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Surgical Bone Adhesives with Potential Maxillofacial Applications: A Systematic Review

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ABSTRACT

The reduction and stabilisation of fractured bone fragments have always been a challenging task for thesurgeon. A micro-platesystem for maxillofacial fracture treatment provides excellent results. However, plates and screws are difficult toadapt to the thin bone, and small fragments often lead to the weakening of bone causing secondary fractures. Surgical bone adhesives promise as a viable alternative for issues with micro-plates, but a lotremains desired for successful usefor clinical application. The present systematic review aims to identify the bone adhesive materials available at various stages in animal or human models in the last decade and enumerate their characteristics for potential use in non-load bearing maxillofacial fractures. PubMed electronic database searched using a combination of keywords to identify English language articles between January 2011 and December 2020 yielded a total of 1204 records, of which 15 were included for final review after applying PRISMA guidelines. Cyanoacrylate was the commonly used adhesive material followed by fibrin glue and calcium phosphate-based materials. Although encouraging, results with each material still lack human randomised control trials thus presenting inconclusive evidence. Studies on these lines are suggested along with the development of newer materials to overcome the shortcomings in the currently available systems.

Keywords: Bone adhesive; Bone cement; Fracture healing; Systematic review; Maxillofacial bone adhesive

1. INTRODUCTION

Surgical advancements in the field of soft and hard tissue wound healing have ensured minimum patient debilitation with quick post-operative recovery. In orthopedics, bone healing is most commonly undertaken by the use of the traction method and casts to approximate and immobilise the fractured fragments. In case sofexcessive loss of bone structure, external or internal pin fixations are used. However, maxillofacial fracture management varies in terms of the armamentarium used for the treatment of non-complicated fractures which utilizes various inter-maxillary fixation and wiring procedures.[1] In complex cases like those of occlusal disturbances and comminuted fragments, Open Reduction and Internal Fixation (ORIF) is required.

For open management of maxillofacial fractures, the micro plating system introduced by Luhr in 1988 has been widely accepted and is currently considered the gold standard for comparison.[2] Over time plate materials have evolved, from stainless steel toVitallium and eventually to titanium (Ti) and its alloys. Advantages of using Tialloy include biocompatibility, reduced risk of allergy, and high corrosion resistance with decreased imaging artefacts.[3] However, the plate systemis difficult to adapt especially in regions with small fragments. It also causes hindrance to growth with potential damage to developing tooth buds in children, while drilling of holes mayinduce stress in bone, causing micro trauma which further makes bone prone tofracture.[4] Additionally, apart from being expensive, the plating also puts the patient at the risk of the development of infection which requires a second surgical intervention for removal.[5]

To either replace the screws with surgical adhesives or omit the plate-screw system and replace it solely with bone adhesives, many attempts have been made to come up with an ideal material. The first bone adhesive was an acrylate, epoxy resins, and gelatin system that was developed in the 1940s. The material had low adhesion and biocompatibility properties with non-biodegradable nature thus warranting for development of enhanced materials[5]. To be clinically useful, an adhesive must have certain properties, of which bond strength during different phases of bone healing is considered to be of prime importance.[6,7] Some of the other desirable properties of a bone adhesive are listed in Table 1.

The present systematic review was conducted to identify developed bone adhesives that have been used

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either in animal models or humans for maxillofacial non-load bearing fracture healing.

2. METHODOLOGY

The current systematic review was conducted following the guidelines of the PRISMA statement. A thorough search of PubMed electronic database was conducted to find the work published between January 2011 to December 2020 using Boolean expressions, combination of MeSH terms and general terms, "Bone Cements"[Mesh], "Fracture Healing"[Mesh], "bone adhesive", "maxillofacial bone adhesive", "recently developed bone adhesives", "non-load bearing bone adhesives", "resorbable adhesive", "PMMA", "cyanoacrylate", "histoacryl", "chitosan", "dermabond", "fibrin glue", "polysaccharide-based bone adhesive", "clearfil", "calcium phosphate-based bone adhesive", "tetracalcium phosphate", and "bone adhesive".

Table 1. Ideal properties of a surgical bone adhesive

Properties of a Bone Adhesive	
Adhesive and Cohesive Properties	- Minimum bond strength of 0.2 MPa - Allow early weight-bearing - Adequate compressive and tensile strength - No late displacement
Biodegradability and Biocompatibility	- Begins resorption in a stipulated time without adverse reactions - By-products should be non-toxic - Non-toxic, non-carcinogenic - Minimum heat production during setting - Should allow bone regeneration
Clinical Manipulation and Properties	- Easy to handle - Sufficient working time - Sets in minimum time - Ability to set in presence of blood, moisture - Minimum shrinkage when set - Ability to deliver drugs locally
Miscellaneous Requirements	- Cost effective - Adequate shelf life - Sterilizable - Stable during storage

2.1 Inclusion Criteria

- Work published in the English language.
- Work published from January 2011 to December 2020.
- Case reports, case series, and randomised control trials.
- Studies were conducted either on animals or humans.

2.2 Exclusion Criteria

- Review papers.
- Studies conducted an only in-vitro analysis of developed adhesive
- Development and use of scaffolds or sponges for bone healing
- Letter to editor and conference proceedings
- Non-availability of the full text
- Use of adhesive for healing of chondral defects, dural defects, or soft tissue defects
- Use of adhesive with plating system for repair of bone defects
- The adhesive is used for reasons other than fracture repair such as vertebroplasty, spinal fusion, etc
- Use as bone cement for repair in weight-bearing regions such as radius, femur, and tibia and not true adhesive
- Studies were conducted on animal or human bones obtained from the previously dead organism
- Use of adhesive material as a bone defect filling material instead of adhering to 2 bone fragments

Rayyan literature managing software was used to decide the inclusion and exclusion of the articles. All the articles were individually reviewed by two authors (VJ and KM)to determine their inclusion or exclusion from the final analysis. In case of any discrepancy, the third author (RB) independently resolved the conflict. The final criteria were reviewed by AB before inclusion in the study.

3. RESULTS

A total of 1204 articles were found using the previously mentioned keywords. Of these, 17 duplicate entries were removed. 30 articles were further removed for being in a language other than English. Of the 1157 records, 1066 records were excluded in the initial screening based on an article title and abstract reading. Of the 91 articles, 26 were excluded for having an only in-vitro assessment, 24 were excluded because the adhesive was used in the weight-bearing region as cement, seven were excluded due to non-availability of full text, and two were excluded for being a letter to the editor and 17 were excluded for other reasons which were not in line with the set inclusion criteria. Thus, a total of 15 articles were included for the final review. The same is depicted via a PRISMA flow diagram in figure 1.

Of the total articles maximum number of articles (three) was published in 2014 while two each were published in 2012, 2018, and 2020. One article each was published in 2011, 2013, 2015, 2016, 2017, and 2019. The distribution of these articles based on the type of bone adhesive used is depicted in Figure 2 while the summary of the reviewed papers is presented in Tables 2 to 7.

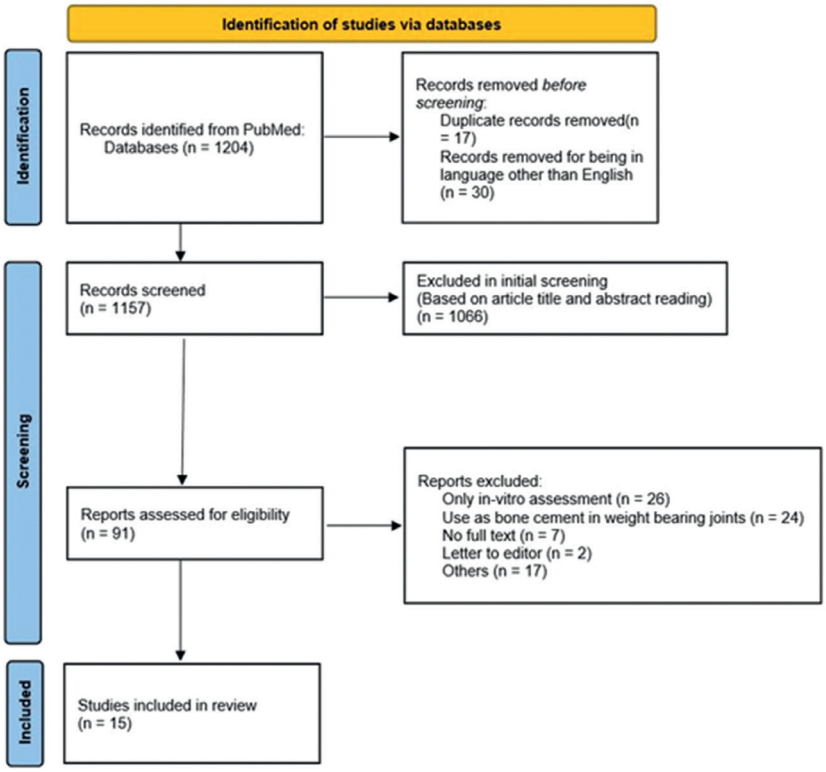

Figure 1. PRISMA flowchart for literature screening.

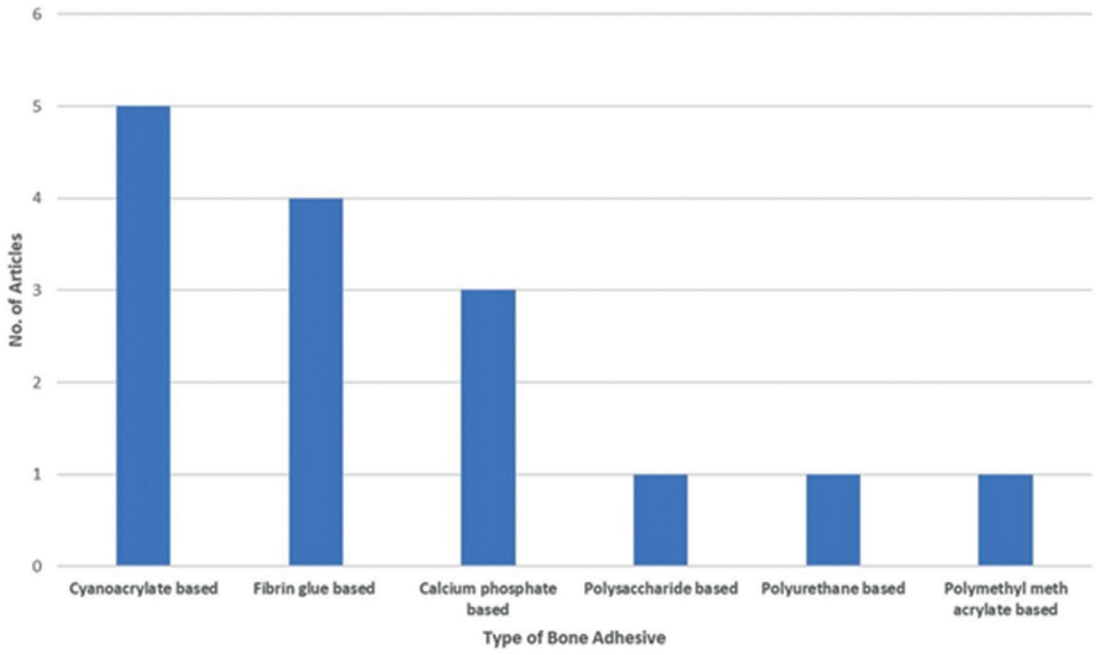

Figure 2. Literature distribution based on the type of bone adhesive used.

4. DISCUSSION

The use of adhesive material for adhering to fractured bone fragments is a desirable alternative to the use of wires, plates, and screws in cases requiring open reduction. Focusing specifically on the reduction of maxillofacial fractures, using an adhesive material minimizes the risk of developing micro stresses incurred during the drilling of screws. It also enables a more friendly approximation of tiny bone fragments which is often difficult with the conventional means. For an adhesive to be clinically helpful and be adapted in practice, it needs to have certain properties which have been listed before (Table 1). Among all these, material injectability is a desirable characteristic that has still not become a universal part

of the currently available systems.Having an injectable adhesive material allows the conduction of minimally invasive surgeries, enabling the defect to be filled in a retrograde manner with minimum entrapment of air. Also, the pressure generated during filling ensures a good fill and tight initial contact with defect walls. In the current review, it was noticed that the studies done in the recent past have made multiple attempts towards the development of injectable material with some positive results.

4.1 Cyanoacrylates (CA) Based Adhesives

Dentin bonding agents (DBA) used in dentistry are CA-based agents which have been adapted and extensively used as a surgical bone adhesive. Under room temperature conditions, CA can rapidly transform from liquid to solid without the additional need of a catalyst or physical initiating agent, thus making them user-friendly. Dentin and bone have similar inorganic composition, primarily consisting of hydroxyapatite (HA), collagen, and water, thereby, successfully enabling the use of DBA on bone, with an initial bond strength of 3–10 MPa and the ability to set under moist conditions. Histoacryl®, Dermabond®, and Clearfil™ New Bond are some of the commercially available and popularly used CA systems that have been widely tested in animals and progressed to clinics for use in humans including repair of maxillofacial structures[8]. CA is available in different forms of which the three most commonly used are ethyl-2-CA (ECA), N-butyl-2-CA (NBCA), and octyl-2-CA (OCA). Observations of the reviewed studies are summarised in Table 2.

Using the material in rabbits, Xavier *et al.*[9] reported the presence of blue marks with the use of color impregnated adhesive in all cases treated using the same. Although no clinical or radiographic abnormal findings were

Table 2. Findings of reviewed literature using cyanoacrylate-based adhesive

Legend: CT: Computed Tomography, **Ti:** Titanium

Author (Year)	Model used	Assessments done	Important findings/ observations reported
Xavier, *et al.* (2014)[9]	New Zealand White Rabbit	• Clinical • Radiological	No variation in operated site appearance in control and experimental groups. Presence of blue marks in sites fixed with adhesive material. No significant variation in graft displacement after 2 weeks in the 2 groups. No graft integration in most subjects after 2 and 4 weeks in both the groups with the superior bone union in the experimental group compared to control after 8 weeks. The incomplete metabolisation of adhesive after 16 weeks.
Esteves, *et al.* (2014)[10]	Wistar Rat	• Histological • Optical microscopy	The incomplete bony union between graft and recipient site with the presence of dense connective tissue at margins after 60 days. An insignificant amount of volumetric loss of graft from day 0 to day 60 in all groups.
Salata, *et al*[11] (2014)	New Zealand White Rabbit	• Micro-CT • Molecular analysis	With adhesive: Mineralised tissue at centre = 50.6% ± 8.3% Mineralised tissue in periphery = 50.3% ± 10.6% • With Ti screws: Mineralised tissue at centre = 32.5% ±3.5% Mineralised tissue in periphery = 33.8% ± 6% • Higher values of trabecular thickness with adhesive (0.29 ± 0.01mm) compared to that seen with Ti screws (0.09 ± 0.01mm) (p-value <0.05). • Higher values of degree of anisotopy in the central region with adhesive (2.4 ± 0.15) compared to that seen with Ti screws (2.55 ± 0.02mm) (p-value <0.05). • Higher values of fractural dimension for Ti screws (2.24 ± 0.04) compared to adhesive (2.55 ± 0.02) (p-value <0.05). • Upregulated osteoclastogenesis-related genes were seen with adhesive use in the initial 4 days.
Nemoto, *et. al* (2015)[8]	Humans (31 patients)	• Clinical	No post-operative disturbances in visual acuity. The collapse of reconstructed bone into the maxillary sinus in 1 patient.
Xu, *et. al*[12] (2020)	Adhesive development + Animal trial (Mouse)	• In-vitro property assessment • Histologic	The two-fold increased amount of calcium content in bioactive modified adhesive compared to non-additive adhesive (0.084 ± 0.008 compared to 0.046 ± 0.004). Tough bonding of various surfaces with adhesive material.

reported with the use of adhesive in comparison to the control treatment, there was incomplete metabolisation of the former reported even after a time of 16 weeks. In another animal study done by Esteves *et al.*[10] in Wistar rats, incomplete bony union in the periphery was reported with an insignificant volumetric loss after 60 days, yet again backing the material used. One of the most comprehensive studies among the reviewed literature was conducted by Salata *et al.*[11] who compared the efficacy of CA adhesive in adhering bone graft with that of the Ti screws. Higher mineralised bone densities in the central, as well as periphery of the used material, were seen with adhesive than with the conventional method. Also, the formed thickness of the trabecular bone was more in experimental sites than in control with higher expression of osteoclastogenesis-related genes. They concluded that the use of Ti screws causes more damage to the applied bone thus supporting the use of adhesives.

Undertaking orbital reconstruction in 31 out of 48 patients, Nemo to *et al.*[8] used ethyl 2-cyanoacrylate (ECA) and reported satisfactory outcomes in 30 patients. They concluded confident use of CA-based adhesive for orbital floor reconstruction.

The use of CA adhesive modified by the addition of bioactive glass was found in one of the reviewed papers which showed favorable results for the new composition[12.] Though the publication reported the materials to use in an animal model, the evidence presented lacked reporting of clinical, radiological, and biomechanical findings thus providing inadequate evidence aimed for in this review paper.

4.2 Polymethyl Methacrylate (PMMA)- based Adhesive

Also known as bone cement, PMMA is a self-curing polymer, that was first time clinically used in orthopedic surgery by Dr. John Charnley for implant placement in a total hip replacement surgery.[13] Primarily used for bone implant cementation its plasticity also allows it to be contoured and be used as a bone filler.[5] To enhancethe adhesive properties, different techniques have been employed by researchers such aspre-treating the bone using an intermediate bonding agent or chemically modifying PMMA by incorporating substances like magnesium[14], HA and chitosan powder[15], nano-sised titania[13], akermanite[16], alkoxysilane, calcium salts[17], cyclodextrin[18], etc. To counter the risk of infection associated with the material used, PMMA has been impregnated with antibacterial agents like tobramycin, gentamicin, vancomycin, and metallic silver particles in varied concentrations without affecting the material's functional properties.[18,19]

According to the criteria of the current review, only a single study was found to be eligible for inclusion which modified PMMA with strontium bioactive glass (SrBG) and subjected the material to in-vitro and in-vivo testing. In the in-vitro testing, they found the setting time and flexural modulus to increase with increasing SrBG content while compressive and flexure strength decreased. In-vivo assessment done in rat model presented no soft tissue formation on histologic evaluation with successful bone formation evident on micro CT[20].

Eliminating the use of screws, in-vivo trials in animals and humans have been conducted where in the plates were placed at the fracture site with adhesive[3,21]. These studies showed satisfactory bond strength for small defects with a range of 1.9-4.1MPa. However, elaborating more on the topic is beyond the scope of this review.

Despite the advantages presented by the material;its clinical use is restricted due to reported shortcomings.The polymerisation reaction of the material generates high temperatures ranging from 70ºC to 100ºC, imposing an injury risk to the tissues.[17,22] The material is also reported to have injectable properties however, these are short-lived[22]. Although nota true adhesive, it has superior bonding properties to cancellous bone compared to the cortical counterpart[6,7]. Thus its effective use requires adequate removal of sclerosed bone to expose the underlying spongious structure which is not a convenient option when midfacial bones are concerned.[3] Some cases of late displacement and non-union with the adhesive usehave also been reported thus raising questions about its regular use[7].

4.3 Calcium Phosphate Cement (CPC)- based Adhesive

CPC is a bioactive and biodegradable material prepared by mixing calcium phosphate powder inan aqueous solution

Table 3. Findings of reviewed literature using polymethyl methacrylate based adhesive

Legend: SD Rat: Sprague-Dawley Rat, **CT:** Computed Tomography, **SrBG:** Strontium bioactive glass, **PMMA:** Polymethyl methacrylate, **ALP:** Alkaline Phosphate

Author (Year)	Model used	Assessments done	Important findings/ observations reported
Cui *et al*(2017)[20]	Fabrication + In-vitro assessment + Animal trial (SD Rat)	In-vitro assessments - Handling properties - Bioactivity - Cell culture - Cytotoxicity In-vivo assessments - Histological - Micro CT	- Setting time increased with increasing content of SrBG. - Compressive and flexure strength decreased with increasing SrBG with the opposite trend seen for flexural modulus. - SrBG PMMA showed higher ALP activity than lone PMMA. - No intervening soft tissue formation on histologic evaluation. - Successful bone formation was seen in micro CT evaluation.

that hardens by precipitation reaction. First reported in 1986 by Brown and Chow[23], the cement is an effective bone void filler that can be adapted to irregular bone surfaces and cavities and have osteoconductive action due to HA formation.[24] In comparison to its counterpart in form of PMMA which is one of the oldest materials, a faster implant-bone contact has been reported with the use of CPC paste although with slower resorption rate[25,26.] Some researchers have also reported opposite results thus requiring further investigation of the material.[27] With wide clinical applications and studies conducted, mixed bags of results have been reported leaving the clinician to decide upon the desired material depending on the requirement.

The current analysed literature found only one published literature that utilised CPC adhesive by the set criteria. In this study, the effects of atmospheric carbon dioxide (CO_2) on the properties of tetra calcium and dicalcium phosphate (TTCP and DCPD) mixture were assessed where in Cahyan to *et al.* reported the formation of low-crystalline apatite under all the tested CO_2 variations.[28] For the three tested CO_2 concentrations, average porosity of 60 per cent was seen with all mixes with non-significant variation in diametral strength. Conducting the in-vivo experiments in a rat model, bone formation was evident on micro-computed tomography (μ-CT) evaluation after 6 months with a significant decrease in residual bone cement content.

The CPC has also been modified by the addition of antibiotic agents to prevent local infection and improve clinical outcomes. In the reviewed literature, only a single study was found which undertook the same in an animal model. The authors found the vancomycin-loaded CPC paste to be an effective agent in controlling the locally induced bacterial infection in the craniotomy cuts.[29] Although CPC with antibiotics has been shown to reduce the material's compressive strength, the use of this combination was advocated in the cranium due to the non-requirement of heavy stresses in the region, thus making the material use a success.

To enhance the injectability and other mechanical properties of CPC adhesives, a range of chemical modifications have been tried some of which include the addition of sucrose fatty acid esters, sugar surfactants, alkylpolyglucosides, magnesium phosphate cement, orthophosphoric acid, sodium alginate, carboxy methyl cellulose, agar polymer, etc.[23,30–32] This has resulted in an up to 36 per cent increase in tensile bond strength with a maximum of 700kPa.[31] A combination of CPC and Fibrin Glue (FG) has also showed enhanced strength although with delayed setting thus making it an area of interest for further exploration.[33,34]

Of all the materials, the most promising so far has been the addition of phosphoserine (PPS) which showed a decrease in setting time with improvement of handling and mechanical properties.[23] This combination is currently commercially available as tetranite™ and awaits food and drug administration (FDA) approval[5.]In-vitro studies have reported the adhesive to have tensile and shear strength of up to 3MPa[35] with results comparable to that of conventional bone repair methods.[36]

The reviewed literature in the current paper had only a single article that used tetranite™ and met the

Table 4. Findings of reviewed literature using calcium phosphate-based adhesive

Legend: SD Rat: Sprague-Dawley Rat, **CT:** Computed Tomography, **CPC:** Calcium Phosphate, **TTCP:** Tetracalcium Phosphate

Author (Year)	Model used	Assessments done	Important findings/ observations reported
Sakamoto, *et al* (2014)[29]	SD Rats	• Clinical • Histological • Bacterial count	-No infection in CPC + vancomycin combination. - Reduced neutrophil count in CPC + vancomycin combination. - Fibrous tissue formation in paste periphery. - Significant reduction in bacterial colonies (p-value <0.05) in vancomycin loaded CPC used.
Cahyanto, *et al* (2018)[28]	Fabrication + Animal trial (Rat)	• Clinical • Micro CT • Histological	- Average diametral strength of 6MPa. - As atmospheric CO_2increased, the amount of unreacted TTCP decreased. - No surgical site infection was seen in any case. - No healing was seen after 1 month on micro-CT evaluation however, completely healed sites were evident on re-evaluation done after 6 months. - Significant decrease in residual cement after 6 months when compared with day 0 and 1 months findings.
Kirillovo, *et al*[3] (2018)	In-vitro assessment + Animal trial (Rabbit)	In-vitro assessments • Bioactivity • SEM In-vivo assessments • Histological	- No clinical adverse effect was seen in an animal model. - Histologic evidence of bone-adhesive contact after 8 weeks. - Rough periphery in the region of tetranite™after 26 weeks with considerable degradation of adhesive material after 52 weeks.

set inclusion criteria. In this assessment by Kirillova *et al.*[35], a biomechanical and animal trial evaluating the properties of the said bone adhesive was undertaken. The material was found to have the ability to harden within 10 minutes in both, dry and aqueous conditions with the requirement of considerable force to pull the joined pieces. Assessing the findings from the animal study, considerable resorption of the material was observed after 26 weeks with almost negligible presence seen after 52 weeks. From weeks 8 to 52 a degradation of 77.5 per cent was reported thus strongly advocating the use of the material for clinical applications.

4.4 Fibrin Glue (FG)-based Bone Adhesive

Autologous FG, also known as fibrin sealant or fibrin gel, or fibrin tissue adhesive, was introduced by Tayapongsak, *et al.*[37] in 1994. It's a dual-component glue consisting of fibrinogen (which contains platelet growth factors), and thrombin which when mixed form a fibrin gel. Factor XIII, a component of fibrinogen is a necessary stabilizer, playing a vital role in the in-vivo adhesion.[7,37]The highest tensile strength has been reported to be achieved within 3 minutes from the commencement of the process. Being an autologous derivative, its use prevents suspected foreign body reactions. A simpler glue preparation has also been proposed by Thorn *et al.*[37]with the procedure being carried out entirely in a blood bank setup.

The FG has a wide range of surgical applications with creditable advantagesdue to 12 times the fibrinogen and 8 times growth factor concentration than that found in platelet-rich plasma (PRP).[38,39] The reviewed literature found only 4 studies to be eligible which indicates still more popular use of the adhesive material compared to the others.

Hao, *et al.*[40] modified the FG by seeding it with bone marrow-derived stem cells (BMMSCs). This formulation was then tested in Lewis rats and simultaneously compared with pin fixation and atrophic non-union cases. They reported good radiographic results for atrophic non-union cases while periosteal bridge formation was seen in the experimental group. The highest torsional stiffness of 1.32±0.25N/mm was seen in the experimental group thus supporting the use of BMMSCs seeded FG.Undertaking a similar attempt, McDuffee, *et al.*[41] incorporated the FG with autologous osteoprogenitor cells derived from the tibial periosteum in an equine animal model. They found a statistically non-significant variation in the healing evident by osteoprogenitor cell enhanced FG and plain FG wherein the effect of time on radiographic grayscale was significant (p-value <0.001). FG has also shown satisfactory results for the repair of traumatic incudostapedial joint and orbital floor reconstruction as evident in the reviewed literature.[42,43]

Additionally, FG has found several applications with resorbable meshes for orbital floor reconstruction however, discussing the same does not meet the set criteria of the current review paper.[44] Platelet gel (PG) is a modification of FG where fibrinogen is replaced by platelet concentrate from a patient's plasma.[39] It was introduced in maxillofacial surgery by Whitman *et al*[45] in conjugation with ablative surgical procedure and the described technique to improve its handling is being currently worked upon to develop more on its properties and clinical uses.[27]

As a double-edged sword, FG presents certain drawbacks which discourage its regular use. It has limited adhesive strength which is acceptable only if tensile and shearing loads are relatively low. Additional use of screws and pins is required in cases requiring greater forces to be exerted on grafts.[45] Late displacement and weak bond strength have been reported with a slight risk of hepatitis due to the use of concentrated blood products.[7]

Table 5. Findings of Reviewed Literature using Fibrin Glue-Based Adhesive

Legend:CT: Computed Tomography, **ABG:**Airborne Gap

Author (Year)	Model used	Assessments done	Important findings/ observations reported
Nikolaidis (2011)[42]	Human (1 patient)	• Clinical	Complete ABG closure (ABG ≤10dB HL). Overclosure in frequencies: 2 and 4 kHz.
McDuffee *et al* (2012)[41]	Equine	• Clinical • Radiographic • Histological	Minor dehiscence in 4 cases. No abnormal clinical findings in other cases. No abnormal radiographic findings. A variable amount of fibrous tissue and bone in the osteotomy gap.
Chen *et al* (2014)[43]	In-vitro assessment + Human trial	• Clinical • CT evaluation	No postoperative clinical complications like diplopia or enophthalmos were observed.
Hao *et al* (2016)[40]	Lewis Rat	• Radiographic • Histologic • Biomechanical	The atrophic non-union group showed limited callus after 2 weeks with visible osteotomy gap after weeks 4 and 8. Continuous periosteal callus formation in the experimental group after 8 weeks with plenty of woven bone formation. Torsional stiffness of 2.64 ± 0.43, 0.21 ± 0.24, and1.32 ± 0.25 Nmm/^{0} respectively for control, non-union and experimental groups.

4.5 Polyurethane (PU) Based Adhesive

PU is a synthetically derived material shown to have good biocompatibility properties. The vast possibility of changing its physical and chemical structure makes PU a versatile material being adapted to the latest technologies.[46] In form of foams and scaffolds, the material has been widely used in the field of dentistry and is still constantly being searched upon.[47] It has also shown a relatively higher tensile strength compared to other bone cement thus, making it an acceptable choice as adhesive.[5] Despite the numerous favorable characteristics, the current review found only single academic writing that used PU adhesive material in line with the set criteria.

Lei *et al.*[48] attempted the development of desirable composition of a new PU-based bone adhesive by varying the water and beta-tricalcium phosphate content. With increasing water content, they reported a decrease in density, compressive strength, and modulus while increased porosity and water sorption were seen. Taking the developed material a step ahead, an animal trial in the rabbit model showed satisfactory healing of the induced osteotomy as observed in μ-CT recordings.

4.6 Polysaccharide-based Bone Adhesive

Chitin, chitosan, chondroitin, dextran, and starch are some important plant and animal-based polysaccharides thathave been utilised as tissue adhesive and hemostatic agents. Their biodegradable and biocompatibleproperties along with theease of application have progressed to be pursued for use as bone adhesive.[49] Like many other bone adhesive materials, only one article using polysaccharide material found its way into the final review. In the included study, Liu *et al*[50] elaborated on the fabrication, in-vitro and in-vivo assessment of the developed adhesive, showing promising results. They reported a compressive strength of 2.1-33.8MPa and modulus of 17.4-233.1MPa with successful bone formation seen on μCT evaluation.

5. MATERIALS OF INTEREST

Mussel, oysters, and limpet are a few marine animals that produce adhesive protein to anchor themselves to underwater substrates.[51] However,these agentspossess high allergic properties which precludedtheir in-vivo application.[17,52] Currently, research is underway to modify these materials and utilise their adhesive properties discussing which is beyond the current scope.

It was evident in the process of conduction of the current systematic review that most of the work related to bone cement and adhesives undertaken so far has been subjected to application in weight-bearing regions in animals with even fewer highlighting its application in humans. In contrast to the reviewed literature wherein, CA-based material was most commonly used, PMMA-based adhesives and cement have been more commonly utilised in the weight-bearing areas.[53–58] Modification of PMMA has been extensively researched by incorporating substances like polyethylene glycol hydrogel, CPC, magnesium, carboxymethylcellulose, alginate, gelatin microparticles, platelet gel, zirconium dioxide, and gentamicin to enhance their properties like handling, porosity, injectability, biodegradability, and antibacterial action.[53,55] Of the 24 excluded articles, only 2 reported human clinical application, both of them using PMMA adhesive for the purpose.[53,57] CPC-based adhesives were the next

Table 6. Findings of Reviewed Literature using Polyurethane-Based Adhesive

Legend: CT: Computed Tomography, **SEM:** Scanning Electron Microscopy

Author (Year)	Model used	Assessments done	Important findings/ observations reported
Lei *et al*[35] (2018)	Fabrication + In-vitro assessment + Animal trial (Rabbit)	In-vitro assessments • Biomechanical • Bioactivity • SEM In-vivo assessments • Micro CT	- Compressive strength: 2.1 to 33.8MPa - Modulus: 17.4 to 233.1 MPa - Increased porosity and water uptake and decreased density with increasing water content during adhesive formulation. - A satisfactory animal trial results in successful bone healing.

Table 7. Findings of Reviewed Literature using Polysaccharide-Based Adhesive

Legend: CT: Computed Tomography, **SEM:** Scanning Electron Microscopy

Author (Year)	Model used	Assessments done	Important findings/ observations reported
Liu *et al*[50] (2020)	Fabrication + In-vitro assessment + Animal trial (Mouse)	In-vitro assessments • Biomechanical • Bioactivity • SEM In-vivo assessments • Micro CT	- Compressive strength: 2.1 to 33.8MPa - Modulus: 17.4 to 233.1 MPa - Increased porosity and water uptake and decreased density with increasing water content during adhesive formulation. - A satisfactory animal trial results in successful bone healing.

commonly used and too demonstrated chemical additions to achieve improved characteristics and bonding strength.[59,60]

All these studies strongly supported the use of these materials inweight-bearing regions however, elaborating more about the same does not fall under the scope of the current work. A separate literature review for bone cement may give more insight into the mentioned subject.

6. CONCLUSION

Available literature for in-vivo use of bone adhesive materials shows a lack of holistic material with all the desired properties. However, cyanoacrylate has shown some promising results and thus has been the most used material with polyurethane and polysaccharide showing a promising clinical future. The materials tested for weight-bearing regions find limited literature support in the reconstruction of the maxillofacial region. Despite the promising results shown through animal experiments, only a few materials have translated to clinical practice with a lack of Randomised Control Trials (RCTs). The authors believe that RCTs with stress on the reconstruction of maxillofacial bone structure will establish the usage of available materials. Further research into newer materials with desirable properties is inevitable to overcome the challenges of conventional systems.

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