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REVIEW

What is the benefit of using amniotic membrane in oral surgery? A comprehensive review of clinical studies

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Abstract

Objectives Since its first use for the reconstruction of tissue defects in the oral cavity in 1985, human amniotic membrane (hAM) has been widely studied in the field of oral surgery. Despite the growing number of publications in this field, there is no systematic review or meta-analysis concerning its clinical applications, outcome assessments, and relevance in oral surgery. The aim of this review is to provide a thorough understanding of the potential use of hAM for soft and hard tissue reconstruction in the oral cavity.

Materials and methods A systematic electronic and a manual literature search of the MEDLINE-PubMed database and Scopus database was completed. Patient, Intervention, Comparison and Outcomes (PICO) technique was used to select the relevant articles to meet the objective. Studies using hAM for oral reconstruction, and conducted on human subjects, were included in this survey.

Results A total of 17 articles were analyzed. Five areas of interest were identified as potential clinical application: periodontal surgery, cleft palate and tumor reconstruction, prosthodontics and peri-implant surgery. Overall, periodontal surgery was the only discipline to assess the efficacy of hAM with randomized clinical trials. The wide variability of preservation methods of hAM and the lack of objective measurements were observed in this study.

Conclusion hAM is already used in the field of oral surgery. Despite this, there is weak clinical evidence demonstrating convincingly the benefit of hAM in this area compared to standard surgery.

Clinical relevance Several studies now suggest the interest of hAM for periodontal tissue repair. Due to its biological and mechanical properties, hAM seems to be a promising treatment for wound healing in various areas of oral reconstruction. However, further randomized clinical trials are needed to confirm these preliminary results.

Keywords Amniotic membrane · Oral surgery · Guided bone regeneration · Guided tissue regeneration

Introduction

Amniotic membrane is the innermost layer of the fetal membrane, lining the amniotic cavity. Human placentas can be recovered after elective cesarean surgery from consenting healthy mothers. It has been shown that human amniotic membrane (hAM) possesses low immunogenicity [1, 2] and exerts an anti-inflammatory [3], anti-fibrotic [4], and an anti-mutagenic effect [5]. Moreover, hAM is a source of stem cells [6] and growth factors [7]. The clinical use of hAM in medicine was first reported by Davis in 1910 for skin replacement. Due to its biological properties, and large availability, hAM is already widely used in the field of ophthalmology and dermatology [8, 9]. In 2014 and 2015, in France, hAM was the third most grafted human tissue after bone and corneal grafts [10, 11]. The use of hAM for the treatment of oral mucosa defects was initially described in 1985 by Lawson et al. [12]. Several preclinical studies also reported the use of hAM for oral reconstruction, with a wide variety of applications [13, 14]. Two studies concluded the efficacy of hAM to promote gingival wound healing [13, 14]. Two studies analyzed the use of hAM

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for periodontal regeneration [15, 16]. Both studies stated that hAM associated with periodontal ligament stem cells improved periodontal regeneration [15, 16]. Finally, to evaluate its potential as a membrane for guided bone regeneration (GBR), hAM was placed over parietal bone defects in mice and rabbits [17–19]. In this model, hAM used alone (without stem cells or any bone substitute) has a limited potential for GBR. Another preclinical study stated that hAM could be used for a GBR procedure around dental implants [20]. A positive result was also obtained in a model of extraction socket in rats [21]. Because preclinical results were contradictory, we have made the decision to complete a comprehensive analysis of the results obtained with hAM used in clinical studies.

The objective of this review was to identify the potential clinical indications and the relevance of hAM use in the field of oral surgery.

Materials and methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22].

Focused question

The following focused question was stated using the PICO reporting system: "In which clinical indications has amniotic membrane been shown effective in the field of oral surgery?"

P (patients): patients who undergo a procedure of oral surgery.
I (intervention): soft or hard tissue repair of the oral cavity involving the use of hAM alone or combined to a biomaterial.
C (comparison): procedures without the hAM.
O (outcomes): oral soft and/or hard tissue reconstruction.

Search strategy

An electronic search of the MEDLINE-PubMed database and Scopus database was realized, for articles published in English, between January 1995 and April 2016. The following keywords were used: ("Amnion" OR "amniotic membrane" OR "amniotic epithelial cells" OR "amniotic mesenchymal stem cell") AND ("oral mucosa" OR "oral surgery" OR "jaw" OR "maxillary" OR "vestibule" OR "guided bone regeneration" OR "bone regeneration " OR "oral cavity" OR "tongue" OR "periodontal guided tissue regeneration" OR "guided tissue regeneration"). Furthermore, additional articles were added after scanning manually the reference lists of all publications included.

Selection criteria

Studies were included if they analyzed the effectiveness of hAM in oral tissue reconstruction, if they were conducted on human subjects and if they were published in English. Prospective (randomized controlled, non-randomized controlled, cohort) and retrospective studies (controlled, case control, single cohort) and case series were included. Only studies during at least 1 month were included. In vitro studies, studies based on the use of hAM cells without their matrix, or amniotic fluid, or hAM associated with chorion, were excluded. Moreover, single case reports were also excluded.

Screening of studies and data extraction

The article selection and data collection were independently performed by three reviewers (M.F, S.C, and J.C.F). Title and abstract were screened according to the question: "Has amniotic membrane been used efficiently for tissue repair/regeneration of either soft or hard tissues in oral surgery?" Full-text articles were assessed if the titles and abstract answered to this screening question. The disagreements between the reviewers were discussed to decide the final article selection.

Tables were generated and used to collect relevant information. The data extracted from the reports were: the general characteristics (authors and year of publication), level of evidence, the number of subjects involved, the techniques of processing and preservation of hAM, the clinical applications, treatment procedures, evaluation criteria, and efficacy of hAM. In the case of missing data in the articles selected, the authors were contacted by email to complete the information.

Due to the available data, the outcomes were reported in a systematic way with an overview of all studies fitting the search descriptions.

Results

Search outcomes

The initial electronic search resulted in the selection of 98 titles from the MEDLINE-PubMed database and 176 from the Scopus database. After inclusion and exclusion criteria were assessed, 17 articles concerning 374 patients were analyzed and relevant data were extracted. Among these 17 studies, 12 were published after 2010, demonstrating the recent interest in the use of hAM in oral surgery. The studies were separated into five areas: periodontal surgery, cleft palate and tumor reconstruction, prosthodontics, and peri-implant surgery. Based on the levels of evidence of National Health and Medical Research Council, four of the 17 studies included were randomized controlled trials [23–26], one was a retrospective cohort study [27], one was a case control study [28], and eleven were case series.

Preservation and methods of hAM use

hAM was prepared in the five following forms: hAM was used dried in three studies, cryopreserved in five studies, lyophilized in five studies, fresh in two studies, or preserved in glycerol in two studies (Table 1). Three studies reported the use of hAM as a multilayer graft (≥ 2 layers). Five authors mentioned which side of the amniotic membrane was placed in contact with the defect, and it was always the mesenchymal side.

Clinical studies were summarized Table 2.

Use of hAM in the field of periodontal surgery

hAM was mainly used in the field of periodontal surgery to repair/regenerate intrabony defects, furcation defects, and gingival recessions.

Guided tissue regeneration

Two randomized controlled clinical trials reported the use of hAM in guided tissue regeneration (GTR) for the surgical treatment of periodontal pockets [24, 25]. Clinical improvements were mainly assessed by the measurement of the clinical attachment level (CAL) and probing pocket depth (PPD). Furcation defect and intrabony defect regeneration were clinically and/or radiographically evaluated. Both studies highlighted the benefit of hAM, when associated with a bone substitute, to treat periodontal pockets. One study compared the regeneration of intrabony defects using either hAM associated with a bone substitute (hydroxyapatite) or hydroxyapatite only in 30 subjects. A highly significant reduction of gingival crevicular fluid IL-1 levels in sites treated with hAM was observed compared to controls ($p \leq 0.001$). Besides, the use of hAM associated with hydroxyapatite increased significantly the bone fill, reduced the pocket depth (PD) and increased the clinical attachment level (CAL) compared to controls [24].

The other study compared the efficacy of hAM associated with xenogenic bone graft versus a collagen membrane currently used in oral surgery associated with the same bone graft in 10 patients [25]. After 6 months, CAL, PD, and probing bone were significantly improved in both groups compared to the initial situation ($P < 0.001$). The difference between the two groups was not significant, indicating that hAM is as effective as a conventional membrane used to treat periodontal pockets.

One study reported the use of hAM in the treatment of periodontal grade II buccal furcation defects [23, 29]. Kothiwale et al. evaluated clinically and radiographically the efficacy of bone graft associated with hAM as guided tissue regeneration (GTR) in the treatment of bilateral mandibular periodontal grade II buccal furcation defects [23]. Ten patients (20 defects) were randomly treated with allograft or xenogenic bone graft with hAM. Clinical and radiographic parameters were analyzed. Nine months after surgery, both therapies resulted in significant improvement in clinical attachment level (CAL) and pocket depth (PD). Radiographically, significant increase was seen over baseline in bone fill and percentage gain with both materials, without significant difference between them ($P = 0.05$). This suggests that hAM is as effective when it is associated with allograft or xenograft to treat moderate furcation defects.

Among these three studies only one highlighted the anti-inflammatory effect of hAM, due to the significant reduction of GCF IL-1β [24]. However, no impact on gingival inflammation could be observed, as there was no difference in the gingival index between the group treated with hAM and the control group.

Root coverage of gingival recession

Three studies evaluated the use of hAM for gingival recession coverage [28, 30, 31]. hAM grafting was associated with a coronally positioned flap. The benefit was evaluated after measuring gingival recession and subjective clinical observation was realized concerning the

Table 1 Preservation method of amniotic membrane

Article	Method of preservation	Number of layer
Gurinsky 2009	Dried	Multiple
Shetty et al. 2014	Lyophilized	1
Sharma and Yadav 2015	Dried	1
Kothiwale et al. 2009	Lyophilized	1
Kumar et al. 2015	Lyophilized	1
Kiany and Moloudi 2015	Lyophilized	2
Lai et al. 1995	Fresh	1
Arai et al. 2012	Dried	1
Khademi et al. 2013	Cryopreserved	1
Kar et al. 2014	Cryopreserved	1
Amemyia 2015	Cryopreserved	1
Rohdeler 2013	Cryopreserved	5
Güler et al. 1997	Lyophilized	1
Samandari et al. 2004	Fresh	1
Sharma et al. 2011	Preserved in glycerol	1
Kothari et al. 2012	Preserved in glycerol	1
Velez et al. 2010	Cryopreserved	1

Table 2 Use of amniotic membrane in oral surgery

Author Year	Levels of evidence	Patients	Indications	Treatments	Evaluation methodology	Results
Gurinsky 2009	IV	5	- Gingival recession (Miller class I and II)	hAM	- Measurement of gingival recession - Subjective clinical observation	- 97% root coverage - No adverse reaction - hAM increased tissue thickness and increased attached gingival tissue
Shetty et al. 2014	III-3	1	- Gingival recession (Miller class I)	(1) hAM (2) PRF	Measurement of gingival recession - Subjective clinical observation	- 100% root coverage - Increased of gingival biotype - More stable results over time with hAM
Sharma and Yadav 2015	IV	3	- Gingival recession (Miller class II)	hAM	- Measurement of gingival recession - Measurement of CAL - Width of keratinized gingiva	- 70% of mean root coverage - Keratinized gingiva significantly increased - CAL significantly decreased
Kothiwale et al. 2009	II	10	- Periodontal furcation defect (grade II)	(1) Bone allograft + hAM (2) Xenogenic bone graft + hAM	- Measurement of CAL - Measurement of PD - Standardized radiographic examination	- Significant improvement of clinical parameters - Significant improvement in bone fill - Adverse reaction was reported in one patient
Kumar et al. 2015	II	30	- Periodontal pockets	(1) HA (2) HA + hAM	- Measurement of CAL - Measurement of PD - Standardized radiographic examination - Measurement of inflammatory and antimicrobial peptide biomarkers	- hAM increased bone fill, reduced PPD and increased CAL - hAM induced a significant reduction of proinflammatory cytokines
Kiany and Moloudi 2015	II	10	- Periodontal pockets	(1) Xenogenic bone graft + hAM (2) Xenogenic bone graft + collagen membrane	- Measurement of CAL - Measurement of PD - Measurement of probing bone - Measurement of gingival recession	- Both groups provided improvement of clinical periodontal parameters - hAM did not induced significant gingival recession compared to collagen membrane - No adverse reaction
Lai et al. 1995	III	150	- Mucosal defect after excision of submucous fibrosis	(1–3): Pharmaceutical therapy (4) Skin graft (5) hAM (6) Buccal fat pad graft	- Measurement of interincisal distance	- hAM improved interincisal distance compared with pharmaceutical therapy, but decreased compared with skin or buccal fat pad grafts
Arai et al. 2012	IV	10	- Mucosal defect after excision of precancerous and cancerous lesions	hAM	- Scoring index of hAM usefulness and its effectiveness (operability, hemostatic status, pain relief, feeding situation, epithelialization, scar contracture, and safety)	- No adverse reaction - hAM was highly effective in 3 patients and effective in 7 patients - hAM was extremely useful in 7 patients - Good operability of hAM
Khademi et al.	IV	50		hAM	- Scoring index of hAM usefulness (granulation tissue formation and epithelialization)	- hAM was very effective in 40 patients and effective in 10 patients

Table 2 (continued)

Author Year	Levels of evidence	Patients	Indications	Treatments	Evaluation methodology	Results
2013			- Mucosal defect after excision of cancerous lesions			- No adverse reaction
Kar et al. 2014	IV	34	- Mucosal defect after excision of precancerous lesions	hAM	- Clinical measurement (swelling, epithelialization, oral opening, and mucosal suppleness) -Subjective parameters (pain and sensory response)	- After 3 months, all patients showed good epithelialization - After 6 months, oral opening was good in 24 patients and fair in 10 patients - 28 patients reported normal sensation and six still had altered sensation after 6 months
Amemiya 2015	IV	5	- Mucosal defect after excision of benign and precancerous lesions	hAM + autologous oral epithelial cells	- Subjective clinical observation	- Complete epithelialization after 1 month - No adverse reaction
Rohleder 2013	IV	4	- Oronasal fistula of the hard palate	hAM	- Subjective clinical observation	- Complete closure of the oral epithelium - No adverse reaction
Güler et al. 1997	IV	20	- Mandibular vestibuloplasty	hAM	- Measurement of blood flow - Subjective clinical observation	- Angiogenic effect of hAM - Complete epithelialization after 21 days - No adverse reaction
Samandari et al. 2004	IV	7	- Mandibular vestibuloplasty	hAM	- Subjective clinical observation - Measurement of buccal depth - Histological analysis	- After 3 weeks, an intra-oral soft tissue layer similar to attached mucosa was observed - After 6 months, the reduction of buccal depth ranged from 17 to 40% - No adverse reaction
Sharma et al. 2011	IV	10	- Mandibular vestibuloplasty	hAM	- Subjective clinical observation - Measurement of buccal depth	- After 3 weeks, an intra-oral soft tissue layer similar to attached mucosa was observed - After 3 months a gain of 4 to 6 mm was noted - No adverse reaction
Kothari et al. 2012	IV	10	- Mandibular vestibuloplasty	hAM	- Subjective clinical observation - Measurement of buccal depth	- After 3 months, the reduction of buccal depth ranged from 17 to 50% - No adverse reaction
Velez et al. 2010	II	15	- Surgical wound after implant surgery	(1) Control (2) hAM	- Clinical measurement (wound size, epithelialization, scarring) - Pain response	- Closure occurred sooner on the membrane side - Significantly fewer subjects reported pain with hAM - No adverse reaction

CAL clinical attachment level, *HA* hydroxyapatite, *PD* pocket depth tissue thickness and the attached gingival tissue. The three studies reported a percentage of root coverage that ranged from 70 to 100%. Furthermore, an improvement of the gingival biotype was noticed.

Interestingly, one case control study was conducted in a patient with a bilateral gingival recession. hAM was compared to platelet-rich-fibrin (PrF). Similar clinical outcomes were obtained but hAM showed more stable results after 7 months [28].

Even if these outcomes seem to be encouraging, studies comparing the use of coronally advanced flap associated with amniotic membrane to this same technique associated with connective tissue graft were missing.

Use of hAM for oral reconstructive surgery after tumor resection

hAM was used as a wound dressing material to cover mucosal defects after benign, premalignant, or malignant tumor resection in five studies. Four studies used hAM as a graft, and one study involved autologous cells transferred on hAM, for covering intra-oral mucosal defect. Evaluation was based on scoring index and/or clinical observation.

Lai et al. assessed the efficacy of hAM for covering mucosal defect after excision of oral submucous fibrosis (OSF). One hundred fifty patients suffering from OSF were treated by either pharmaceutical or surgical therapies. Surgical therapies involved the excision of fibrotic tissue to cover the wound with split-thickness skin, buccal fat pad or hAM grafts. The evaluation was based on mouth opening measurements. hAM grafts improved mouth opening compared to pharmaceutical therapy, but it was much more increased when the wounds were covered by autologous skin or buccal fat pad grafts. Therefore, the author stated that fresh hAM grafts would not appear to be effective in a single layer over deep buccal defects [27].

Similarly, Khademi et al. evaluated the efficacy of hAM for wound healing after the surgical removal of oral and pharyngeal cancerous lesions in a prospective study which included 50 patients. A scoring index was used to assess pain relief, granulation tissue formation, and epithelialization. Authors observed that hAM adhered well to the wound in all cases. On clinical follow-up, a good epithelialization, a satisfactory pain relief, and an adequate granulation tissue formation with surface epithelialization were observed in all patients. Authors concluded that hAM was very effective in 40 patients and effective in 10 patients [32].

Kar et al. grafted hAM to repair post-surgical mucosal defects after precancerous tumor resection in the oral cavity. This prospective study included 34 patients. Several scoring criteria involving clinical parameters were used to assess the efficacy of hAM. Three months after surgery, all patients showed good epithelialization. Six months after surgery, oral opening was good in 24 patients and fair in 10 patients and 28 patients reported normal sensation, and six still had altered sensation. Their results suggested that hAM promoted healing and epithelialization without specific complications [33].

Arai et al. assessed the usefulness and the effectiveness of hAM as a wound dressing material in the treatment of 10 patients who had developed secondary defects in the tongue and oral mucosa after the surgical removal of cancerous or precancerous lesions. hAM was evaluated by scoring clinical parameters. One month after surgery, epithelialization was good (entire wound healing) in three cases, fair (nearly entire wound healing) in six cases, and poor (inadequate wound healing) in one case. Scar contracture of the wounds was assessed 2 months after surgery and categorized as "good" in four cases (none or little) and "fair" (< 50%) in six cases. Besides, the membrane was found to be easy to handle as an oral-dressing material [34].

hAM seems able to act as a wound dressing material to cover mucosal defects after tumor resection. hAM induces rapid epithelialization and prevents mouth opening decrease due to scar contracture in case of superficial mucosal defects.

One study reported the use of autologous transplantation of oral mucosal epithelial cells cultured on hAM to cover intra-oral mucosal defects in five patients. After excision of benign and precancerous lesions, autologous oral mucosal epithelial cells cultured on hAM were grafted on the surgical wound. Clinical observation was performed. No adverse reaction was observed in the postoperative course, and an entire epithelialization was noted 1 month after surgery. The authors suggested that oral mucosal epithelial cells cultured on hAM could represent a useful biomaterial and feasible method for oral mucosal reconstruction [35].

Use of hAM to repair oronasal fistulae

One study evaluated the use of hAM to close oronasal fistulae in four patients. hAM was grafted after removing the epithelium covering the fistula margins. The follow-up was based on clinical observation. All patients showed complete closure of the fistulae [36]. Multilayer amniotic membrane is useful for oronasal fistula repair and has the advantage of preventing donor site morbidity.

Use of hAM for prosthodontic surgery

In four studies, a vestibuloplasty surgical procedure was carried out with hAM grafting. All patients underwent mandibular ridge vestibuloplasty using Clark's technique and amniotic membrane was applied as a graft material.

Güler et al. first introduced the use of hAM in mandibular vestibuloplasty in 1997. hAM was grafted and sutured to the exposed periosteum in 20 patients. Measurements of blood flow and clinical observation were obtained. They established that hAM had an angiogenic effect as monitored by a rapid increase of blood flow in the graft region. hAM had macroscopically disappeared by the 14th day, and an entire epithelialization was observed 3 weeks after surgery [37].

Another study assessed the clinical use of hAM as a graft for vestibuloplasty in seven patients. Clinical observation, measurement of buccal depth, and histological analysis were realized. Two weeks after surgery, histological analysis showed that hAM remained in only small areas. Samandari et al. observed a reduction of buccal depth that ranged from 17 to 40% after 6 months, and the graft area could not be differentiated from non-grafted tissue after 3 months [38].

Sharma et al. used the same surgical procedure in 10 patients. Clinical observation and measurement of buccal depth were noted. hAM had macroscopically disappeared by the third week. They observed a reduction of buccal depth ranged from 30 to 40% after 3 months leading to a gain of buccal depth ranged from 4 to 6 mm [39].

Kothari et al. used the same surgical procedure and evaluation methodology in 10 patients. Three months after surgery, they observed a relapse of buccal depth from 17 to 50% and one patient had a complete relapse. No adverse reaction was observed during the postoperative course [40].

Finally, they all concluded that hAM might be an appropriate graft material for vestibuloplasty.

Use of hAM for peri-implant surgery

Velez et al. assessed the usefulness of hAM for soft tissue management after dental implant surgery in a randomized study. Ten patients who received at least two bilateral implants were included. After implant placement, hAM was placed over the surgical wound in the experimental group before closure, whereas the other site was closed without hAM. Clinical measurement and pain assessment were noted. Even if no difference in the final outcome was found, epithelialization and pain relief occurred significantly sooner in the experimental group [26]. hAM seems to accelerate gingival healing around dental implants and to reduce pain.

Discussion

The aim of this comprehensive and thorough review was to report the clinical applications of hAM and to evaluate evidences for its use. This review revealed that hAM (i) has already been used to repair soft tissues and alveolar bone in the oral cavity, (ii) improves oral wound healing, and (iii) seems to exert an antalgic effect. However, it is difficult to draw conclusive evidence due to the wide heterogeneity concerning hAM preservation methods and use and the clinical indications. Therefore, some limits need to be underlined.

First, we observed a great heterogeneity concerning the conditioning methods of hAM. hAM is an abundant tissue, easy to obtain since it is usually discarded after parturition. In regenerative medicine, hAM was first used by Davis in 1910 as a graft on a leg skin ulcer. Then, interest in hAM decreased in the 1980s with the emergence of HIV and the risks of viral transmission. Since the 1990s, new methods of conditioning and preserving hAM have emerged, arousing a renewed interest in the use of this membrane in reconstructive surgery. These conditioning methods have reduced the risk of transmission (by exceeding the period of viral incubation) and made a large quantity of material immediately available [41]. However, among the 22 studies included, hAM was used fresh in only two studies. Otherwise, hAM was preserved in glycerol at 4 °C in two studies, cryopreserved in five studies, dried in seven studies, and lyophilized in four studies. In two studies, the preservation procedure was not mentioned. Cryopreservation preserves hAM at −80 °C for 6 months, which requires thawing before use. The other methods of preservation (dehydration, lyophilization, and preservation in glycerol) allow a longer conservation time of hAM. Indeed, the dehydrated or lyophilized hAMs are sterilized by γ-rays and can be maintained at room temperature several years. The methods of dehydration and freeze-drying also appear to induce limited changes in the biological properties of hAM [25, 34]. Glycerol-preservation of hAM is easy to implement, is cost-effective, and preserves also the morphological and biological properties (antibacterial and weak immunogenic properties) of the hAM [39, 42]. However, the wide variability of the preservation methods used in the 22 studies included makes the comparison of the results difficult.

Then, hAM was used as either a monolayer or a multilayer graft. Several studies established that monolayer hAM was easy to handle and easy to use. Besides, the stiffness and the thickness of hAM allow an easy adaptation to the surgical site, without shriveling and suturing [25, 29, 34, 43]. However, it must be specified that the physical properties of hAM do not afford any space maintenance capabilities. To overcome this disadvantage, several authors suggested using hAM multilayers. This has the advantage of increasing the stability of the graft [36], and to control the thickness of the membrane through the number of layers [20].

Moreover, as there were no or few randomized clinical trials were found in this field, we decided to include and analyze all clinical studies including case series using hAM in oral surgery. This allowed us to identify five areas of interest. Periodontal surgery, cleft palate surgery, tumor reconstruction surgery, prosthodontics, and peri-implant surgery were identified as clinical applications of hAM. Among the 17 clinical studies included, only four were randomized clinical trials and the great majority had poor clinical relevance (case series). Besides, objective measurements and statistical analysis were often missing for these clinical trials. Therefore, only preliminary conclusions can be drawn and there is an obvious need for further research comparing hAM to conventional treatments.

Several studies reported the ability of hAM to stimulate healing and, especially, to enhance epithelial regeneration of the buccal mucosa [13, 26]. It could be explained by the growth factors content of hAM, such as EGF and VEGF [7, 8]. Moreover, the basal membrane of hAM promotes the proliferation and differentiation of epithelial cells [38], and hAM can act as an anatomic barrier against fibrous tissue proliferation [44, 45]. In addition, hAM promotes early neovascularization of the surgical site [13, 45].

Another reported that the advantage of hAM was the anti-inflammatory effect of hAM and its potential to reduce adverse reaction after surgery. First of all, in the 17 clinical studies included, hAM was always used as an allograft and no immune rejection has been reported. This can be explained by the low antigenicity of hAM due to HLA-G cells expression. HLA-G is an antigen of the major histocompatibility complex class I, which, unlike the HLA-A, B, and C alleles, does not induce specific immune response, but it is thought to be involved in the induction of immune tolerance. Also, no infection or inflammatory reaction was observed postoperatively in selected studies. hAM has anti-inflammatory properties, secreting interleukin-1 receptor antagonist proteins [3, 24], as well as antibacterial properties [46, 47]. It has also been suggested that the physical properties of hAM could also explain the absence of infection or inflammatory reaction observed. Indeed, the hAM is easy to handle, which makes it possible to obtain a more intimate contact with the surgical site, especially on irregular wound surfaces, compared to autografts or xenografts [48]. Many authors observed that hAM is easy to adapt on surgical wounds and also did not require suturing because of its good adhesion properties to the receiving substrates [23, 28, 31, 32, 34, 49, 50]. Thus, with regard to the risk of postoperative infection, hAM may be a better option for reconstruction in oral surgery than the use of an autograft or a dermal membrane [33].

Few studies have examined the resorption of hAM. Some authors only described its disappearance macroscopically. Thus, when hAM was used as a graft in the vestibuloplasty, Güler et al. described a complete resorption of hAM on the 14th day because it was no longer macroscopically visible [37]. Sharma et al. macroscopically observed complete disappearance of hAM after 3 weeks [39]. These results corroborate those of Samandari et al., who observed a significant resorption of hAM after the second week of healing [38]. Moreover, its resorption does not interfere with tissue healing, in a particular bone, since it does not lead to the formation of foreign bodies or empty spaces [24].

In addition, one of the frequently reported advantages of hAM was its anti-fibrotic properties. hAM inhibits the expression of TGF-β (transforming growth factor ß), thereby inducing a decreased fibroblastic proliferation [4, 51]. Nevertheless, in a study where hAM was grafted on deep mucosal defects in patients with oral submucous fibrosis, the authors observed a fibrous retraction [27]. The use of fresh monolayer hAM seems unsuitable for deep mucosal defects. However, hAM was also used cryopreserved for mucosal healing after the resection of oral carcinomatous lesions. The authors observed less shrinkage secondary to local radiotherapy when the lesion was covered with hAM compared to conventional techniques for reconstructing the oral mucosa after cancer excision [32]. The ability of hAM to reduce the formation of fibrous scars was also observed by Tsuno et al. [52]. hAM could decrease the formation of scar tissue in growth-sensitive areas, which could be a great alternative in oral surgery, especially in the field of cleft palate surgery, where fibrous scar can interfere with the growth of the maxilla [36, 53]. However, only one study reported the use of hAM to treat an oronasal fistula of the hard palate, whereas several preclinical studies randomly assessed the efficacy of hAM as a wound dressing for cleft palate surgery. They concluded that hAM is a suitable dressing material for the treatment of cleft palate: closure occurred sooner in animals and it could decrease the formation of fibrous scars [36, 52, 53].

hAM has also been shown to reduce pain following its application in oral surgery [32, 33, 38–40, 43]. In their study, Velez et al. observed a lower number of patients reporting pain and patients were pain-free sooner with hAM compared to the control group [26]. These results corroborate to those of Munoyath et al., which compared the application of hAM to a collagen membrane in the management of facial skin trauma in maxillofacial surgery. Assessment of pain was significantly lower in patients who had received hAM [54].

Another interesting aspect would be to assess the potential of hAM to repair and/or regenerate both soft and hard oral tissues. Among the 17 clinical studies, a large majority reported the use of hAM for soft tissue repair and ligament regeneration. Indeed, hAM was used in periodontal surgery (gingival recession $n = 3$, periodontal furcation $n = 1$, periodontal pockets $n = 2$), cleft palate ($n = 1$), and mucosal tumor reconstruction ($n = 5$), prosthodontics ($n = 4$), and peri-implant surgery ($n = 1$). These results are supported by several case reports which report the interest of hAM to repair soft oral tissue [28, 29, 43, 49, 50, 55].

Studies performed on patients with periodontitis highlighted the potential of hAM to regenerate the ligament and to improve bone repair. However, we could not draw definitive conclusions because no histological analyses had been completed. Besides, it appears that hAM is rarely ever used alone to regenerate the bone. One possible approach to enhance bone repair properties of hAM could be to culture cells on hAM prior to its transplantation onto the surgical defect. hAM has been already used as a scaffold seeded with cells to improve bone repair in preclinical studies [15, 16, 18, 19, 21]. It was shown that cells seeded on hAM could enhance tissue regeneration because the cells were transplanted to the surgical defect along with their extracellular environment and without disruption of cell-to-cell contact [18]. Authors observed that, after stem cells transplantation, hAM still had adequate mechanical properties for surgical manipulation; this observation could provide the impetus for further clinical investigation. Moreover, one clinical trial already reported the use of cells seeded on hAM to repair oral mucosal defect [35]. It suggested that cultured oral mucosal epithelial cell sheets on hAM induced rapid epithelialization of oral mucosa. hAM could represent a useful scaffold for cell proliferation and differentiation, and a feasible method for oral mucosal reconstruction [35, 56]. However, the lack of controls and the small number of patients included were recognized limitation of these studies.

hAM could become an alternative to autograft or other substitute materials, which could reduce the morbidity of the donor site or decrease the cost of the substitute materials used. In four studies, hAM was compared to other membranes. hAM has been compared to collagen membranes currently used in oral surgery in one preclinical study [20] and one clinical study [25]. One preclinical study assessed the efficacy of hAM compared to a dermal substitute [53] and one study compared hAM to PRF [28]. Authors suggested that, hAM seemed to be at least as efficient as conventional membranes for these indications. However, the restricted number of studies does not allow to draw definitive conclusions, and further studies with higher level of evidence are needed to compare hAM to conventional membranes.

Conclusion

Some clinical studies suggest that hAM could be a useful membrane in the field of periodontology and oral surgery. However, randomized clinical trials are needed to confirm the efficacy of hAM in comparison with standard treatment strategies.

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Compliance with ethical standards

Conflict of interest The three authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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