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RESEARCH ARTICLE

THE EFFECTIVENESS OF STEM CELLS GRAFTING ON REGENERATION OF DENTAL PULP: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Great advances in tissue engineering open a new biological path to regenerate the damaged pulpal tissue**.** The new approach of stem cell transplantation to regeneration of tissues had been used in many medical fields with promising results including dental therapy. Aim of this istoreviewthe efficacy of stem cell grafting in regeneration of dental pulp from available animal and human studies for a systematic and meta-analysisreview.

Methodology: AComprehensive electronic search with time and language restrictions was conducted. Several known databases were included Ex: "PubMed, The Cochrane Library, Web of Science" from 2000 to 2020.We combined the search terms and limited the study to the English language. Depending on PRISMA checklist, we removed duplicates, articles were screened based on title, abstract, and full text. The search resulted in 325 hits which after removing duplicates, exclusion studies the number of studies became 10.

Results: In this review, The total samples used in this review was 40 samples from which 13 human patients had been included (mean age of 26.8 years old), 12 dogs, 3 mice and 12 inbred male miniature pigs using 94 teeth and molar. Moreover, all the used stem cells for dentine regeneration were adult mesenchymal stem cells however, the source of harvesting these stem cell differs between studies including adipose tissue and pulp CD31-SP, DPSCS, PDLSCs, *Gdf11* gene,bone morphogenetic protein-2 (BMP-2),MDPSCs and SCAP. Furthermore, all types showed promising results however, some types gave better results over other including superior of adipose tissue CD31 SP over bone marrow CD31 SP and pulp stem progenitor (CD 105) cells over adipose CD105 cell.

Conclusion: It was observed that stem cell grafting shows promising results in the regeneration of dental pulp in both animal and human studies with no side effect or toxicity. Therefore, we recommend widening the application of these techniques in human trials because of its safety and efficacy. Choice of carriers or type of stem cells up to our review should depend on the expenses, as there are no significant differences between them in both safety of efficacy profiles.

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Introduction:-

The significant role of human teeth in his nutrition and physiology of mouth in grinding food cannot be replaceable [Nakashima, M. et al , 2011]. Dental tissues are composed of complex structure that characterized by both hardness and durability. Still, this structure can be affected by trauma and microbial infections [Kabir, R. et al, 2014]. Microbial infections as caries is common where bacterial damage the dentin of the teeth making dental pulp exposed [Nakashima, M. et al , 2004]. Dental pulp tissue plays a significant role in homeostasis of teeth therefore the maintenance of the function of this tissue is vital in maintenance of the teeth it selves and quality of life [Murakami, M. et al, 2015]. Therefore, after any external damage of dental tissue, regeneration of tooth may delay the loss of the whole tooth however, it is happen only of the damage is in reparable condition [Kabir, R. et al, 2014]. The goal of operative dentistry and endodontology is regeneration of the damaged dentin and dental pulp [Nakashima, M. et al , 2011]. Conventionally, deep caries and pulp exposure is treated with some endodontic treatment as pulp capping or pulp amputation to repair the damage however, success of these treatments is limited [Huang GT. et al ,2010]. However, these conventional endodontic treatment focuses on the three-dimensional mechanism of preparation, disinfection and obturation of the root cancel space with no steps for regeneration of pulpal tissues [Fawzy El-Sayed. et al,2015]. Recently, great advance in tissue engineering open a new biologically path to regenerate the damaged pulpal tissue [Rosa, V. et al,2013]. The new approach of stem cell transplantation in order to regeneration of tissues had been used in many medical fields with promising results including in treatment of cardiovascular disease and periodontal regeneration [Psaltis, P.J. et al 2008, Monsarrat, P. et al 2014]. In general, this new approach is depending on modulating of local microenvironment in order to be more inductive for endogenous cells [Ilic, D. et al,2012, Shin, L. et al,2013] and favor the biosynthesis of extracellular matrix components for start of the regeneration of tissue [Hynes, K. et al,2012].

The term of stem cell was first used in 1909 by Russian histologist called Alexander Maksimov suggesting the presence of hematopoietic cell that has the morphological appearance of lymphocytes and has the ability to migrate into blood to different tissue and then proliferate and differentiate [Ramalho-Santos M.et al,2007]. From this time and the science of tissue engineering had been developed. In this science they require three key element; stem cell itself, matric and growth factors called morphogens [Malhotra N. et al.2012]. Stem cells have the ability to renew themselves through cell division for long time under certain conditions and some conditions induce their infiltration and become cells with special functions [Jesse K. et al ,2014]. Tissue engineering using stem cells had been used in treatment of many conditions including liver disease, diabetes and regenerate of dental pulp.

At present, we can isolate the mesenchymal stem cell populations which have the higher proliferative capacity and differentiation from dental issues [Hao J. et al,2009] including DPSCs or Dental Pulp Stem Cells, SHEDs or Stem cells from Human Exfoliated Deciduous teeth, SCAPs or Stem Cells from Apical Papilla and DFPCs or Dental Follicle Progenitor Stem Cells. To regenerate dental pulp, mesenchymal stem/progenitor cells are transplanted into treated tooths canals and cells would proliferate to renew the dental pulp. Until now, most of studies that conducted to assess efficacy of stem cells grafting in order to regenerate dental pulp was done in animal experiments because of the remaining doubts about its safety besides ethical constraints. To move on and start to see outcomes of such intervention from animals' models to human clinical trials, a critical and systematic appraise of design and the results of this intervention in animal studies should be conducted to determine the gaps in their validity and assess the efficacy and safety in these studies. Therefore, the goal of this systematic review is to critical review the efficacy of stem cell grafting in regenerating of dental pulp from available animal and human studies.

Materials and Methods:-

This review was reported in the light of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Search methods for identification of studies

A complete electronic search with time and language restrictions was conducted. Several known databases would be included Ex: “Google Scholar, PubMed, The Cochrane Library, Web of Science” from 2000 to 2020.

Eligibility criteria and study selection

Inclusion criteria

1. Participants: Human, animal and invitro studies would be included
2. Interventions: Stem cells grafting in order to regenerate dental pulp

3. Randomized controlled clinical trials were to be included.
4. Published in English.
5. Published in a year between 2000 to 2020

Exclusion criteria

1. Trials involving other applications of stem cells grafting for other conditions than dental pulp regeneration
2. Unsupported opinion of expert.
3. Replies to the author/editor.
4. Books'/conferences' abstracts.
5. Published in any language other than English
6. Published papers before 2000.

Data Analysis

In Several known database which would be searched Ex: Google Scholar, PubMed, The Cochrane Library, Web of Science. We would combine the search terms and limited the study to the English language. Depending on PRISMA checklist we would remove duplicates, articles were screened based on title, abstract, and full text. Then collected data would be analyzed using a forest plot design.

Results:-

Study selection

The electronic search strategy conducted in this review ended in 325 hits which after removing of duplicated reduced to 112 studies. These 112 studies were considered eligible for further evaluation, from which 102 studies were excluded for different reasons as 52 studies on the basis of title and abstract, 33 studies do not relevant to the subject of this study, 11 consider replies of authors, 1 book, 2 systematic review and 3 were reviews. At end, 10 articles were included in the qualitative synthesis of the present review (Figure 1).

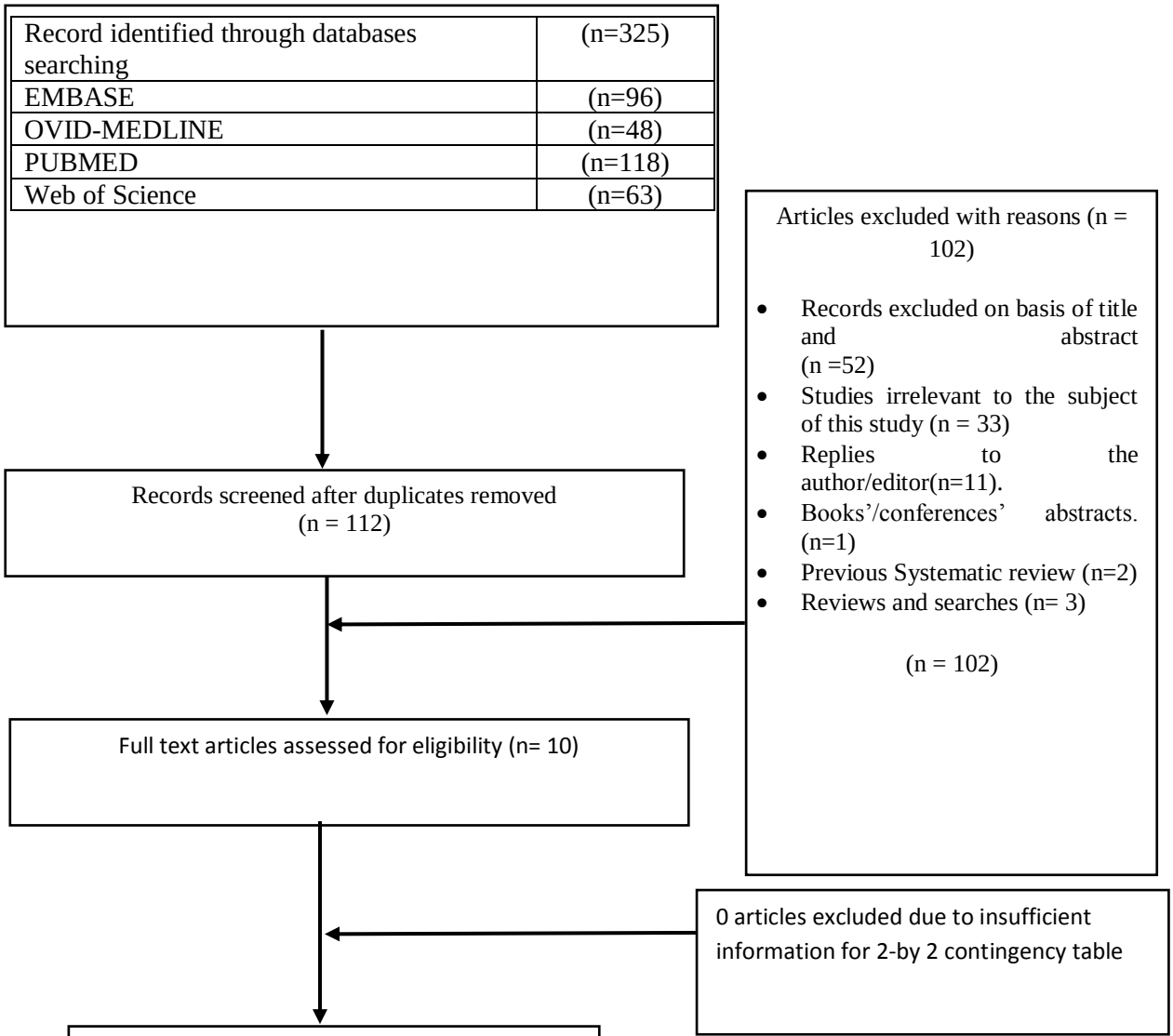


Figure 1:- The PRISMA figures showing the steps to choose the studies for systematic review.

General Results

In table 1, we explore the general characteristics for the ten studies chosen for this review. Among these studies, four studies had been conducted in Japan (Nakashima, M. et al , 2011, Nakashima, M. et al , 2004, Fawzy El-Sayed. et al,2015, Monsarrat, P. et al 2014) while three studies had been conducted in China (Kabir, R. et al, 2014, Murakami, M. et al, 2015, Psaltis, P.J. et al 2008) and three had been conducted in USA (Huang GT. et al ,2010, Rosa, V. et al,2013, Ilic, D. et al,2012). All had been published as journal papers and/or dissertations in English between 2000 and 2020. Moreover, seven studies had been conducted as in-vivo design (Nakashima, M. et al , 2011, Kabir, R. et al, 2014, Fawzy El-Sayed. et al,2015, Rosa, V. et al,2013, Psaltis, P.J. et al 2008, Monsarrat, P. et al 2014, Ilic, D. et al,2012) for which two studies had been conducted as human trials (Kabir, R. et al, 2014, Fawzy El-Sayed. et al,2015) and five studies had been conducted in animal trials (Nakashima, M. et al , 2011, Rosa, V. et al,2013, Psaltis, P.J. et al 2008, Monsarrat, P. et al 2014, Ilic, D. et al,2012), while three studies had been conducted in vitro depending on two animal sample (Nakashima, M. et al , 2004, Murakami, M. et al, 2015) and one depending on human sample (Huang GT. et al ,2010). In this review, each study depended on different technique of stem cells in regeneration of dental pulp. Moreover, however, the different of aims, all studies had been conducted in order to examine the efficacy of implantation of stem cells in regeneration of dental pulp except one study which had been conducted to determine the efficacy of using stem cells of damage own cells (Ilic, D. et al,2012) and another to evaluate the safety of this technique (Fawzy El-Sayed. et al,2015). Table 1, showed the different characteristics of each study.

No	Authors	Setting	Techniques	Vitro/ Vivo (Animal/ human)	Aims of study
1	**Ryo Ishizaka et. al. 2011**	Japan	Regeneration of dental pulp following pulpectomy by fractionated stem/progenitor cells	Vivo (Animal)	Comparing the efficacy of canine SP cell subfractions derived from pulp, bone marrow and adipose tissues of the same individual for pulp regeneration.
2	**Ming Lei et. al. 2014**	China	vivo transplantation of Mesenchymal stem cell	Vivo (Human)	To characterize cells attained from in vivo- (re-DPCs) and (re-PDLCs) as a result of ectopic transplantation of human DPSC and PDLSC sheets
3	**MISAKO NAKASHIMAet.al 2004**	Japan	*Ex Vivo* Gene Therapy Using Dental Pulp Stem Cells Electro transfected with *Growth/differentiation factor 11*	Ex Vivo (Using animal sample)	Designing an substitute method using transplantation of *Gdf11*-electrotransduced pulp cells into the exposed dental pulp tissue which might allow rapid and effective induction of reparative dentin,
4	**Y. Zheng et. al 2012**	China	Dentin Regeneration Using Deciduous Pulp Stem/Progenitor Cells	Ex Vivo (Using animal sample)	Investigation of stem/progenitor cell-based tissue engineering for dentin regeneration in a large animal model.
5	**Wei Wang et, al 2016**	USA	Injectablenanofibrous microspheres and stimulated by controlled BMP-2 release	Ex vivo (Using human sample)	To investigate the effects of PLLA nanofibrous microspheres (NF-MS) as a cell delivery carrier in combination with controlled release of BMP-2 from

					PLGA microspheres on the induction of odontogenic differentiation of human stem cells of apical papilla (SCAP).
6	**Misako Nakashima ET.AL 2017**	Japan	transplantation of dental pulp stem cells in pulpitis	Vivo (Human)	to assess the safety, potential efficacy, and feasibility of autologous transplantation of MDPSCs in pulpectomized teeth.
7	**George T.-J. et. al. 2010**	USA	Deposited Continuous Layer of Dentin	Vivo (Animal)	to regenerate lost dental pulp and dentin via stem progenitor cell–based approaches and tissue engineering technologies
8	**Sijia Na 2019**	China	Three-dimensional and scaffold-free stem-cell sheet-derived pellet	Vivo (Animal)	To design a three-dimensional (3D) and scaffold-free stem-cell sheet-derived pellet (CSDP) with the necessary physical and biological properties.
9	**KoichiroIohara 2011**	Japan	Transplantation of CD105+ Stem Cells with Stromal Cell-Derived Factor-1	Vivo (Animal)	regeneration of pulp using new techniques
10	**Dominick J Alongi 2010**	USA	Usage of inflamed human dental pulp	Vivo (Animal)	To determine whether DPSCs can be identified and isolated from IPs; and if they can be successfully cultured, whether they retain tissue regeneration potential *in viv*o
re- DPCs: regenerated dental pulp-like tissues, re-PDLCs: periodontal ligament (PDL)-like tissues, DPSC: dental pulp stem cells, PDLSC: PDL stem cells, Gdf11*: Growth/differentiation factor 11,* PLLA; Poly(L-lactic acid),					
Table 1:-The different characteristics of each study.					

Results of individual studies and synthesis of result:

In Table3, we showed the characteristics of the different experiments applied in these studies. The total samples used in this review was 40 samples from which 13 human patients had been included (mean age of 26.8 years old), 12 dogs, 3 mice and 12 inbred male miniature pigs using 94 teeth and molar.The mean time before harvesting was 53 days (Confidence interval of 95 % was 41.97 and 64.032).

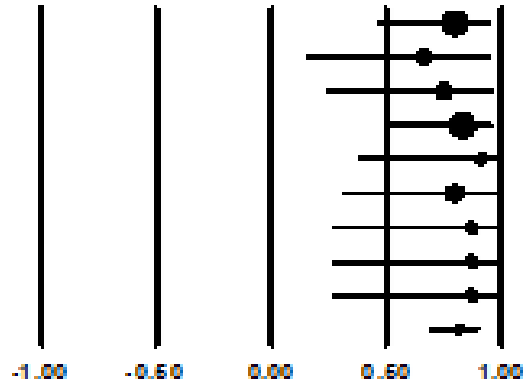
In the first study, they compared the use of adipose tissue CD31-SP cell as a source of stem cells instead of ordinary pulp derived cells. They found that adipose CD31-SP cell grafting would yield the same amount of regenerated tissues as pulp derived cells do besides that former cells would increase rate of matric formation over other tissue CD31-SP used. Moreover, when they use bone marrow cells with the same procedures, the cell yielded significantly less regenerative tissue than bother other cells. The new generated pulp had the same mRNA expression of normal dentin pulp and was similar in the three tissue CD31-SP (Nakashima, M. et al , 2011). The use of re-isolated cell from vivo generated dental pulp-like and PDL-like tissues would lead to differentiation to chondrocytes as the normal generated DPSCs do. Moreover, re -DPCs and re-PDLCs had the same adipogenic capabilities as normal teeth. This give an evidence that DPSCS and PDLSCs are both highly potent cell population that have the ability to differentiate to dentin pulp and can be used in regeneration of dental pulp (Kabir, R. et al, 2014).The efficacy of using of PDLSCs had been investigated again, in which the PDPSCs had been combined with scaffolds finding that after grafting into damaged teeth, the PDPSCs had been engrafted to some extent at the treated site and contributed with host endogenous cells and success to regenerate a dentin-like structures and nearly restored the pulp chamber

roof defects. The proper dose of PDLSCs was 2 ×107 PDLSCs combined with scaffolds in order to regenerate the dentin pulp in bone defects of 3 mm width, 7 mm length and 5 mm depth (Murakami, M. et al, 2015).The use of three-dimensional pellet culture of *Gdf11* geneand implantation of it in amputated tooth to promote the differentiation of odontoblasts showed promising results of viability of more than 85 % and efficiency about 70 %. Moreover, the expression of markers that indicate odontoblast differentiation as alkaline phosphatase and dentin *sialo-phosphoprotein* was steadily elevated when we use three-dimensional pellet culture of pulp derived progenitor/stem cells (Nakashima, M. et al , 2004). Another technique including the use of nanofibrous microspheres (NF-MS)which is the nanofibrous architecture in a porous scaffold mimicking collagen fiber, as a cell delivery carrier in combination with controlled release ofbone morphogenetic protein-2 (BMP-2)showed promising results as it promoted odontogenic differentiation of human SCAP and formation of dentin like tissue in both vitro and vivo studies (Huang GT. et al ,2010). Human MDPSCs (mobilized dental pulp stem cells) with granulocyte colony-stimulation factors (G-CSF) was found to have good safety and efficacy profile in regeneration of pulp/dentin as no toxicity or adverse effects had been detected and MRI showed that regenerated tissue after 24 weeks was similar to that of normal dental pulp (Fawzy El-Sayed. et al,2015). Using a stem-progenitor cell–mediated tissue generated from human DPSCs and SCAP and carried on PLG scaffold disk produced a dentin-like structure in damaged teeth in vitro. Moreover, odontoblast-like cells had been found by detecting dentin sialo phosphoprotein, bone sialoprotein, alkaline phosphatase, and CD105. The cells in regenerated pulp-like tissue reacted positively to anti-human mitochondria antibodies, indicating their human (Rosa, V. et al,2013). Moreover, the usage of pulp stem progenitor (CD 105) cells with the use of stromal cell derived factors 1 yielded successfully regenerated pulp including nerves and vasculature after 14 day of grafting in empty root canal with results better than these of use of adipose CD105 cell with the same activators (Rosa, V. et al,2013). Moreover, it is found that stem/progenitor cells can be successfully isolated from inflamed pulps which showed containing higher levels of mesenchymal stem cell markers compared to normal pulps and can be used successfully in regeneration of dentin pulp (Ilic, D. et al,2012).Furthermore, CSDPs (scaffold-free stem-cell sheet-derived pellet) is another carrier which can be used to carry the SCAPs besides three-dimensional pellets to regenerate the dentinal pulp. The CSDPS in vitro showed increased production of alkaline phosphatase and dentine sialoprotein than cell sheets (CSs) indicating that CSDPS have greater potential odontogenic and osteogenic. In vivo, the root space in which CSDPs had been applied showed complete dental pulp-like with well-stablished vascularity indicating that SCAP-CSDPs had strong capacity to form a heterotopic dental dentine complex in empty root canals (Psaltis, P.J. et al 2008).

Metanalysis Results

In this review, we use system of comprehensive meta-analysis version 3 to calculate the total rate of success in grafting of different type of stem cells on regeneration of dental pulp. We found that the rate of success of grafting of different type of stem cells on regeneration of dental pulp was 81.9 % (Confidence interval of 95 % was 0.686 and 0.904). Figure 2; shows the event rate and 95 % CI of each study and total scores.

Study name	Event rate	Lower limit	Upper limit	Z-value	p-value	Event rate and 95 % CI
Ryo Ishizaka et. al. 2011	0.800	0.459	0.950	1.754	0.080	
Ming Lei et. al. 2014	0.667	0.154	0.957	0.565	0.571	
MISAKO NAKASHIMA et.al 2004	0.750	0.238	0.966	0.951	0.341	
Y. Zheng et. al 2012	0.833	0.523	0.958	2.078	0.038	
Wei Wang et, al 2016	0.917	0.378	0.995	1.623	0.105	
Misako Nakashima ET.AL 2017	0.800	0.309	0.973	1.240	0.205	
George T.-J. et. al. 2010	0.875	0.266	0.933	1.287	0.198	
Sijia Na 2019	0.875	0.266	0.933	1.28	0.19	



				7	8	
KoichiroIohara 2011	0.875	0.266	0.933	1.287	0.198	
Total	0.819	0.686	0.904	4.065	0.000	
Figure 2:- the event rate and 95 % CI of each study and total scores.						

Discussion:-

In this review, we assessed the efficacy of stem cells grafting on regenerate dental pulp in animal and human population. Therefore, we conducted a systematic review of found studies published between 2000 and 2020 in English ending in 10 studies. The studies include in -vivo and invitro studies that depended on animal and human samples. Moreover, different techniques had been applied through these studies as we had found that many types of cells and carriers had been applied in in vivo and vitro studies to assess their efficacy finding that all of these materials had the ability to regenerate dental pulp in animal and human sample with no reported side effect in human based studies.

Results	**1.** Adipose tissue CD31_ SP cell transplantation yielded the same amount of regenerated tissue as pulp derived cells. However, bone marrow CD31_ SP cell transplantation yielded significantly less regenerated tissue in pulpectomized root canals in dogs. **2.** The rate of matrix formation was much higher in adipose CD31_ SP cell transplantation compared to pulp CD31_	**1.** Quantitative analysis showed no significant difference between the adipogenic capabilities of re-isolated cells and their original stem cells before transplantation ($P > 0.05$) **2.** the results indicated that re-DPCs and re-PDLCs could differentiate into chondrocytes, similar to DPSCs and PDLSCs	The viability after electrotransfection was more than 85%, and the efficiency was about 70%	the PDPSCsmixedwith β-TCP significantly regenerated thedentin-like structures and nearly completelyrestored the pulp chamber roof defects	The results demonstrated that BMP-2 enhanced human SCAP odontogenic differentiation both in monolayer culture and on 3D NF-MS in spinner flask culture in vitro

	SP cell transplantation on day 28. Microarray **3.** Microarray analysis demonstrated similar qualitative and quantitative patterns of mRNA expression characteristic of pulp in the regenerated tissues from all three cell sources.				
Technique used in analysis	two-dimensional electrophoretic analyses	flow cytometric analysis	**flow cytometry**	CT imaging histomorphometric techniques	measuring alkaline phosphatase activity
Time of harvesting before results	after 14 days and 28 days, respectively	Two months	**10 days of culture**	16 weeks	After 4 weeks
Number of implanted cells	5 _ 105 cell	2 _ 103 cells		5×105 PDPSCs	
Activator/ carrier	SDF-1		***growth/differentiation factor 11***	beta-tricalcium phosphate (β-TCP) scaffold	PLLA nanofibrous microspheres (NF-MS)
The used tissue	pulp, bone marrow and adipose CD31_ SP cells with SDF-1	generated dental pulp-like and PDL-like tissues (termed re-DPCs and re-PDLCs,	**pulp cells electrotransfected**	Porcine deciduous pulp stem/progenitor cells (PDPSCs)	human stem cells of apical papilla (SCAP)
Sample	10 Dog (30 teeth)	3 human (3 molar) (22-28 years old)	**dog**	Twelve inbred male miniature pigs(56 premolars)	5 patients (5molar)
Authors	**Ryo Ishizaka et. al. 2011**	**Ming Lei et. al. 2014**	**MISAKO NAKASHIMAet.al 2004**	**Y. Zheng et. al 2012**	**Wei Wang et, al 2016**

Results	**1.** The clinical and laboratory	the root canal space was filled entirely by a pulp-like tissue with well-	The root space with CSDPs was filled	he root canal was successfully filled with	Flow cytometry analysis showed that DPSCs from both NPs and IPs	

	evaluations demonstrated no adverse events or toxicity. **2.** The signal intensity of magnetic resonance imaging (MRI) of the regenerated tissue in the root canal after 24 weeks was similar to that of normal dental pulp in the untreated control cone beam computed tomography demonstrated functional dentin formation in three of the five patients.	established vascularity. In addition, a continuous layer of dentin-like tissue was deposited onto the canal dentinal wall. This dentin-like structure appeared to be produced by a layer of newly formed odontoblast-like cells expressing dentin sialo phosphoprotein, bone sialoprotein, alkaline phosphatase, and CD105. The cells in regenerated pulp-like tissue reacted positively to anti-human mitochondria antibodies, indicating their human origin	entirely with a dental pulp-like tissue with well-stablished vascularity, and a continuous layer of dentine-like tissue was deposited onto the existing dentine.	regenerated pulp including nerves and vasculature by day 14, followed by new dentin formation along the dentinal wall.	expressed moderate to high levels of CD146, stage-specific embryonic antigen-4, CD73 and CD166.
Technique used in analysis	Dental radiography	Flow cytometry	root apical papilla (SCAPs)-based CSDPs	Two-dimensional electrophoretic analyses	immunohistochemical analysis
Time of harvesting before results	12 weeks		6week		
Number of implanted cells	1 × 106 cells		2_106		
Activator/ carrier		synthetic scaffolds consisting of poly-D,L-	scaffold-free stem-cell sheet-	Stromal Cell-Derived Factor-1	

	PLLA nanofibrous microspheres (NF-MS)	lactide=glycolide	derived pellet (CSDP)		
The used tissue	MDPSC	apical papilla and dental pulp stem cells	root apical papilla (SCAPs)-based CSDPs	Autologous pulp stem/progenitor (CD105)	DPSCs
Sample	Five patients (28.6 ± 10.0)	Mice	mice	dogs	mice
Authors	**Misako Nakashima ET.AL 2017**	**George T.-J. et. al. 2010**	**Sijia Na 2019**	**KoichiroIohara 2011**	**Dominick J Alongi 2010**

Development in tissue engineering in the last decades showed a promising new therapy in the field of dentistry, with many new regenerative methods for regeneration the natural structure of damaged and diseased dental tissue [Nakashima M, et al , 2003, Gupte MJ. Et al, 2012, Wang J. et al ,2010]. It is critical in these therapies to proper select of appropriate stem cell type and design of optimal micro-environment which allow favorable interaction between stem cells and normal cell and increase the stability [Huang GT. et al,2009, Wang J. et al, 2011]. In this review, all the used stem cells for dentine regeneration were adult mesenchymal stem cells however, the source of harvesting these stem cell differs between studies including adipose tissue and pulp CD31-SP, DPSCS, PDLSCs, *Gdf11* gene,bone morphogenetic protein-2 (BMP-2),MDPSCs and SCAP. This is similar to other systematic review conducted in 2018, in which dental pulp stem cells were the cell of choice in most cases, however, they reported usage of SCAP, SHED, non-dental source as bone marrow and adipose derived stem cells [Bakhtiar, H. et al , 2018]. In our review, all types showed promising results however, some types gave better results over other including superior of adipose tissue CD31 SP over bone marrow CD31 SP and pulp stem progenitor (CD 105) cells over adipose CD105 cell. Therefore, the choose of proper stem cell should be mostly because of low price especially when the main problem in operating this type of therapy is the cost.

In this type of therapy, we should be considered that the differentiation of stem cells would not be normally stimulated and even they stimulated, they could differentiate to any type of cell. Therefore, it is important to control the process of differentiation of stem cell using mean of appropriate growths factors and carriers [Chen Y. et al, 2015]. The soluble proteins of dentine matrix used as a carrier can provide a suitable environment for stem cell differentiation into odontoblast like cells and then into dentine-like tissue. Moreover, proper grafting of stem cell in dentine peripheral to pulp area could help in creation of odontoblast-like cell [Jiao L. et al , 2014]. In this review, many different carriers had been developed to act as a carrier to deliver cells and regenerate irregularly-shaped tissue defects including scaffold, three-dimensional pellet, nanofibrous microspheres (NF-MS),PLG scaffold disk and CSDPs[Jayasuriya AC. et al ,2010, Francisco AT. et al,2013]. Therefore, optimization of scaffold designs and usage of proper growth factors besides the use of proper stem cells are the vital keys to provide maximally induction of odontogenic differentiation in human stem cell for dental tissue.

Conclusions:-

From this review we can conclude stem cell grafting show promising results in regeneration of dental pulp in animal and human studies with no side effect or toxicity. Therefore, we recommend widening the application of these technique in human trials because of its safety and efficacy. Choose of carriers or type of stem cells up to our review should be depended on expense as there is no significant difference between them in both safety of efficacy profiles.

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