponding to the facial nerve. When the contralateral nerve is selected, the patient can achieve a more symmetrical and natural effect when producing different facial expressions because the stimulation transmitted by the lateral nerve can be transferred to the muscles innervated by the corresponding facial nerve on the affected side, and this effect is the same as that of other facial nerves. Neural switching methods cannot be achieved [61]. In recent years, there have even been improvements to this technique. Watanabe et al. used another motor nerve to provide the main force, while the lateral nerve was mainly responsible for transmitting and controlling the stimulation of facial expressions. The two nerves controlled the repair together, which achieved better results [62], while Jeong et al. improved the incision method and transferred the lateral nerve to the affected side through the intraoral approach, avoiding the appearance problems caused by the facial incision [39].

5.4. Fibrin glue

In the case of short nerve gaps, fibrin glue can also be used for nerve repair, and it can replace direct suture to a certain extent. Studies have shown that the use of fibrin glue can reduce the occurrence of inflammatory reactions compared with direct suture, and the final prognosis of the two is almost the same [27,63]. The direct application of fibrin glue to repair short neural gaps also appears to be an ideal method for physicians who are not yet fully proficient in microsurgery. Wu et al. also used alginate as a suture replacement material, which also showed good repair effects in the facial nerve injury model of experimental animals [64].

5.5. Stem cells

Stem cells have been widely studied for the treatment of nerve injuries in the past two decades because they not only have the potential to differentiate into nerve cells but also have the ability to self-replicate. Diseases (such as spinal cord injury, brain injury, and peripheral nerve injury) are promising [65–67]. Currently, more research on mesenchymal stem cells, fat stem cells, dental pulp stem cells, etc., is being conducted [68–70]. In the maxillofacial region of the human body, most jaws and teeth develop from the neural crest. Therefore, in the oral cavity, the source of mesenchymal stem cells is very rich, and it has been verified that mesenchymal stem cells can be extracted from the pulp, gingiva, oral mucosa, apical papilla, and periodontal ligament of adult teeth [71–75]. Many studies have shown that mesenchymal stem cells can differentiate into Schwann cells, and Schwann cells can promote the formation of myelin in the damaged area, so when mesenchymal stem cells are applied to the surrounding injured area, they can promote nerve regeneration and repair [76]. In summary, mesenchymal stem cells have sufficient sources, are easy to obtain, can rapidly proliferate, multidirectionally differentiate into cells, and easily integrate with the host. These characteristics make them an ideal cell source for promoting nerve regeneration.

Adipose-derived stem cells and bone marrow-derived stem cells, which are mesenchymal stem cells derived from adipose tissue and bone marrow, respectively, are commonly used in research. Trials of the use of these stem cells to promote peripheral nerve regeneration have also achieved promising results [77–79]. Although some basic experiments on the promotion of facial nerve regeneration by stem cells have achieved satisfactory results in many studies, it is still necessary to continue to observe and explore this aspect in depth to evaluate whether the use of animal models in previous experiments is appropriate as well as to reduce the number of animal experiments required. Notably, the obtained results may introduce clinical risks [80,81].

5.6. Neurotrophic factors

Neurotrophic factors are polypeptide systems that support cell survival, proliferation, differentiation and morphogenesis in mammalian nerves; these factors include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophic Factor 3 (NT-3) and neurotrophic Factor 4/5 (NT-4/5). The positive effects occur mainly through the strengthening of the intrinsic transduction potential and the modulation of retrograde uptake mediated by receptors post-interaction with molecular and mechanistic signaling cascades. Nerve growth factor is mainly secreted by glial cells and neurons. When peripheral nerve trauma occurs, the presence of nerve growth factor can maintain the microenvironment of nerve fiber regeneration. The role of neurotrophic factors in neuronal survival and the ability to promote axonal outgrowth in the peripheral nervous system has been extensively studied [82,83]. Further studies have shown that in nerve-injured animals, the expression of nerve growth factor secreted by neurons is down regulated [84]. Unfortunately, endogenous neurotrophic factors cannot meet the needs of axonal myelination and nerve growth [85], and exogenous neurotrophic factors need to be administered to provide nutritional support for axon regeneration for a long time to obtain a better curative effect. The study by Hui et al. showed that local injection of nerve growth factor can reduce the apoptosis of facial motor neurons in rats with facial nerve injury, which proves that neurotrophic factors can protect the injured facial nerve and relieve the symptoms of facial paralysis [86].

To achieve the purpose of axon regeneration, many studies have loaded neurotrophic factors into nerve scaffolds/catheters to improve the speed and accuracy of damaged nerve recovery [82]. For example, in 1993, Spector et al. placed nerve growth factors into a silica gel tube to repair a rabbit facial nerve injury. Compared with catheters without neurotrophic factors, nerve catheters loaded with neurotrophic factors promote the induction of axon growth and the regeneration of target nerves at the nerve gap injury. The

nerve conduit can not only protect neurotrophic factors from the interference of various enzymes and prolong their action time but also carry multiple neurotrophic factors concurrently to improve the repair effect.

In addition to neurotrophic factors, other growth factors also have corresponding facial paralysis repair effects. Raimondo et al. used vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1) to improve the muscle motor function in mouse and rabbit models of facial paralysis [87]. Xu et al. also demonstrated the repairing effect of VEGF in a rat facial nerve injury model by overexpressing vascular endothelial growth factor in rat dental pulp stem cells [88].

5.7. Drugs

The ideal drug would suppress nerve cell inflammation and edema, reduce neurodegeneration and stimulate regeneration. Steroid hormones have a similar effect. After Seth et al. [89] applied dexamethasone to a rat facial nerve injury model, they found that the amplitude level of the rat's compound muscle point was significantly improved. Longur et al. also proved that dexamethasone influenced facial nerve regeneration. However, Yanilmaz et al. [90] did not observe a significant improvement in facial nerve function after applying methylprednisolone in the facial nerve buccal branch injury model of New Zealand rabbits; however, they found that melatonin acts as an amine hormone on facial nerve injuries and has a recovery-promoting effect and that aminoguanidine compounds alone have similar effects [91]. In addition to hormonal drugs, many other medications have been proven to promote facial nerve regeneration, including etanercept [92], bumetanide [91], polyethylene glycol [93], p-acetylcysteine [94], and danhong [95]. These drugs reduce the inflammatory response caused by injury to varying degrees, slow the degeneration of nerve fibers caused by axonal injury, and promote nerve repair. It can be inferred that in the early stage of facial nerve injury in bedridden patients, one or more drug interventions can be applied to minimize the consequences of the injury. However, many drugs have not been effective in repeated studies, and dexamethasone is still one of the few drugs that is widely believed to alleviate facial nerve damage.

6. Discussion

In summary, among the various methods of treating facial nerve injury mentioned above, many studies have used one or more methods to conduct animal experiments, such as administering relevant stem cells, neurotrophic factors, drugs, etc. Regarding the recovery effect, in the case of minimal damage, flat ends, and small gaps, the method of direct nerve suture can obtain a very good curative effect, and all patients can experience notable recovery of facial muscle function after surgery. The possible reason for this is that when nerve fibers are directly sutured, it can effectively avoid axonal regeneration in the wrong direction, resulting in a decrease in the number of collateral branches and an increased possibility of reestablishing connections between neurons and the correct target, thereby achieving better neuromuscular control [96]. However, when the degree of injury is large, the broken end is difficult to track, the gap is wide, and it is difficult to anastomose the broken nerve directly, no matter what method is used for repair, it is difficult to obtain an ideal curative effect, and the improvement effect is limited, especially for the damaged nerve. Although these treatment methods can also reduce the formation of collateral branches during axonal regeneration, the ultimate performance of facial motor function is still limited by factors such as nerve excessive gap, rejection reaction of implants, inability to maintain drug and growth factor concentrations. Moreover, patients who are not treated in time experience minimal effects. Therefore, in the field of facial nerve repair, in addition to timely intervention and early repair of damage, more research and breakthroughs in long-term damage repair are needed.

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Declaration of competing interest

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