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The clinical outcomes of minor salivary gland transplantation for severe dry eye disease secondary to chronic Stevens-Johnson syndrome

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ABSTRACT

Purpose: To study the outcomes of minor salivary gland transplantation for severe dry eye disease secondary to chronic Steven Johnson Syndrome.
Methods: It was an ambispective, interventional case series conducted at Rajendra Prasad Centre for Ophthalmic Sciences, Delhi, India from 2022 to 2023 evaluating the outcomes of minor salivary gland transplantation with anchorage of the minor salivary glands to superior rectus muscle in twenty cases of severe dry eye disease secondary to chronic Steven-Johnson Syndrome. The pre-operative clinical parameters were compared to those at post-operative 1 year follow-up.
Results: At 1 year follow-up, there was an improvement in mean Schirmer-1 value ($p = 0.0004$), hyperemia score ($p = 0.0004$), keratinization score ($p = 0.04$), corneal epithelial defect score ($p = 0.0004$), corneal opacification score ($p = 0.001$), corneal neovascularization score ($p = 0.001$), palisades of Vogt score ($p = 0.007$), corneal keratinization score ($p = 0.04$) and corneal conjunctivalization score ($p = 0.08$).
Conclusion: The minor salivary gland transplantation is a viable management option for cases with severe dry eye disease secondary to chronic Steven Johnson Syndrome with clinical improvement in corneal and conjunctival parameters of the ocular surface.

1. Introduction

Stevens-Johnson syndrome (SJS) is a complex immunological disorder involving the mucocutaneous surfaces of the body. It predominantly involves oral mucosa and conjunctiva [1–3]. The inciting factors include various medications and less commonly infections [4,5]. The reported incidence of SJS varies from 1.2 to 6 per million [5]. Various ophthalmic manifestations of SJS occur due to chronic inflammation, tissue desiccation, and scarring. Ocular manifestations include severe dry eye disease, limbal stem cell deficiency (LSCD), loss of palisades of Vogt, conjunctivalization of the cornea, superficial punctate keratitis, and lid margin keratinization [6]. Various medical and surgical options are available to manage these manifestations of SJS. The commonly used medical options include the use of preservative-free eye drops, autologous serum, corticosteroids, other immunosuppressive therapy, topical all-trans retinoic acid and use of scleral contact lens. Surgical options include punctal occlusion, mucous membrane grafting, minor salivary gland transplantation, keratoplasty and keratoprosthesis.

In SJS, there is persistent inflammation of the ocular surface following the acute damage and longstanding surface irritation secondary to repeated ocular surface trauma from adnexal changes incurred in the acute phase. The severe dry eye disease is due to obliteration of ducts of the lacrimal gland in fornices. Repeated blinking leads to corneal microtrauma which results in corneal scarring and poor vision. These patients require multiple lubricating drops to alleviate these symptoms, which are often inadequate [7].

Murube del Castillo described minor salivary gland transplantation (MSGT) as an option to treat severe dry eye disease. Minor salivary glands are present in large numbers in labial, buccal and palatal mucosa and they can be transplanted together with overlying mucosa as a complex graft in severe dry eye patients [5,6]. MSGT has been shown to be useful in improving ocular surface lubrication and alleviation of

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symptoms in severe dry eye patients. Lubrication plays an important role in the survival of corneal and limbal graft which is often required in SJS patients. Various techniques have been described for the same, one of them being grafting of minor salivary glands to superior rectus muscle underneath the superior bulbar conjunctiva. There is a paucity of literature regarding the outcomes of minor salivary gland transplantation using this technique in chronic Steven Johnson Syndrome. This study was planned with the aim to study the clinical outcomes of the same.

2. Methods

This was an ambispective, interventional case series. The study was planned according to the tenets of the Declaration of Helsinki and ethical clearance was obtained from the institutional ethics committee (Ref.No. IEC-500/August 03, 2023). The patients with severe dry eye disease secondary to chronic Steven Johnson syndrome, who underwent minor salivary gland transplantation at Dr R.P Centre for Ophthalmic Sciences, AIIMS, Delhi with a minimum follow-up of 1 year were included in the study. A thorough history was taken for all patients including drug intake preceding onset of Steven Johnson syndrome, history of previous treatments and allergy history. The patients who had history of SJS following anti-epileptic drugs, were shifted to safer drugs like Levetiracetam or Lamotrigine after consulting the physician, while others were explained to avoid any future exposure to sulpha drugs. All data (prospective and retrospective) were entered in the pre-designed structured proforma from the case records. A written informed consent was taken from all the patients before performing the surgery. All cases who's data were taken additionally signed a consent to participate in the study (at enrolment – before surgery or at follow up).

The diagnosis of SJS was based on confirmatory history of acute onset of high fever, serious mucocutaneous illness with skin eruptions and involvement of at least two mucosal sites including the ocular surface. All the patients included in the study had severe aqueous deficiency (Schirmer test values < 5 mm). Cases with unilateral or bilateral involvement were included. In cases with eyelid abnormalities, lid correcting procedures were performed at least 6 weeks prior to MSGT. Other than lid correcting procedures, no other surgical procedures were done in the included cases. The patients with severe dry eye disease with underlying etiology other than SJS, any active corneal infection, corneal melt or corneal perforation or not willing to participate in the study or follow up were excluded from the study.

In patients with bilateral involvement, the eye with worse visual acuity and poorer ocular surface parameters was included in the study. They were started on lubricant drops (Sodium Hyaluronate 0.1 %). The frequency was based on their clinical symptoms. A complete ophthalmic examination of all the enrolled patients was done pre-operatively and post-operatively up to 1 year which included visual acuity, intraocular examination and fundoscopic evaluation. B scan ultrasound

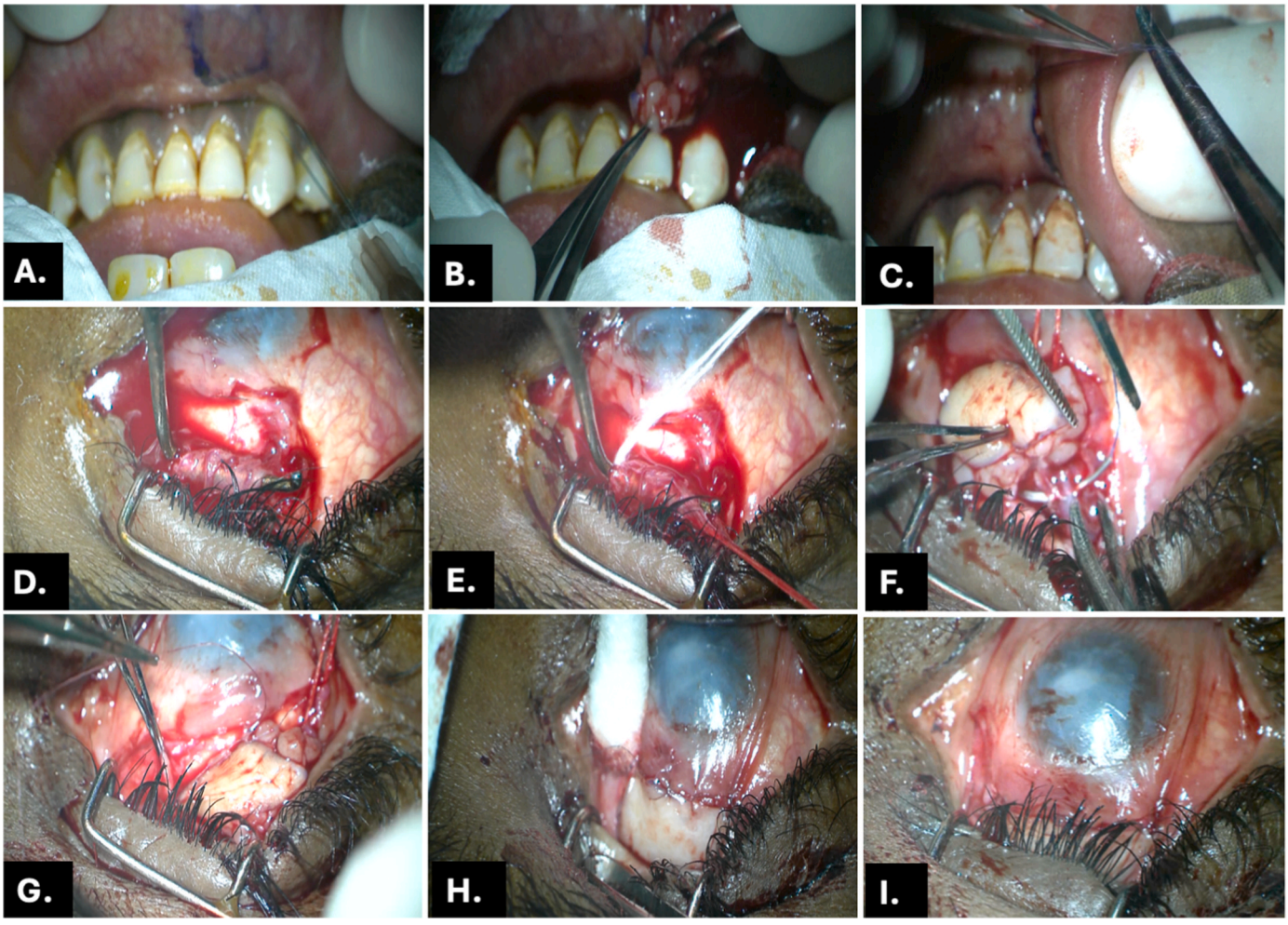

Fig. 1. (A) The inferior labial mucosal fold was exposed and marked (approximately 15 × 15 mm) (B) Dissection at deeper level using scissors to involve minor salivary glands (C) The mucosa was closed using 8-0 polyglactin (D) After superior peritomy, the superior rectus was identified using muscle hooks (E) A bridle suture was passed through superior rectus muscle (F) The mucosa-gland-muscle complex was trimmed and placed on recipient site (G) The complex was sutured to superior rectus with gland facing the sclera (H) The graft was sutured to conjunctiva and tenon's tissue (I) Peritomy was closed using 8-0 polyglactin.

examination was performed if the fundus was not visible. Slit lamp bio microscopy examination was done to examine the ocular surface parameters. All the ocular surface parameters were graded according to grading criteria specified in a study by Sharma et al. It included Schirmer score, hyperemia score and scores for conjunctivalization, keratinization, palisades of Vogt, corneal neovascularization, superficial punctate keratitis, and corneal opacification [8]. Chlorhexidine or Betadine gargles were prescribed pre-operatively at least 1 week prior to the procedure.

3. Surgical procedure

The patients were planned for minor salivary gland transplantation under general anesthesia. All the steps have been illustrated in Fig. 1.

The excision area of the lower labial mucosa was marked of approximately 15 × 15 mm size. It was infiltrated with 1–2 mL of combined two percent lignocaine and 1:200000 adrenaline and the initial superficial incision was given with a 15-number surgical blade. Deeper dissection was carried out using scissors to involve minor salivary glands and muscle layers. It was ensured that the graft contained at least 10 gland count. The graft was harvested and the wound was closed using 8-0 polyglactin suture. The recipient site was prepared by dissecting the conjunctiva and tenons capsule 6 mm posterior to the limbus. A subconjunctival pocket was created posteriorly. The superior rectus muscle was isolated and a bridle suture was passed through it. The harvested mucosa–gland–muscle complex was trimmed to size, and the tissue was placed on the recipient bed created earlier with the salivary glands facing the sclera and the mucosa oriented towards the surface. A 6-0 polyglactin suture was used to suture the muscle fibres present in the graft with the superior rectus muscle. The rest of the graft was sutured to the conjunctiva and tenons using 8-0 polyglactin sutures.

Postoperatively, the patients were advised to avoid hot and spicy food and apply lignocaine gel before meals. They were asked to continue Chlorhexidine mouthwash and betadine gargles for a week after the surgery. Topical moxifloxacin 0.5 % eye drops (Vigamox, Alcon Laboratories, Fort Worth, Texas, USA - three times a day for 2 weeks), prednisolone acetate 1 % eye drops (Predforte, Allergan pharmaceuticals - six times a day for a week, tapered over 6 weeks) and lubricants (Sodium Hyaluronate 0.1 %) were prescribed. The dosages of the lubricant drops were titrated according to the severity of signs and symptoms of the patients. Oral analgesics were prescribed after consulting the attending physician.

4. Statistical analysis

Statistical analysis was carried out using SPSS software version 22 (IBM Corp., Armonk, NY). Data were expressed as median ±standard error, mean ± standard deviation and percentage as applicable. The power of the study was kept at 80 % and the level of significance was 0.05. Nominal data were compared using the chi-square test or Fisher exact test, as appropriate. Non-parametric quantitative data were compared using Kruskal Wallis and Mann-Whitney U tests. One-way analysis of variance was used to compare intergroup means for parametric quantitative data, and Bonferroni correction was used to analyse post-test results.

5. Results

Twenty eyes of 20 patients who underwent MSGT during the study period were included in the study. The mean age of the patients in the study was 28.6 ± 13.1 years (range 12–70 years). There were 12 female and 8 male patients. Twelve of twenty patients (60 %) gave a history of intake of antipyretics and analgesics before developing SJS while the other causative agents included antiepileptic drugs, various eyedrops and antitubercular treatment (ATT) drugs. They had history of oral Non-steroidal anti-inflammatory drugs (most common being Ibuprofen) while rest had history of use of antiepileptic drugs, oral Doxycycline (n = 1) and unknown drug intake (n = 2). Twelve patients had history of pain or fever for which they used oral medications while five cases had gave history of epilepsy for which they were advised anti-epileptic drugs.

Ten of twenty (50 %) patients presented with a history of 5–10 years before the onset of Stevens-Johnson Syndrome, while 30 % presented with a history of shorter duration (less than 5 years) and 20 % had history of longer duration (more than 10 years). The mean time of presentation of patients was 6.42 ± 3.94 years. Two patients had unilateral ocular involvement, while rest cases had bilateral involvement. All patients underwent unilateral surgery. There were no major intra-operative complications reported. Six patients (30 %) required symblepharon release intra-operatively.

Outcome measures

All the outcome parameters were compared from baseline (presentation) to the final follow up (1 year post-operatively). There was a significant improvement in mean post-operative best-corrected visual acuity (BCVA) in 10 of 20 patients (50 % cases). The mean pre-operative BCVA was log MAR 1.99 ± 0.57 which improved post-operatively to log MAR 1.76 ± 0.41 at 1-year follow-up (p = 0.002).

The Schirmer test scores improved significantly in 15 eyes (75 %) (p = 0.0004). The hyperemia score improved from 2.3 to 1.4 and all eyes were non-inflamed at 1-year follow-up (p = 0.0004). The corneal epithelial defect score showed significant improvement from its baseline value (p = 0.0004).

There was a significant decrease in corneal opacification score (p = 0.001), which led to improved corneal transparency in 14 out of 20 eyes (70 % cases).

The corneal neovascularization score (p = 0.001), corneal keratinization score (p = 0.04) and palisades of Vogt score (p = 0.007) also showed significant improvement. There was a trend towards improvement in corneal conjunctivalization score, however it did not reach statistical significance (p = 0.08). The results specifying the baseline parameters and those at 1-year follow-up are specified in Table 1.

Sixteen out of 20 eyes (80 %) had reduced frequency and dependency on lubricating agents after surgery. In 16 eyes, the frequency of eyedrops decreased from 1 to 2 hourly to qid dosage, while in 4 eyes, the frequency remained same.

The procedure did not result in any serious sight-threatening complications in the operated eye. One patient developed intraoperative buccal hematoma, which resolved spontaneously after one month. Oral mucosal epithelialization was achieved within 2–3 weeks. None of the patients experienced surgical site infections, diplopia, proptosis, or ptosis.

The representative image of a case in the study is shown in Fig. 2.

Discussion

Patients with chronic SJS have severe dry eye disease, which leads to ocular discomfort and pain. These patients usually require multiple and frequent lubricating eyedrops which ameliorates ocular discomfort and leads to improvement in the quality of life [4]. Sulfonamide antibiotics and anti-epileptics drugs were the most common predisposing factors in various studies [4,8]. In the present study, 60 % of patients reported developing episodes of SJS after taking antipyretics and analgesics. This corroborates with findings observed by Ueta et al. [9] This could be due to easy availability of these medications over-the-counter in developing countries The time of presentation of patients in the chronic stage of SJS varies among different studies [4,5]. In the present study, 70 % of the patients had an acute episode of SJS 5 years back. This possible causes for the delay could be late presentation, follow up or referral to tertiary eye care centre. SJS involves both eyes and the level of involvement can be asymmetric which was reported in various studies. Sixty percentage

Table 1
The various clinical parameters of dry eye disease at baseline (presentation), at 1 year follow up after minor salivary gland transplantation and their comparison.

Parameter	Baseline (Mean ± SD)	1 year follow-up (Mean ± SD)	Median Baseline	Median 1 year follow-up	Range (Minimum – maximum)	P value (mean)
BCVA (log MAR)	1.99 ± 0.57	1.76 ± 0.417	2	2	2.6–0.8	0.004
Schirmer Score	0.85 ± 1.26	5.05 ± 2.16	0	4	0–10	0.0004
Hyperemia Score	2.3 ± 1.08	1.4 ± 1.27	2	1	0–5	0.0004
Superficial Punctate Keratitis (SPK) Score	2.3 ± 0.65	1.55 ± 0.99	2	1.5	0–3	0.0004
Corneal Opacity Score	2.7 ± 1.03	2.3 ± 0.97	3	2	0–4	0.001
Neovascularization Score	3.25 ± 1.01	2.7 ± 1.12	3.5	3	0–4	0.001
Keratinization Score	2.1 ± 1.16	1.8 ± 1.15	2	2	0–4	0.04
Palisades of Vogt Score	3.05 ± 1.2	2.7 ± 1.13	3.5	3	0–4	0.007
Conjunctivalization Score	2.6 ± 1.31	2.3 ± 1.12	3	2.5	0–4	0.08

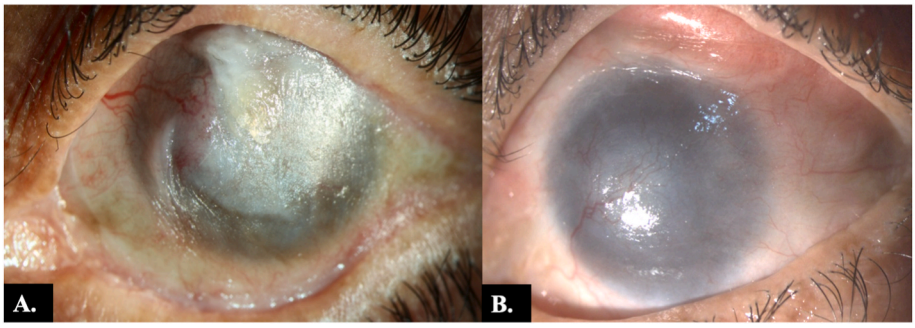

Fig. 2. Representative Image (A) Pre-operative image showing dry keratinized ocular surface with vascularised opaque cornea (B) Post-operative image at 1 year follow up with improved corneal transparency and wettability and reduced neovascularization and keratinization.

of the patients in the present study were females. Women may be at higher risk of developing immune-mediated conditions like SJS due to altered immune system in various stages of life.

The mean age of the patients in the present study was 28.6 ± 13.1 years. In a study by Vazirani et al., the median age of the patients was reported 38 years [10]. This difference in age could be due to the asymmetric distribution of the patients in the 2 studies. In a study previously done by Sharma et al., the mean age of the patients was 31.69 ± 16.67 years and 27.92 ± 12.48 years in two study groups [11].

Various studies reported encouraging results with minor salivary gland transplantation (MSGT) in patients with severe dry eye disease [10,12]. The present study includes patients with chronic SJS developing severe dry eye disease. SJS leads to cicatrizing changes leading to severe dry eye. Transplantation of minor salivary glands aims to improve the ocular surface of the patients by providing an additional source of tears. Secretion from the salivary gland has similar antibacterial and anti-inflammatory properties to tears and they have similar composition [6]. The constituents of human tears are water, mucin, lipids, lysozyme, lactoferrin, lipocalin, lacritin, immunoglobulins (IgA and IgM), glucose, urea, sodium and potassium. Similarly, human saliva is made up of water, electrolytes (potassium, magnesium, calcium, phosphate), mucus (proteins, salts, sugars), enzymes (lipases and amylases), antimicrobial agents (secretary IgA, Ig M and lysozymes) [13]. The immunoglobulin A, lysozyme, lactoferrin, and human beta-defensin present in saliva offer antimicrobial properties that safeguard the ocular surface against infections. Additionally, the epidermal growth factor and transforming growth factor-B, support the normal growth of ocular surface epithelium and promoting corneal reepithelization. The continuous secretion of mucosal salivary glands maintain lubrication of the ocular surface even during sleep.

The salivary glands and lacrimal glands even share common acinar-ductal anatomy. They have numerous acinar cells for production of secretions, which drain in the central lumen. The collected fluid, then drains through ductules in their respective target anatomical space [14]. Minor salivary gland tissue was procured from patient's buccal mucosa and the graft complex included mucosa (with non-keratinized epithelium), minor salivary glands and muscular sheath. After transplantation, on integration with the superior rectus muscle, it develops vascularity to remain viable. It helped in secretion of salivary fluid acts as functional tears thereby lubricating and protecting the ocular surface. Minor salivary gland transplantation doesn't cause reflex epiphora due to a lack of autonomic innervation [15,16].

The minor salivary glands located in the submucosa of the oral cavity can be used in the visual rehabilitation of patients with SJS. These glands are classified as labial, buccal, glossopalatine, and palatine. The minor labial salivary glands, which are present on the inner surface of the upper and lower lips, are the glands most commonly used in severe dry eye treatment. Unstimulated and SLD-stimulated minor mucous gland secretions were then collected and the median percentage contributions to whole saliva were calculated to be 8 and 7 per cent, respectively [17].

Steven Johnson syndrome affects the oral and ocular mucosa of the body. However, in the oral cavity it generally causes ulceration and blisters. They gradually heal with re-epithelization of the surfaces. Steven Johnson syndrome does not cause targeted destruction of the salivary glands. Few case studies do report decreased salivary production after acute Steven Johnson Syndrome but these are majorly due to secondary causes like infection or effect of drug [18].

Minor salivary gland transplantation is a well-established and proven technique in the treatment of severe dry eye disease with chronic SJS. A study by Vazirani et al. studied the long term outcomes of MSGT till 3 years follow up [10]. Studies with longer follow up to 10 years will help in analysing the long term outcomes of the graft.

In the present study, the site of harvesting the graft was from the lower lip. The location was selected due to higher density of glands in the area as compared to other areas and the ease of harvesting the gland from the site. Other minor salivary gland tissue sources are the upper lip, buccal mucosa and palate tissues. The glands were harvested using blunt

dissection of the tissue using scissors as opposed to mucotome preferred in some studies. It helped in depth titration manually such that minor salivary glands could be visibly be dissected and counted. As documented in a previous study done by Vazirani et al. anchoring the harvested minor salivary glands to the superior rectus muscle in the superior fornix leads to faster revascularization due to improved blood supply [10]. In the present study too the harvested graft was sutured with superior rectus muscle. However, this study included a substantial proportion of very severe cases, with 60 % of participants showing a Schirmer value of zero.

There was a significant improvement in BCVA in 50 % of the patients. In a study done by Sant ana et al., there was an improvement in BCVA in 42 % of patients after minor salivary gland transplantation [15]. In the present study, the Schirmer test showed improvement in basal tear secretion in 75 % of patients. These patients had improved lubrication in the eyes which led to better ocular comfort and decrease in frequency of lubricant drops in them. Sant ana's study showed that 73 % of patients had improvement in their Schirmer test score which was similar to what was shown in the present study [15]. Due to improved lubrication in the eye, degree of superficial punctate keratitis or epithelial defect and hyperemia was significantly reduced in these patients. In the present study, 70 % of patients showed improvement in their hyperemia score and corneal epithelial defect scores. Neovascularization scores also improved in the present study. Corneal transparency score improved in 70 % of patients which led to improvement in best-corrected visual acuity (BCVA) in these patients.

The study's strengths lie in its structured approach, focusing on the benefits of Minor Salivary Gland Transplantation for severe dry eye disease in eyes with chronic Stevens-Johnson Syndrome with no prior ocular surgeries, except lid correcting procedures. Notably, the sample size and follow-up period were adequate compared to previous studies, enhancing the study's robustness. The technique employed transplantation of minor salivary glands to the superior rectus and covering with superior conjunctiva. This facilitates early vascularization and gland viability, contributing to improved clinical outcomes. Additionally, the objective evaluation of improvement in dry eye disease adds credibility to the findings.

However, there are certain limitations. Firstly, the study lacks subjective evaluation and quality of life analysis of the cases before and after surgery. It could provide valuable insights into patient experiences and satisfaction with the procedure. Secondly, the lack of immunohistochemistry in the post-operative period to demonstrate the viability of transplanted glands is a notable gap, as it could further elucidate the mechanism and efficacy of MSGT. Lastly, a longer follow-up duration, extending beyond 10 years, would have allowed for a more comprehensive analysis of the long-term outcomes and durability of the intervention.

To conclude, the minor salivary gland transplantation is a viable and effective treatment option for cases of severe dry eye secondary to Stevens-Johnson syndrome. The various advantages include similar biological properties of conjunctiva and mucous membrane and tears with saliva, easy accessibility and universal availability, relatively easy procurement of donor tissue and low-cost and simpler surgical technique, nil risk of allogenic graft related problems and repeatability with minimum complications. For cases of chronic SJS for which limited treatment options available, the pre-operative status of the patient's eye acts as control and post-operative outcome have been compared to the pre-op status of eye [19–22]. Addressing the limitations of the study, a future randomized study could enhance the understanding and applicability of minor salivary gland transplantation in managing severe dry eye disease secondary to chronic Steven Johnson Syndrome. However, given the facts that SJS is not a common disorder with many variables in natural history of the disease and feasibility of treatment modality is based on clinical assessment and willingness of the patient to undergo surgery and follow up, conducting a randomized case control study in this patient population with comparable baseline parameters may be extremely challenging.

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CRediT authorship contribution statement

Namrata Sharma: Writing – review & editing, Supervision, Conceptualization. **Vishal Kumar:** Writing – original draft, Data curation. **Aafreen Bari:** Writing – review & editing, Conceptualization. **Renu Venugopal:** Conceptualization, Resources, Validation, Writing – review & editing. **Shivam Sharma:** Writing – original draft, Formal analysis. **Tushar Agarwal:** Writing – review & editing, Conceptualization. **Tanuj Dada:** Validation, Conceptualization. **Neelam Pushker:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2024.08.010.

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