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Role of Polylactic Acid in Bone Regeneration –A Systematic Review

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Abstract:

Bone regeneration is a complex, physiological process of bone formation, which can be seen during normal fracture healing, and is involved in continuous remodeling throughout adult life. However, there are complex clinical conditions in which bone regeneration is required in large quantity, such as for skeletal reconstruction of large bone defects created by trauma, infection, tumor resection and skeletal abnormalities. The use of bone grafts is the standard to treat skeletal fractures, or to replace and regenerate lost bone. The most commonly used is auto graft, its use can lead to complications such as pain, infection, scarring, blood loss, and donor-site morbidity. An ideal bone graft or scaffold should be made of biomaterials that imitate the structure and properties of natural bone. However, creating living tissue constructs that are structurally, functionally and mechanically comparable to the natural bone has been a challenge so far. An electronic search was conducted for articles in PubMed database to screen for articles from 1966 to sept 2014 discussing the role of polylactic acid in bone regeneration using selected keywords. Critical appraisal was done for selected articles, Search yields a total of 383 articles of which 318 full text article were obtained, 30 articles were selected after reading the abstract out of which 10 met the inclusion criteria and 308 were excluded and hand search was done with the reference of the selected articles. The article selected used polylactic acid for bone regeneration. The present Systematic review indicates, when polylactic acid is modified with osteoinductive material such as beta tricalcium phosphate and hydroxyl appetite crystals shows better acceptance than plain polylactic acid.

Keywords: Polylactic acid, Polylactic acid scaffold, 3d printed polylactic acid Osseo conduction, bone regeneration, bone repair, bone remodeling, Osseo induction

INTRODUCTION:

Bone, as a living tissue has the ability to heal by itself, however if the defect exceeds the critical size it will not heal spontaneously. [1] So helping measures are required for completion of healing process of such defect where various bone grafts and bone substitutes have been tried by several clinicians to healing of those large defects. A bone graft is defined as an implanted material that promotes bone healing alone or in combination with other material(s) [2]. The selection of an ideal bone graft relies on several factors such as tissue viability, defect size, graft size, shape and volume, biomechanical characteristics, graft handling, cost, ethical issues, biological characteristics, and associated complications [3]

The materials used in bone grafting can be divided into several major categories, including auto grafts, allografts, and xenografts. Synthetic and biologically based, tissue-engineered biomaterials and combinations of these substitutes are other options. Autogenous bone are gold standard for bone regenerative material for several reasons including biocompatibility, no adverse reaction and they enclose osteoblasts that participate in new bone formation. There are limitations to obtaining autogenous grafts, however such as donor site morbidity and limited donor site. [4]

One of the most recent developments in the defect is application of barrier membranes to occlude skeletal defects against invasion of soft tissue and thus allow osseous regeneration to fill the space underneath the membrane. This technique is termed as guided tissue regeneration or guided bone regeneration. [5]

This systematic review was attempted to analyze existing literature on polylactic acid and their role on osseous regeneration of fractured bone and induced defects in both human and animal models.

MATERIAL AND METHODS:

SOURCES USED:

An electronic search was conducted for articles in PubMed database to screen for articles from 1966 to sept 2014 discussing the role of polylactic acid in bone regeneration selected keywords and additionally hand searching was done.

SEARCH TERMS USED IN PUBMED:

(Maxilla) OR Mandible) AND (Polylactic acid) OR Polylactic acid scaffolds) OR PLA) OR PLA scaffolds) OR Poly-L-lactide) OR Poly-L-lactide scaffolds) OR PLLA) OR PLLA Scaffolds) OR Polylactide) OR Polylactide scaffolds) OR 3d printed polylactic acid) OR 3d printed PLA) OR 3d printed poly-L-lactide) OR 3d printed PLLA) OR 3d printed Polylactide)) OR Polylactic acid screws) OR Polylactic acid powder) OR Polylactic acid fibers) OR Polylactic acid plates) OR 3d printed polylactic acid) OR 3d printed polylactic acid scaffold)))) AND (Osseo conduction [Mesh Terms]) OR Bone regeneration [Mesh Terms]) OR Bone formation) OR Bone growth) OR Bone repair) OR Osseo induction) OR Bone remodeling) OR Hematoxin eosin staining) OR Micro radiograph) OR Histophotometry) OR SEM)

SELECTION OF STUDIES:

Titles and abstracts of the search were initially screened for relevant articles and hand search of selected journals and in the reference selected articles were also done. And articles were further screened using inclusion and exclusion criteria.

Inclusion criteria:

Studies that fulfilled the following criteria were included in the study.

1. Studies on polylactic acid
2. Studies on different types of polylactic acid used
3. Studies on Osteogenesis
4. Studies on both humans and animals
5. Studies with follow up of minimum up to 4 weeks duration

Exclusion Criteria:

1. Studies on surface treated polylactic acid
2. Studies on scaffolds other than polylactic acid
3. Studies on regeneration other than bone.
4. Articles in other languages
5. Review article

Results of the electronic search:

The systematic search revealed total of 383articles of which 318 full text article were obtained. 30 articles were selected after reading the abstract out of which 10 met the inclusion criteria and 308 were excluded. The article selected used polylactic acid for bone regeneration. Finally, selected articles were subjected to data extraction. The search flow chart is as shown in Fig.1.

RESULT:

Table: 1 General Characterization of the Included Animal Studies

Table: 2 Characterization of Included Human Studies

Table: 3 Polylactic Acid Used as a Scaffold or Graft Material

Table: 4 Polylactic Acid Used as Plates and Screws.

FLOW CHART FOR SEARCH STRATERGY

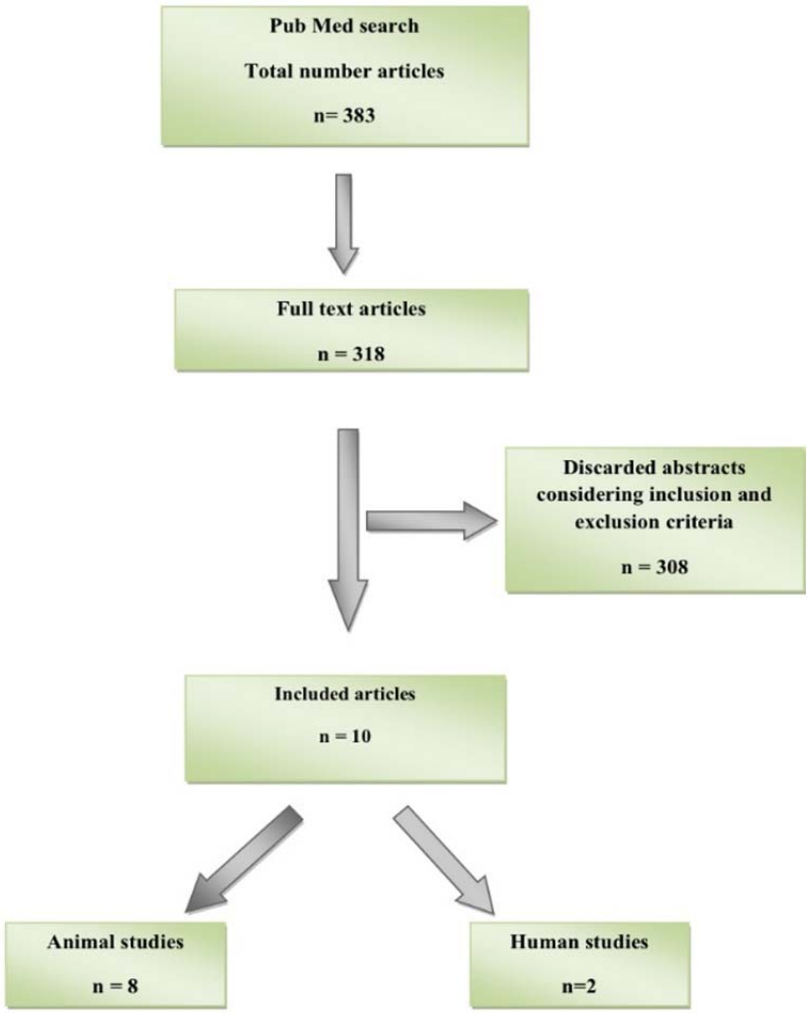

TABLE 1: General Characterization of the Included Animal Studies

S.No	AUTHOR	STUDY DESIGN	MATERIALS AND METHODS	TYPE OF STUDY MODEL	INVESTIGATIONS	LIMITATIONS	CONCLUSION
01	Henning Schliephak 1998	Animal study	**Group 1** –In 5 animals 2 cm mandibular defect were created on both sides of mandible and bridged by Polylactic acid (PLA) tube. **Group 2** – In 5 other animals' defects 4 cm in length were created bilaterally Polylactic acid (PLA) and human basic fibroblast growth factor is used. **Group 3** – In 5 other animal's bilateral 2 cm defect was created and left empty on one side and bridged with empty PLA tube on other side.	Fifteen Gottingen minipigs	1.Histological evaluation 2.Radiological findings	Data were presented showing a decrease in the MW of the polylactic acid during the experimental period. In vivo study model needs for the evidence.	Repair of segmental defects using bio resorbable membrane appears to be possible. Mandibular segmental defect by GBR using PLA tubes appears to be unsuccessful. Scaffold for conduction of bone regeneration seems to enhance the bone fill in defect area.
02	Sergio L. da Silva Pereira 2000	Animal study	Buccal osseous dehiscence was surgically created on distal roots of mandibular third and fourth premolar and defect were exposed to plaque accumulation for 3 months. **Group 1** – GTR with bioobsorbable membrane(PLA) **Group 2** – GTR with non-resorbable membrane(ePTFE) **Group 3** – Control group	Six Mongrel dogs	1.Histometric measurements 2.Histologic observation 3.Clinical observation	Small sample size	Favorable osseous response observed in bioobsorbable membrane (PLA) when compared to non-reabsorb able membrane. It is concluded that the bioobsorbable membrane (PLA) tested is an option for GTR procedure.
03	Leticia Algarves Miranda 2006	Pilot study	18 class II furcation defects were surgically produced in mandibular and maxillary premolars and exposed to plaque accumulation for 21 days. The teeth were randomly distributed in 3 groups. **Group 1** – GIC barrier **Group 2** – Polylactic acid absorbable barrier **Group 3** – CTR with no barrier placement.	Three Beagles dogs	1.H&E staining 2.Histometric assessment	Small sample size for the purpose of pilot study	GIC & GUI Group prevented epithelial migration and promoted the formation of periodontal tissue in experimentally induced class II furcation defects in dogs.
04	Harri Pihlajamaki 2006	Animal study	A hole, 3.2 mm in diameter, was drilled centrally through the intercondylar portion of the distal femur in a proximal direction toward the intramedullary cavity of the bone. Group 1 – 10 PLLA screw was inserted. Group 2 – 16 metallic screw was inserted in rabbit femora and remaining 32 knees were left intact to serve as controlled.	32 New Zealand rabbits of both sexes with mean weight of 3.6 Kgs	1.Plain Radiograph 2.Histological sections 3.Microradiography 4.Histomorphometry	More studies should be performed In vivo study model needs for the evidence	Macrophage activity might be associated with formation of the connective tissue at the tissue-implant interfaces of the PLLA screws replacing the original implant. No significant differences between the bioobsorbable PLLA and the metallic screws in biocompatibility could be established, and no signs of inflammatory foreign-body reactions occurred. Presence of bone regeneration in both the group
05	Giuseppe Polimeni 2007	Animal study	Animals were divided into three groups. **Group 1** – 15 animals receiving PLA device. **Group 2** – 5 animals sham surgery **Group 3** – 1 animal control. Animals were sacrificed at 3, 5, 7 and 12 months post-surgery to provide histopathological observation. Control animal was sacrificed at 3 months.	Twenty-one young adult male Sprague-Dawley rats were used.	1.Histological examination	–	The result suggest that the PLA device may induce bone resorbing foreign body reactions. Importantly, the PLA device does not resorb within a 12-month healing interval. These biomaterials properties may influence new bone formation and maintenance when applying the device for GBR/GTR. +

06	Yasuji Harada 2013	Animal study	1 mm drill hole was created in the patellar and tibial tuberosity was made and PLLA fibers were then tied to the distal end of the quadriceps femoris muscle and tibial tuberosity. Twelve helical PLLA fibers and 12 non helical PLLA fibers control were implanted in the right knee joint and sacrificed at 2 and 4 weeks	Twelve Fischer rats	1.Histological examination	Degradation rate of implanted PLLA was not mentioned	Formation of osseous tissue around helical PLLA fibers was more significant than around non-helical control fibers at 4 weeks after their implementation. These results suggest that helical PLLA fiber may be useful for the surgical suture or artificial ligament, which connects the bone.
07	Hanako Nishimoto 2012	Animal study	Medial collateral ligament defect was surgically created in the knee joint and then reconstructed using stent shape PLLA scaffolds. Rabbits were sacrificed at 3 time points.4, 8 and 16 weeks post operatively.	23 Japanese white rabbits	1.Histological analysis 2.Immunohistological analysis	A detailed analysis of the regenerated tissues origin was not performed. Observation of PLLA fibers degradation is not measured.	Stent shaped PLLA scaffolds are allowed for MCL regeneration with type I collagen expression and fibrocartilage formation and resulted in sufficient mechanical function. This provides novel insight for new technologies to aid in regeneration of ligament tissues.
08	Guillermo E.Chacon	Animal study	Animals were divided into 3 groups Bilateral tibial onlay graft were placed in mandible GROUP 1=Titanium fixation GROUP 2 = Bioresorbable fixation GROUP 3 = Control	15 New Zealand Rabbits	1.H&EStaining	Small sample size only microscopic examination is done	Bioabsorbable implants will be a good alternative to titanium for graft fixation

TABLE: 2 Characterization of Included Human Studies

S.No	AUTHOR	STUDY DESIGN	MATERIALS AND METHODS	INVESTIGATIONS	LIMITATIONS	CONCLUSION
01	Leonhart	Human Study	60 patient were divided into two groups GROUP 1 = PLA (INION) GROUP 2 = Titanium	1. Clinical examination 2.Pre and post radiograph	-	PLA plate are biocompatible and strong enough to treat mandibular fractures
02	Takahio Suzuki	Human study	14 patient Male = 12 Female =2 of mean age 23 yrs. condylar fractures treated with PLLA implants	1.Radiological findings	Small sample size and comparison with other material is not done	PLLA system provide stability for fixation of condylar process

Table- 3
Polylactic Acid Used As a Scaffold or Graft Material

S.NO	AUTHOR	SAMPLE	STATISTICAL ANALYSIS	RESULT
1.	Hanako Nishimoto 2012	23 Japanese white rabbits with Medial collateral ligament defect were surgically created in the knee joint and then reconstructed using stent shape PLLA scaffolds. Rabbits were sacrificed at 3 time points.4, 8 and 16 weeks post operatively.	Mann-Whitney and ANOVAwere used to compare within the groups	Stent shaped PLLA scaffolds are allowed for MCL regeneration with type I collagen expression and fibrocartilage formation and resulted in sufficient mechanical function. This provides novel insight for new technologies to aid in regeneration of ligament tissues
2.	Yasuji Harada 2013	Twelve Fischer rats with 1 mm drill hole was created in the patellar and tibial tuberosity was made and PLLA fibers were then tied to the distal end of the quadriceps femoris muscle and tibial tuberosity. Twelve helical PLLA fibers and 12 non helical PLLA fibers control were implanted in the right knee joint and sacrificed at 2 and 4 weeks	Student's t- test	Formation of osseous tissue around helical PLLA fibers was more significant than around non-helical control fibers at 4 weeks after their implantation which connects to the bone

TABLE: 4 Polylactic Acid Used As Plates and Screws.

S.No	AUTHOR	SAMPLE	METHODS	RESULT
01	Guillermo E.Chacon	15 New Zealand Rabbits	Rabbits were divided into 3 groups Bilateral tibial onlay graft were placed in mandible **GROUP** 1=Titanium fixation **GROUP 2** = Bioresorbable fixation **GROUP 3** = Control	Bioabsorbable implants will be a good alternative to titanium for graft fixation
02	Harri Pihlajamaki 2006	32 New Zealand rabbits of both sexes with mean weight of 3.6 Kgs	**Group 1** – 10 PLLA screw was inserted. **Group 2** – 16 metallic screw was inserted in rabbit femora and remaining 32 knees were left intact to serve as controlled	Macrophage activity might be associated with formation of the connective tissue at the tissue-implant interfaces of the PLLA screws replacing the original implant.
03	Leonhart	60 patient	60 patient were divided into two groups GROUP 1 = PLA (INION) GROUP 2 = Titanium	PLA plate are biocompatible and strong enough to treat mandibular fractures
04	Takahio Suzuki	14 patient	Patient of mean age 23 yrs. condylar fractures treated with PLLA implants	PLLA system provide stability for fixation of condylar process

DISCUSSION:

Literature search performed in PubMed reveled insufficient cohesive database or studies with similar parameters. Although polylactic acid material was used in various studies they were either used as polylactic acid in tube forms, scaffolds, or fibers, screws and as plates they have been compared with surface modified polylactic acid. Because of the insufficient cohesive database of the study, meta-analysis were not performed.

The literature search indicated towards the increase in use of polylactic acid material as a synthetic graft and in screws and plate forms. And also a viable option as an alternative to other graft materials. The interactive factors which play a role in osseous regeneration are discussed below.

1. BONE REGENERATION USING POLYLACTIC ACID

Animal study conducted Using polylactic acid tubes on one side of the mandible and empty defect on other side, another group treated with polylactic acid combined with recombinant human basic fibroblast growth factor (rhbFGF) there were no bone regeneration seen with polylactic acid tube. Group combined with growth factor showed adequate bone regeneration. Author suggested that use of beta tricalcium phosphatase scaffold along with polylactic acid will have an advantage in bone regeneration Sergio. L.da & silva Pereira studied with GTR using polylactic acid and non-resorbable membrane (polytetrafluoroethylene) it shows that polylactic acid has increase in bone area width compared with non-resorbable membrane. Bone formation is confirmed using histological analysis and histometric analysis. [2]

Yasuji HARADA studied using helical and non-helical (PLLA) fibers using piezoelectric charge under tensile stress. The relationship between tensile forces applied to PLLA fibers which in turn generates piezoelectricity was accessed and same piezoelectric stimulus was correlated to osteogenic stimulation. Significantly there was higher ossification was observed around helical PLLA Fibers [6]

Letica algavarves Miranda studied using an experimental barrier of resin-modified GIC in one group and polylactic acid barrier in another group. It shows that both GIC barrier and polylactic acid barrier showed epithelial migration and promotes formation of new periodontal tissues, GIC group is more effective than polylactic group in terms of regeneration.

If the scaffolds using for bone regeneration is porous in nature, there will be faster degradation of the scaffolds. Bone regeneration were evaluated using (micro CT). [9]

2. DEGRADATION OF POLYLACTIC ACID:

When polylactic acid is used as the synthetic scaffolding material, it is important to measure the degradation of the polymer. Only 2 studies measured the degradation of PLA in animals, shows that polylactic acid has slow degrading property that starts only after 4 weeks of duration and the complete degradation will be taken place only after 12 months. [3, 5]

3. HISTOLOGICAL FINDINGS:

Many studies reported that PLA membrane was surrounded by external surface of bone and connective tissues. [2] Leticia alga rives and harri studied that defect was completely filled with connective tissues and varying amount of bone and epithelial proliferation at 8 weeks shows bone regeneration. [3] Giuseppe study shows PLA was surrounded by fibrous capsule and multinucleated giant cell, some macrophages and lymphocytes confirms there were evidence of new bone formation. [5]. Presence of numerous spindle shaped mesenchymal cells were observed in PLA fiber in 2 weeks. PLA fiber surface was attached to trabecular bone where osteoblast lines of ossification were observed on the bone around the fiber. [6]

Polylactic acid was covered with smooth connective tissue at 4 weeks post operatively, presence of spindle shaped cells associated with Type I and type III collagen is seen in 4, 8 and 16 weeks. [7]

Use of pla in humans

Many studies has been used polylactic acid in humans in plate and screw forms for fracture fixation and in socket preservation. PLA has given promising results in union of fractured bone in humans. [10]

Limitations:

In the reviewed articles, limitations of the studies were no specific form or peculiar type of polylactic acid material was repeatedly tried, still more detailed analysis of polylactic acid is required. The review of the selected articles suggests that polylactic acid scaffold can be used for osseous regeneration of fractured bone. More intensive investigations are necessary to identify the factors that influence the efficiency of osseous regeneration.

CONCLUSION:

Repair of segmental defect using the bio absorbable membrane (PLA) appears to be a promising alternative for synthetic graft which can replace the entire lost bone or can be used as the scaffolding material for GTR / GBR and in fractured bone. The present review indicates, when polylactic acid is modified with osteoinductive material such as beta tricalcium phosphate and hydroxyl appetite crystals shows better acceptance in animal model than plain polylactic acid

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