ROLE OF GROWTH FACTORS IN ORTHODONTIC TOOTH MOVEMENT

Dissertation

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ORTHODONTICS AND DENTOFACIAL ORTHOPAEDICS

By

Dr. Kamran Javaid

Under the guidance of

Dr. Rohit Khanna

Professor and Head

Department of Orthodontics and Dentofacial Orthopaedics

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES, LUCKNOW

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Dr. Rohit Khanna , Professor and head , Department of Orthodontics and Dentofacial Orthopaedics, Babu Banarasi Das College of Dental Sciences, Babu Banarasi Das University, Lucknow, Uttar Pradesh.

Date: 20/3/23

Place: Lucknow

Dr. Kamran Javaid

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GUIDE

Dr. Rohit Khanna
Professor and Head

CO- GUIDE

Dr. Rana Pratap Maurya
Reader

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Dr. Rohit Khanna
Professor & Head
Department of Orthodontics &
Dentofacial Orthopaedics
BBDCODS, BBDU
Lucknow

Dr. Puneet Ahuja
Principal

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Dr. Kamran Javaid

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S.NO	ABBREVIATIONS	FULL FORM
1	OTM	Orthodontic tooth movement
2	PDL	Periodontal ligament
3	LLLT	Low Level Laser Therapy
4	LIPUS	Low intensity pulsed ultrasound
5	IL	Interlukins
6	PGs	Prostaglandins
7	PDGF	Platelet derived growth factors
8	BMP	Bone Morphogenic protein
9	TGF	Transforming growth factor
10	PRP	Platelet-rich-plasma
11	PRF	Platelet rich fibrin
12	APRF	Advanced platelet rich fibrin
13	LPRF	Leukocyte platelet rich fibrin
14	IPRF	Injectable platelet rich fibrin
15	CSF	Colony-stimulating factor
16	VEGF	Vascular endothelial growth factor
17	EGF	Epidermal growth factor
18	PDEGF	Platelet derived endothelial growth factor
19	CHA	Carbonated hydroxyapettite
20	RANKL	Receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells ligand
21	OPG	Osteoprotegerin
22	MMP	Matrix metalloproteinase
23	RAP	Regional acceleratory phenomenon

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Aim: To evaluate the role of growth factors in Orthodontic tooth movement using split mouth study design.

Material and method: . Sample included 32 extraction sockets of 8 patients (mean age 19 ± 2.4 years), who were undergoing fixed orthodontic treatment with extraction of all first premolars, and divided into two groups as Group I (control group 16 extraction socket of left side N=16) and Group II (experimental group where APRF was used on 16 extraction of right side N=16). After leveling and alignment atraumatic extraction were done, APRF was prepared freshly and inserted in extraction socket of premolar and canine retraction was started on 0.017 X 0.025 SS wire using NiTi closed coil spring at force of 150 grams. Study model were taken at T0 (at commencement of tooth movement after extraction) T1 (after 1st month), T2 (after 2nd month) and T3 (after 3rd month). Amount of tooth movement was measured on Study models on both sides by digital vernier caliper and result were tabulated and adequated comparison were made using (Paired t-test)

Result: Overall tooth movement as observed for 3 months (T0-T3) was significantly more on experimental group (2.44±0.46 mm) than control group (1.94±0.40 mm).Amount of tooth movement during first (T0-T1) and third month (T2-T3) was significantly higher for experimental group first month (0.81 ± 0.32 mm), third month (0.84±1.23 mm) as compared to control group first month (0.54±0.16 mm) and third month (0.70±0.20 mm) Similar trend was seen for second month (T1-T2) but difference was not statistically significant (experimental group (0.78 ± 0.30 mm) > as compared to control group (0.69 ± 0.29 mm).For each group, amount of tooth movement between different time intervals 1st , 2nd and 3rd months showed statistical non significant difference.

Conclusion: The decrease in overall duration of treatment might be attempted using APRF, especially in adult patients who has specific treatment time goals.

Orthodontic tooth movement is caused by modelling and remodelling of supporting alveolar bone under the influence of various changes at cellular and molecular level in periodontal ligament (PDL). The oldest theory of Orthodontic tooth movement (OTM) that is pressure tension theory stated that side towards which tooth movement occurs undergoes resorption with compression of PDL fibres whereas on the opposite side, that is tension side deposition occur with stretching of PDL fibres. Signaling molecule involved in OTM are neurotransmitters, cytokines, growth factors, colony-stimulating factors, and arachidonic acid metabolites[1].

As increased number of adult patients are undergoing Orthodontic treatment there has been increased search for techniques that accelerates the Orthodontic tooth movement (OTM). Several methods are used in practice to accelerate the Orthodontic tooth movement such as physical or mechanical methods, pharmacological methods and surgical methods[2].

Physical or mechanical methods used for accelerating orthodontic tooth movement includes use of cyclic forces(accelerated device) or mechanical vibration (vibratory tooth brushes) , Low Level Laser Therapy(LLLT), Low intensity pulsed ultrasound (LIPUS) and Direct electric current. The cyclic vibratory method is to give light alternating forces on the teeth via mechanical radiations. The response of cells to mechanical stress appears within 30 minutes. Nishimura et al[3], in 2008, used a Ni-Ti expansion spring on the 1st molar, showed increased orthodontic tooth movement. Pavlin[4] and co-workers in 2015 showed low-level cyclic loading with AcceleDent increased the rate of orthodontic movement.

LLLT also known as Photobiostimulation**,** is a form of light therapy which involves the therapeutic application of light in the visible, near-infrared spectrum. Shaughnessy et al[5]. studied the effects of intraoral photobiomodulation on the initial alignment phase. LIPUS is one of the non-invasive, nonpharmacological methods to accelerate OTM that has been used in the medical field for six decades as in sports medicine, myofunctional therapy, joint

stiffness reduction, increase muscle mobility, and healing of non-healing bone fractures. A study done by Xue et al[6]. on Wistar rats showed that the rate of orthodontic tooth movement in the LIPUS application group was increased.

Pharmalogical agent like Interlukins (IL), Prostaglandin E_2, Prostaglandin E_1, Misoprostol, 1 25-Dihydrocholecalciferol and Parathyroid hormones act as biomodulator for accelerating tooth movement, however these agents also have unwanted side effects that should be consider before prescribing them.

Prostaglandins (PGs) are inflammatory mediator and a paracrine hormone that acts on nearby cells; it stimulates bone resorption by increasing directly the number of osteoclasts. Yamasaki[7] found that local injections of prostaglandins have shown to increase the orthodontic tooth movement . Seifi et al[8]. in 2003 stated the importance of calcium ions working in association with PGE2 in stabilizing root resorption. Local application of PGE1, PGE2, or analogs of PGE1, PGE2, or thromboxane A2 in animals had increase the speed of orthodontic tooth movement.

1,25 dihydroxycholecalciferol is a hormonal form of vitamin D and plays an important role in calcium homeostasis with calcitonin and parathyroid hormone and also acts on bone cells to increase bone remodelling. Sinclair et al[9], found that weekly intraligamentous injection of a 1,25D solution increased amount of orthodontic tooth movement. Yamamoto et al[10], found that that the local injection of 1,25 dihydroxy vitamin D3 accelerated orthodontic tooth movement in animals.

Parathyroid hormone is a major hormone regulating bone remodeling and calcium homeostasis. Animal studies (by Li et al[11], by Khurshid et al[12]) shown that continuous global infusion or chronic local injection of parathyroid hormone accelerated orthodontic tooth movement.

Various surgical methods are available for accelerating tooth movement. Heinrich Kole[13] was first to describe corticotomy-facilitated orthodontics in 1959. Wilcko et al[14] combined corticotomy-facilitated orthodontic technique with alveolar augmentation using particulate bone graft. Dibart et al[15] in 2009, introduced a flapless method of corticotomy, using piezosurgery.

Recently , local use of growth factors to promote regeneration and repair had been advocated in tooth extraction socket, sinus agumentation and surgical implant placement for better healing. Growth factors have the potential to improve wound healing by means of several mechanism like they have chemotactic activities which attract the inflammatory cell and fibroblasts into the wound, stimulate angiogenesis, and the ingrowth of new blood vessels, stimulate cellular proliferation, and Influence the synthesis of cytokine[16].

Orthodontic tooth movement also requires good vascularity with increased proliferation of various inflammatory cell and fibroblast. As growth factors enhance this process, hence it was anticipated that these will accelerate Orthodontic tooth movement as well.

Growth factors like platelet derived growth factors(PDGF), Bone Morphogenic protein(BMP), Transforming growth factor(TGF) involved in Wound healing were thought to influence Orthodontic tooth movement as well. Platelet activation results in formation of blood clots and platelet plugs which lead to secretion of bioactive proteins for tissue repair and regeneration[17]. Platelet derived growth factor(PDGF) are produced by platelets, fibroblast which plays a role in each stage of wound healing.

Platelet-rich-plasma(PRP) and leukocyte platelet-rich fibrin (LPRF) are two main autologous products derived from platelets, rich in growth factors and cytokines which have the ability to improve bone healing and accelerate orthodontic tooth movement. Rashid et al[1] evaluated the effect of PRP in six skeletally mature mongrel dogs aged 11-15 months and found that local

injection of PRP accelerated OTM. Gluec et al[18] found that high concentration of PRP was more effective than moderate concentration of PRP in accelerating OTM in a sample of seventy six rats. Compare to PRP and LPRF, PRF have demonstrated more sustained release of growth factors from the fine and flexible fibrin matrix in their structure. The presence of high concentration of LPRF compared to PRF plays a significant role in enhanced release of some crucial growth factors such as Transforming growth factor-beta 1.

Teranchi et al[19], evaluated the effect of leukocyte platelet rich fibrin (LPRF) on OTM in thirty extraction socket and concluded that application of LPRF accelerated the orthodontic tooth movement in extraction cases. He used similar material but he measure movement as distance between second premolar and distal to canine which could reduce because of movement of both second premolar and canine. Injection platelet-rich-fibrin had (IPRF) also been effective in OTM. Karakasli et al[20], stated that i-PRF accelerate tooth movement and can help shorten orthodontic treatment duration. Choukroun[16] a developer of PRF further modified to Advanced platelet-rich-fibrin (APRF) similar to LPRF, APRF there was a sustained release of TGF-β-1, PDGF, and the presence of monocytes/macrophages further facilitated tissue regeneration and wound healing. APRF is used in periodontal reconstructive surgery, sinus lift, and implants and is furthermore used with freeze-dried bone allograft for improving bone osteogenesis and alveolar stability at the site of implants. Alhasyim et al[21], found that intrasulcular injection of carbonated hydroxyapatite incorporated with APRF can locally reduce orthodontic relapse in rabbits.

Since there are limited studies had been there to find the effect of Orthodontic tooth movement by APRF. Locally injected IPRF had been found to be effective in accelerating tooth movement so it was decided to evaluate OTM by placement of APRF in extraction socket (1st premolar extraction socket) and retraction of canine by using NiTi coil spring.

Hence, the aim of present study was to measure and compare the amount of tooth movement with APRF on one side and without APRF on contralateral side using miniscrew implant for anchorage and NiTi coil spring for retraction of canine on the both sides.

Aim

The aim of this split mouth study design was to evaluate and compare the rate of tooth movement by the use of growth factors (APRF) in subjects who have undergone extraction of all first premolar.

Objectives

1. To evaluate the rate of tooth movement on the experimental side (Right side) by the use of growth factors at the end of 1^{st} , 2^{nd} and 3^{rd} month.
2. To evaluate the rate tooth movement on the control side (Left side) where growth factors will not be used at the end of 1^{st} , 2^{nd} and 3^{rd} month.
3. To compare the rate of tooth movement on the control side (Left side) and on the experimental side (Right side).at the end of 1^{st} , 2^{nd} and 3^{rd} month.
4. To compare the overall rate of tooth movement between experimental side (Right side) and the control side (Left side) at the end of 3^{rd} month.

Choukroun J et al (2006)[16] conducted a study to investigate the biology of PRF and to determine the potential fields of application for this biomaterial. The results showed that PRF can be considered as a healing biomaterial. It features all the necessary parameters permitting optimal healing. These consist of a fibrin matrix polymerized in a tetramolecular structure, the incorporation of platelets, leukocyte, and cytokines, and the presence of circulating stem cells. Cytokines trapped in PRF are gradually released and able to accelerate the cellular phenomenon, the structure of the fibrin network is the key element of all improved PRF healing processes. Finally, from clinical aspect, this biomaterial appears to accelerate physiologic healing.

El-Sharkawy H, Kantarci A, et al (2007)[22] conducted a study to analyze the growth factors in PRP and the effects of PRP on monocyte cytokine release and lipoxin A4 (LXA4) generation. PRP was prepared from healthy donors. Platelet derived growth factor (PDGF)-AB, PDGF-BB, transforming growth factor-b1, insulin-like growth factor-I, fibroblast growth factor-basic (FGF-b), epidermal growth factor (EGF), vascular endothelial growth factor, interleukin-12 (p40/70), and regulated on activation, normal T-cell expressed and secreted (RANTES) levels were evaluated by enzyme-linked immunosorbent assay and bead-based multiplexing. Peripheral blood monocytes were isolated and cultured with or without PRP. Cytokine, chemokine, and LXA4 levels as well as monocyte chemotactic migration were analyzed. The results showed that PRP is a rich source of growth factors and promoted significant changes in monocyte-mediated proinflammatory cytokine/chemokine release. LXA4 was increased in PRP, suggesting that PRP may suppress cytokine release, limit inflammation, and, thereby promote tissue re-generation.

Tae-Min You et al (2007)[23] conducted a study to evaluate the effects of autogenous bone grafts and platelet-enriched fibrin glue in the treatment of peri-implantitis. Thirty-six

screw-type commercially pure titanium implants with rough acid-etched surfaces were inserted into 6 mongrel dogs 3 months after extraction of mandibular premolars. After 3 months of healing, peri-implantitis was induced by placing gauze and wire around the implants. Once peri-implantitis was created, surgical treatments involving a combination of autogenous bone grafts and platelet-enriched fibrin glue, autogenous bone grafts alone, or a conventional flap procedure only (control) were carried out. The amount of reosseointegration was significantly higher in peri-implantitis defects treated with combined autogenous bone grafts and platelet-enriched fibrin glue as compared with the other 2 treatment procedures. Surgical treatment involving the combined use of autogenous bone grafts and platelet-enriched fibrin glue might effectively promote re-osseointegration in lesions resulting from periimplantitis.

Chung-Hung Tsai et al (2009)[24] investigated the biologic effects of PRF on human GFs, PDL cells, oral epithelial cells, and osteoblasts. Blood collection was carried out on 10 healthy volunteers. PRF was obtained by centrifugation at 3000 rpm for 12 minutes with a PC-02 table centrifuge. Primary cultured human GFs and PDL cells, the GNM oral epithelial cell line, and the U2OS osteoblast cell line were used to evaluate cell viability and proliferation resulting from PRF according to trypan blue and tetrazolium bromide reduction assays. The results revealed that PRF did not interfere with cell viability of periodontally related cells ($P > 0.05$). PRF stimulated cell proliferation of osteoblasts (135% of the control), PDL cells (130% of the control), and GFs (120% of the control) during a 3-day culture period. However, PRF suppressed oral epithelial cell growth to as low as 80% of the control. In addition, GFs, PDL cells, and osteoblasts were observed to attach at the margins of PRF by phase-contrast microscopy.

Ling He, Ye Ling et al (2009)[25] conducted a comparative study showing the effect of biologic characteristics of PRP and PRF on proliferation and differentiation of rat

osteoblasts. Blood samples were collected from 14 healthy volunteers (7 male) with a mean age of 23.2 ± 2.24 years. PRP and PRF were prepared with standard protocols. The exudates of PRP and PRF were collected at the time points of 1, 7, 14, 21, and 28 days. The levels of platelet-derived growth factor AB (PDGF-AB) and transforming growth factor β1 (TGFβ1) were quantified in PRP and PRF. Then the exudates of PRP and PRF were used to culture rat calvaria osteoblasts. The biologic characteristics of osteoblasts were analyzed in vitro for 14 days. PRF released autologous growth factors gradually, and expressed stronger and more durable effect on proliferation and differentiation of rat osteoblasts than PRP in vitro.

David M et al (2010)[17] conducted a study on the cell composition and three-dimensional organization of Choukroun's Platelet-Rich Fibrin Clot and Membrane. The results showed that approximately 97% of the platelets and >50% of the leukocytes were concentrated in the PRF clot and showed a specific three-dimensional distribution, depending on the centrifugation forces. Platelets and fibrin formed large clusters of coagulation in the first millimeters of the membrane beyond the red blood cell base. The fibrin network was very mature and dense. Moreover, there was no significant difference in the PRF architecture between groups using the different tested collection tubes and compression techniques, even if these two parameters could have influenced the growth factor content and biologic matrix properties.

Simonpieri A, Choukroun J (2011)[26] conducted a study to assess the relevance of sinus lift and implantation with leukocyte and platelet rich-fibrin (LPRF, choukroun's technique) as sole subsinus filling material. Twenty three lateral sinus elevations (SA4 sinus) were performed on 20 patients with simultaneous implant placement. Seven patients were treated with 19 Astra implants (AstraTech) and 13 patients with 33 IntraLock implants (Intra-Lock Ossean). L-PRF membranes were used to cover the Schneiderian membrane and the

subsinus cavity was finally filled with L-PRF clots. Clinical and radiographic follow-up was performed just after implant placement, after 6 months, 1 year and so on. The maximum follow-up was 6 years, and all patients were followed up for a minimum of 2 years. No implant was lost during this 6-year experience, and the vertical bone gain was always substantial, between 8.5 and 12 mm bone gain (10.4 ± 1.2). The use of L-PRF as sole filling material during simultaneous sinus-lift and implantation seems to be a reliable surgical option promoting natural bone regeneration.

Thorat MK et al (2011)[27] investigated the clinical and radiological effectiveness of autologous PRF in the treatment of intra-bony defects of chronic periodontitis. Thirty-two intra-bony defects (one site/patient) were treated either with autologous PRF or a conventional open flap debridement alone. Clinical parameters such as plaque index (PI), sulcus bleeding index (SBI), probing depth (PD), clinical attachment level (CAL) and gingival marginal level (GML) were recorded at baseline and 9 months post-operatively. In both the groups, by using the image analysis software intra-bony defect fill was calculated on standardized radiographs. For all clinical and radiographic parameters test group was performed better than control group, and the difference was found to be statistically significant. Furthermore, images analysis revealed significantly greater bone fill in the test group compared with control.

Y-C Chang et al (2011)[28] studied the effects of platelet-rich fibrin on human periodontal ligament fibroblasts and application for periodontal infrabony defects. PDLFs were derived from healthy individuals undergoing extraction for orthodontic reasons. Blood collection was carried out from healthy volunteers. PRF was obtained from a table centrifuge centrifuged at 3000 rpm for 12 minutes. The effects of PRF on PDLFs were determined by measuring the expression of phosphorylated extracellular signal-regulated protein kinase (p-ERK), osteoprotegerin (OPG) and alkaline phosphatase (ALP) activity. Moreover, the

feasibility and safety of reconstructing the periodontal infrabony defects with PRF in six patients was retrospectively examined. PRF was found to increase ERK phosphorylation and OPG in PDLFs in a time-dependent manner. ALP activity was also significantly upregulated by PRF. Application of PRF in infrabony defects exhibited pocket reduction and clinical attachment gain after six months. Periapical radiography revealed radiographic defect filled in grafted teeth.

Sharma et al (2011)[29] designed a study to evaluate the effectiveness of autologous PRF in the treatment of mandibular Grade II furcation defects compared with open flap debridement (OFD). A split-mouth study was designed where 18 patients with 36 mandibular degree II furcation defects were randomly allotted and treated either with autologous PRF and OFD or OFD. Plaque index, sulcus bleeding index, probing depth, relative vertical and horizontal clinical attachment level, gingival marginal level, and radiographic bone defect were recorded at baseline and 9 months postoperatively. All clinical and radiographic parameters showed statistically significant improvement at the sites treated with PRF and OFD compared to those with OFD alone.

Lekovic et al (2011)[30] conducted a study to examine the suitability of autologous PRF as regenerative treatment for periodontal intrabony defects in humans and to examine the ability of Bovine porous bone mineral BPBM to augment the regenerative effects exerted by PRF. It was concluded that PRF can improve intrabony periodontal defects, and BPBM has the ability to augment the effects of PRF in reducing pocket depth, improving clinical attachment levels and promoting defect fill.

Rao et al (2012)[31] conducted a study to explore the clinical and radiographic effectiveness of autologous platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) in the treatment of intrabony defects in patients with chronic periodontitis. Ninety intrabony defects were

treated with either autologous PRF with open-flap debridement or autologous PRP with open-flap debridement or open-flap debridement alone. Clinical and radiologic parameters, such as probing depth (PD), clinical attachment level (CAL), intrabony defect depth, and percentage defect fill, were recorded at baseline and 9 months postoperatively. There was similar PD reduction, CAL gain, and bone fill at sites treated with PRF or PRP with conventional open-flap debridement. Because PRF is less time consuming and less technique sensitive, it may seem a better treatment option than PRP.

Milinkovic et al (2012)[32] studied a split-mouth design, treated 17 paired intrabony defects, either with PRF or with PRF-BPBM combination to examine the ability of autologous PRF as regenerative treatment for periodontal intrabony defects in humans and to examine the ability of BPBM to augment the regenerative effects exerted by PRF. Preoperative pocket depths, attachment levels and transoperative bone measurements were similar for the PRF-BPBM groups. Postsurgical measurements revealed a significantly greater reduction in pocket depth in the PRF-BPBM group when compared with the PRF group. The PFR-BPBM group presented with significantly greater attachment gain than the PFR group. Defect fill was also greater in the PRF-BPBM group than in the PRF group.

Knapen et al (2013)[33] conducted a study to evaluate the positive effect of leukocyte- and platelet-rich fibrin (L-PRF) on osteogenesis. A total of 72 hemispheres were implanted on the calvaria of 18 rabbits and filled with three different space fillers: L-PRF, bovine hydroxyapatite (BHA), BHA + L-PRF, and an empty hemisphere was used as control. Six rabbits were sacrificed at three distinct time points: 1 week, 5 weeks, and 12 weeks. Histological and histomorphometrical analyses were carried out. According to the presentstudy, L-PRF does not seem to provide any additional effect on the kinetics, quality, and quantity of bone in the present model of guided bone regeneration.

Ghanaati et al (2014)[34] studied protocols for standard platelet-rich fibrin (S-PRF) (2700 rpm, 12 minutes) and advanced platelet-rich fibrin (APRF) (1500 rpm, 14 minutes) were compared to establish by histological cell detection and histomorphometrical measurement of cell distribution the effects of the centrifugal force (speed and time) on the distribution of cells relevant for wound healing and tissue regeneration. Platelets were detected throughout the clot in both groups, although in the A-PRF group, more platelets were found in the distal part, away from the buffy coat. T- and B-lymphocytes, stem cells, and monocytes were detected in the surroundings of the buffy coat in both groups. Decreasing the rpm while increasing the centrifugation time in the A-PRF group gave an enhanced presence of neutrophilic granulocytes in the distal part of the clot. In the S-PRF group, neutrophils were found mostly at the red blood cell (RBC) buffy coat interface. Neutrophilic granulocytes contribute to monocyte differentiation into macrophages. Thus, A-PRF might influence bone and soft tissue regeneration, especially through the presence of monocytes/macrophages and their growth factors.

Angelo T , Marcel W (2015)[35] conducted a study to investigates on a clinical level the biomechanical stability of augmented sites in maxillary bone when a new class of moldable, self-hardening calcium-phosphate biomaterials (SHB) is used with and without the addition of Platelet Rich Fibrin (aPRF) in the Piezotome-enhanced subperiosteal tunnel-technique (PeSPTT). 82 patients with horizontal atrophy of anterior maxillary crest were treated with PeSPTT and randomly assigned biphasic (60% HA/40% bTCP) or monophasic (100% bTCP) SHB without or with addition of aPRF. 109 implants were inserted into the augmented sites after 8.3 months. It was observed that the use of SHB alone or combined with aPRF seems to be favourable in achieving a superior (bio)mechanical stable restored alveolar bone.

Pradeep et al (2015)[36] conducted a study to evaluate the efficacy of PRF, 1% MF gel and PRF+1%MF gel, with open flap debridement (OFD), in the treatment of intrabony defects in chronic periodontitis (CP) patients. One hundred and twenty patients with single defects were categorized into four treatment groups: OFD alone, OFD with PRF, OFD with 1% MF and OFD + PRF+1% MF. Clinical parameters like site specific plaque index (PI), modified sulcus bleeding index (mSBI), probing depth (PD), relative attachment level (RAL) and gingival marginal level (GML) were recorded at baseline, before surgery and 9 months post-operatively. Percentage radiographic intra-bony defect depth reduction was evaluated using computer-aided software at baseline and 9 months. PRF, 1%MF and PRF+1% MF groups showed significant PD reduction and RAL gain than OFD group. Mean PD reduction and mean RAL gain was found to be greater in PRF+1% MF group as compared to PRF alone or MF alone at 9 months. Furthermore, PRF+1% MF group sites showed a significantly greater percentage radiographic defect depth reduction as compared to MF alone, PRF alone and OFD at 9 months.

Agarwal et al (2015)[37] conducted a randomized, split mouth, clinical trial was to determine the additive effects of PRF with a DFDBA in the treatment of human intrabony periodontal defects. Sixty interproximal infrabony defects in 30 healthy, non-smoker patients diagnosed with chronic periodontitis. Clinical [pocket depth (PD), clinical attachment level (CAL) and gingival recession (REC)] and radiographic (bone fill, defect resolution and alveolar crest resorption) measurements were made at baseline and at a 12- month. Compared with baseline, 12-month results indicated that both treatment modalities resulted in significant changes in all clinical and radiographic parameters. However, the PRP/DFDBA group exhibited statistically significantly greater changes compared with the DFDBA/saline group in PD, CAL, REC, bone fill, indicating that a combination of PRF

and DFDBA is more effective than DFDBA with saline for the treatment of infrabony periodontal defects.

Miron et al (2016)[38] conducted a study to compare growth factor release over time from platelet-rich plasma (PRP), platelet-rich fibrin (PRF) and advanced-PRF (A-PRF). Eighteen blood samples were collected from six donors. Samples were incubated in a plate shaker and assessed for growth factor release at 15 min, 60 min, 8 h, 1 day, 3 days, and 10 days. In general, following 15– 60 min incubation, PRP released significantly higher growth factors when compared to PRF and A-PRF. At later time points up to 10 days, it was found that A-PRF released the highest total growth factors. The results indicate that the advantage of PRP is the release of significantly higher proteins at earlier time points where as PRF displayed a continual and steady release of growth factors over a 10-day period. It was also observed that the new formulation of PRF (A-PRF) released significantly higher total quantities of growth factors when compared to traditional PRF. Based on these findings, PRP can be recommended for fast delivery of growth factors whereas A-PRF is better-suited for long-term release.

Munoz F , Jimnez C (2016)[39] conducted a pilot prospective study involving a cohort of 11 patients. A Wilcko's modified PAOO technique with L-PRF (incorporated into the graft and as covering membrane) was performed. Post-surgical pain, inflammation and infection were recorded for 10 days postoperatively, while the overall orthodontic treatment and post-treatment stability were followed up to 2 years. It was concluded that L-PRF is simple and safe to use in PAOO. Combination with traditional bone grafts potentially accelerates wound healing and reduces post-surgical pain, inflammation, infection without interfering with tooth movement and or post-orthodontic stability, over a 2 years period.

Calin L D , Rusu A (2016)[40] conducted a study on 16 patients to evaluate the clinical results of sinus lift procedure through the lateral window antrostomy in the right sinus using A-PRF and bone substituents (Cerabone) and simultaneous insertion of a single implant as well as the evaluation of healing time. It was observed that use of the combination of A-PRF and Cerabone in sinus lift technique speeded healing time by approximately 50%, thus favoring implant osseointegration and there was no postoperative complications and showed good acceptance by the patient.

Fujioka et al (2017)[41] conducted a study to characterized how centrifugation speed (G-force) along with centrifugation time influence growth factor release from fibrin clots, as well as the cellular activity of gingival fibroblasts exposed to each PRF matrix. Standard L-PRF served as a control (2,700 revolutions per minute [rpm]-12 minutes). Two test groups using low-speed (1,300 rpm-14 minutes, termed advanced PRF [A-PRF]) and low-speed + time (1,300 rpm-8 minutes; A-PRF+) were investigated. Each PRF matrix was tested for growth factor release up to 10 days (eight donor samples). As a result The low-speed concept (A-PRF, A-PRF+) demonstrated a significant increase in growth factor release of platelet-derived growth factor (PDGF), transforming growth factor (TGF)-b1, epidermal growth factor, and insulin-like growth factor, with A-PRF+ being highest of all groups. Both A-PRF and A-PRF+ demonstrated higher levels of human fibroblast migration and proliferation compared with L-PRF. It was concluded that modifications to centrifugation speed and time with the low-speed concept favor an increase in growth factor release from PRF clots. This, in turn, may directly influence tissue regeneration by increasing fibroblast migration, proliferation, and collagen mRNA levels.

Rashid A et al (2017)[1] conducted a study to evaluate the effect of platelet-rich plasma (PRP) on the rate of orthodontic tooth movement. : The sample comprised of six skeletally mature male mongrel dogs. The maxillary second premolar in each dog was extracted

bilaterally. PRP was prepared and injected around the first premolar in one randomly selected maxillary quadrant while the other quadrant served as the control. Coil springs (150 g) were used to distalize the first premolars for 63 days using TAD as anchorage. As a result maxillary tooth movement was significantly faster on the experimental side than on the control side. Therefore, local injection of PRP in the present animal study resulted in accelerated orthodontic tooth movement with no obvious clinical or microscopic side effects.

Gulec A et al (2017)[18] conducted a study to determine the effect of different concentrations of PRP on alveolar bone density and orthodontic tooth movement. Seventy six rats were divided into 2 groups: a moderate concentration PRP injection group (n=38) and a high concentration PRP injection group (n=38). Before orthodontic mesilization of maxillary first molars, moderate and high concentrations of PRP were injected on the right side of the molar buccal sulcus and left side served as controls. Tooth movement were measured on 3-D digital models. As a result alveolar bone density was decreased in the experimental group compared with control group (P= 0.0001) at 3, 7,14 and 21 days. On day 3, osteoclastic activity of the experimental group was higher than controls (P=0.044, P=0.0001). Injection of both moderate and higher concentrations of PRP may accelerate orthodontic tooth movement by enhanching osteoclastic activity.

Tehranchi A et al (2018)[19] conducted a study to evaluate the effect of LPRF, placed in extraction sockets, on orthodontic tooth movement (OTM). In one randomly selected quadrant of each jaw, the extraction socket was preserved as the experimental group by immediate placement of LPRF in the extraction socket. The other quadrant served as the control group for secondary healing. The amount of OTM was measured at eight time points with 2-week intervals for 3 months. LPRF may accelerate Orthodontic tooth movement

Alhasyimi and P. P. Pudyani (2018)[21] conducted a study To evaluate the effect of carbonated hydroxyapatite-incorporated advanced platelet-rich fibrin on relapse and bone remodelling in rabbits. Forty-five rabbits were divided into 3 groups a control group, carbonated hydroxyapatite (CHA) and carbonated hydroxyapatite incorporated advanced platelet-rich fibrin (CHA-aPRF) group. The lower incisors were subjected to an orthodontic force of 50 cN. During the retention period, CHA and CHA-aPRF hydrogel were gently injected in the mesial gingival sulcus every 7 days and appliances were debonded to allow relapse. It was observed that intrasulcular injection of hydrogel CHA incorporated aPRF can locally reduce orthodontic relapse in rabbits.

Nemtoi et al (2018)[42] conducted a study to evaluate the effect of platelet-rich fibrin (PRF), placed in extraction sockets, on bone regeneration and orthodontic tooth movement in adolescents. Fourty extraction sockets from twenty patients requiring extraction of first premolars based on their orthodontic treatment plan participated in this split-mouth clinical trial. Immediately, the teeth adjacent to the defects were pulled together by a NiTi closed-coil spring with constant force. The bone regeneration and the amount of orthodontic tooth movement was evaluated and it was concluded that PRF may accelerate orthodontic tooth movement, particularly in cases with extraction treatment plan.

Akbulut et al (2019)[43] conducted a study to evaluate e the effects of platelet-rich plasma on orthodontic tooth movement in rats. 48 male albino rats into 3 groups control group, platelet-rich plasma group, and platelet-poor plasma group. The rats in all study groups had orthodontic tooth movement of their maxillary right first molars. Either platelet-rich plasmaor platelet-poor plasma was injected into the animals in the platelet-rich plasma and platelet-poor plasma groups, respectively; the rats in the control group had no injection. The rats in the platelet-rich plasma group showed less tooth movement than those in the control group at day 3. At day 14, maximum tooth movement was observed in all groups.

Nakornnoi et al (2019)[44] conducted a study to evaluate the effects of a local injection of leukocyte-platelet-rich plasma (L-PRP) on orthodontic tooth movement in rabbits. L-PRP was injected submucosally at the buccal and lingual areas of the first premolar in one random side of the maxilla and the other side served as the control and received normal saline. The amount of tooth movement was assessed on three-dimensional digital models on days 0, 3, 7, 14, 21, and 28. The L-PRP group showed significantly greater cumulative tooth movement at all observed periods. However, a significantly higher rate of tooth movement was observed only on days 0–7 and 7–14.

Soham et al (2019)[45] conducted a study to evaluate e efficacy of PRF on soft tissue outcomes when used as an adjunct to a variation of PAOO technique and also assess the time duration to achieve complete space closure on a 23 year old patient with class II div 1 malocclusion. Therapeutic extraction of upper 1st premolars and lower 2nd premolars were performed. To facilitate lower molar protraction and PAOO procedure was performed along with PRF and the clinical outcomes were assessed at the end of 6 months. It was concluded that PAOO when combined with PRF not only results in faster space closure but also the vast growth factors released from PRF not only improve post-operative healing, but also increases the soft tissue thickness.

Timamy et al (2020)[46] conduted a study to investigate the effect of local injection of PRP on the rate of orthodontic tooth movement. Sixteen female patients were randomly allocated in a split-mouth study design to receive PRP injections with CaCl2 activating solution on one side (intervention side) while the other side received CaCl2 injection only (control side). Canine retraction was performed on 0.017 X 0.025-inch stainless steel archwire applying 1.5 N retraction force. PRP and CaCl2 injections were done at 0, 3, and 6 weeks. The duration of the study was 4 months. The rate of canine retraction was faster on the intervention side in the first 2 months, with a statistically significant difference in

the first month . On the other hand, the rate was statistically significantly slower on the intervention side in the third month. PRP showed a positive potential to accelerate the rate of tooth movement when injected in the first 2 months.

Pacheco et al (2020)[47] conducted a study to evaluate the distalization rate and changes in inclination of the maxillary canines in alveoli preserved with leukocyte-platelet–rich fibrin (L-PRF) membranes in adult patients. A total of 21 adult patients, who had an indication of extraction of the maxillary first premolars and orthodontic distalization of the maxillary canines were included in this study. A randomized controlled clinical split-mouth trial was conducted; the experimental maxillary side was treated with L-PRF membranes, and the other side served as the control. . The distalization rate and inclination of the canines were greater on the control side than on the side treated with L-PRF. The use of L-PRF in young adult patients decreased the rate of distalization and changes in inclination of the maxillary canines compared with the control group.

Ibrahim et al (2020)[48] conducted a study to evaluate root surface changes and bone density accompanying two different methods of accelerated orthodontic tooth movement by use of Piezocision technique and i-PRF injection. The study involved twenty patients with bimaxillary dento-alveolar protrusion or Angle Class II Division 1 malocclusion. The line of treatment was the extraction of the upper first bicuspids and then cuspid distalization. It was found that Piezocision technique and i-PRF injection are efficient procedures that reduce the time needed for canine distalization. No significant differences regarding volumetric root resorption were observed in both groups between the experiential side and the control one after canine retraction.

Suparwitri et al (2020)[49] conducted a study to determine the effect of carbonate apatite (CHA) hydrogel-aPRF on osteoblastogenesis during relapse in rabbits. Forty-five rabbits

were divided into three groups: the control, CHA, and CHA-autologous platelet-rich fibrin (aPRF) groups. An open-coil spring was compressed between brackets to distalize the lower incisors of the rabbits by delivering a force of 50 cN for 1 week. The new position of the teeth was retained for 14 days, and CHA hydrogel-aPRF was injected every 7 days. The appliances were then debonded to allow relapse. After debonding, transforming growth factor (TGF)-β1 and bone morphogenetic protein (BMP)-2 expression was examined. It was observed that TGF-β1 expression in the CHA-aPRF group is statistically higher than that in other groups, BMP-2 expression in the CHA-aPRF group was also statistically higher than that in the other groups after debonding.

Rokia et al (2021)[50] conducted a study to evaluate the effectiveness of injection I- PRF to accelerate alignment and levelling of the upper anterior teeth and reduce the time required for treatment. 16 patients including (10 females, 6 males)in need of orthodontic treatment and who have crowding at the level of the upper anterior teeth. Patients were divided into two 2 groups: the experimental group would be injected with platelet-rich fibrin (I-PRF) and a control group for which only brackets would be applied. The treatment progress was evaluated at 3-time stages. It was seen that platelet-rich fibrin injection I-PRF was ineffective in accelerating the alignment and the levelling process as well as in reducing the time required for treatment.

Erdur et al (2021)[51] conducted a study to evaluate the efficiency of injectable platelet-rich fibrin (i-PRF) in accelerating canine tooth movement and to examine levels of the matrix metalloproteinase-8 (MMP-8), interleukin-1b (IL-1b), receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells ligand (RANKL), and osteoprotegerin (OPG) in the gingival crevicular fluid during orthodontic treatment. Twenty patients with Class II Division 1 malocclusion were included in a split-mouth study. The treatment plan for all patients was extraction of maxillary first premolars followed by canine distalization

with closed-coil springs using 150 g of force on each side. The study group received i-PRF two times, with a 2-week interval, on one side of the maxilla. The contralateral side served as the control and did not receive i-PRF. i-PRF significantly increased the rate of tooth movement, and stimulation in the levels of inflammatory cytokines. The IL-1b, MMP8, and RANKL values were significantly increased in the study group compared with the control group, while the OPG values were significantly decreased. As a result, i -PRF-facilitated orthodontics is an effective and safe treatment modality to accelerate tooth movement, and this method can help shorten orthodontic treatment duration.

Bhaskaran et al (2021)[52] conducted a study to compare the osteoblastic activity in periodontally accelerated osteogenic orthodontics (PAOO) with and without the platelet-rich fibrin (PRF) membrane by evaluating the gingival crevicular fluid (GCF), alkaline phosphate (ALP) levels and also to explore the efficiency of PRF membrane in terms of healing. As a result there was a statistically significant increase in GCF ALP levels in the test site (PAOO with PRF membrane) 2 weeks post-surgically compared to the control site. Adjunctive use of PRF resulted in statistically significant early healing in the first postoperative week compared to the control site. It was concluded that PRF membrane is an effective and paramount biomaterial that can be used as an adjunct to PAOO.

Karci et al (2021)[53] conduted a study to evaluate and compare the effects of local platelet-rich fibrin (PRF) injection and piezocision applications on tooth movement during canine distalization, as well as to evaluate any changes in the periodontal parameters. Twenty-four patients were randomly divided into 2 groups. A randomly selected side of the maxillary arch received either PRF injection or piezocision. The contralateral sides of both groups served as the controls. After piezocision and PRF injection applications, canine distalization was initiated in both groups with a 150 g force. Patients were followed every 2 weeks for a total 12 of weeks. As a result the amount of canine distal movement was found

to be greater in the experimental sides than in the control sides in both groups at 12 weeks. It was concluded that PRF and piezocision accelerated tooth movement, but there were no differences between the 2 applications in terms of amount, speed, duration of tooth movement, or periodontal parameters during canine distalization.

Zeitounlouian et al (2021)[54] conducted a study to investigate the effectiveness of i-PRF in accelerating maxillary canine retraction. A split-mouth design was applied in 21 participants (6 men, 15 women; mean age: 20.85 ± 3.85 years) whose class II division I malocclusion required the extraction of both maxillary first premolars. The right and left canines were randomized into intervention and control sides. After the initial leveling and alignment phase and immediately before canine retraction, i-PRF obtained from the brachial vein was injected into the mucosa on the buccal and palatal aspects of the intervention sides. The injection was repeated one month later. Study casts were taken at the initiation of canine retraction (T0) and at monthly visits up to 5 months (T1 through T5). As a result e average rates of canine retraction were greater on the experimental side at T2, T3, and T4. but this difference with the control side was statistically significantly different only at T2. It was concluded that The rates of canine retraction following the injection of platelet-rich fibrin were not statistically significantly greater on the experimental than the control sides except at the second month (T2).

Karakasli et al (2021)[20] conducted a study to evaluate the efficiency of platelet-rich fibrin (PRF) injection on maxillary incisor retraction rate. The study included 40 patients (23 women and 17 men) with Class II Division 1 malocclusion. The treatment plan for all patients was extraction of the maxillary first premolars and canine distalization, followed by retraction of the maxillary incisors. Patients were randomly divided into two groups. The study group received injectable platelet-rich fibrin (i-PRF) two times with an interval of 2 weeks; the control group did not receive i-PRF. In both groups, the measurements

were bilaterally assessed as the distances between the lateral and canine teeth on the plaster models at five time points. As a result the average movements of incisors were significantly higher in the study group than the control group. It was concluded that the use of i-PRF significantly increased the rate of maxillary incisor retraction at all time intervals. Platelet-rich fibrin injection can be an effective method for shortening treatment duration.

Mathur et al (2022)[55] conducted a study to compare tooth movement using PRP and the conventional method in patients with moderate crowding during the leveling and aligning phase.Fifty patients with moderate crowding in the maxillary arch were chosen. Split-mouth design was planned with one quadrant allotted as the experimental group (PRP side) and the other as the control group. Five injection sites were pre-defined distal surface of the root of the central incisor, mesial and distal root surfaces of the lateral incisor and canine. After the extraction of the permanent maxillary first premolars, PRP was injected at various sites on the experimental side while the other side served as the control group. There is a Significant amount of tooth movement was seen at 21 days. No significant difference in tooth movement was found at 42 days and 63 days after injection.

Barhate et al (2022)[56] conducted a study to evaluate the effect of L-PRF on the rate of maxillary canine retraction. Fifteen females with Class I bimaxillary dentoalveolar protrusion malocclusions were included. After levelling and alignment of maxillary arches, 1st premolars were extracted from both sides. Canines were retracted immediately after the extraction of 1st premolars in control sides and placement of L-PRF plugs in the experimental sides. The amount of canine retraction was evaluated from study models recorded before the extraction of 1st premolars (T_0) and at 1-week (T_1), 2-weeks (T_2), 4-weeks (T_3), and 8-weeks (T_4) after the beginning of canine retraction by using digital model superimpositions. Total canine retraction during T_0-T_4 was statistically greater in

experimental sides (2.43 ± 0.46 mm) than control sides (2.08 ± 0.28 mm). Over an 8-week period, autologous L-PRF statistically accelerated the rate of maxillary canine retraction.

Balu et al (2022)[57] conducted a study to compare the rate of extraction space closure between periodontally accelerated osteogenic orthodontics (PAOO) using platelet-rich fibrin (PRF) and PAOO using demineralized bone xenograft (DMBM). : A two-arm prospective single blind pilot study with a split-mouth design was used in which 14 patients requiring premolar extraction were divided into two groups: PRF and DMBM. En-masse space closure was carried out with using mini implants after the PAOO procedure. The amount of space closure was measured at five time points with 2-week intervals within 2 months. As a result the rate of extraction space closure was faster in the experimental quadrant at all time points (T1-T4) in the PRF group and at time points (T3, T4) in the DMBM group.. It was concluded that PRF, when used with PAOO procedure, produces a faster rate of space closure.

Wakhloo T , Shukla S (2022)[58] conducted a study to assess the regenerative potential of advanced platelet-rich fibrin (APRF) in the regenerative treatment of necrotic immature permanent teeth (NIPT) in the maxillary incisor region. 10 children aged between 8 and 14 years with NIPT in the maxillary incisor region undergoing APRF treatment were enrolled in a prospective clinico-radiographic exploratory observational study and Patients were followed up at 3, 6, and 12 months posttreatment. It was observed that patients showed periradicular healing and showed a clear hard tissue bridge formation at various levels in the root canal on postoperative radiographs.

Joseph et al (2022)[59] conducted a study to determine whether corticotomy procedure done using piezocision technique along with platelet-rich fibrin placement that has enhanced tooth movement, improved wound healing, and reduced adverse effects including root

resorption and damage to periodontium. It was concluded that the orthodontic tooth movement was increased postsurgery, thereby lessening treatment duration and patient discomfort.

Shetye et al (2022)[60] conducted a study to assess the effect of advanced platelet-rich fibrin (APRF) and concentrated growth factor (CGF) on tissues around implants in the maxillary anterior region. Thirty subjects were divided into three groups with 10 dental implants in each group i.e, Group 1: Control group, Group 2: Endosseous implant placement with APRF, and Group 3: Endosseous implant placement with CGF. It was concluded that CGF and APRF accelerated osseointegration. Furthermore, they had a positive effect on stabilization values.

Fakhry et al (2022)[61] conducted a study to to determine whether submucosal local injection of i-PRF may affect orthodontic relapse by increasing bone density. Forty-five adult male albino rabbits were randomly divided into three groups: group I (control) with 15 rabbits injected with 200 µl of phosphate-buffered saline (PBS), group II with 15 rabbits injected with 200 µl of i-PRF, and group III of 15 rabbits inject with 400 µl of i-PRF. The lower incisors of rabbits moved distally by a modified orthodontic appliance for 2 weeks; then, the appliance was maintained in position to retain the gaining space for 2 weeks. As a result I-PRF groups showed a significant reduction in the amount of relapse at 10, 13, 17, and 20 days compared to the control group, indicated by the highest percentage of relapse for the control group at the end of the study (20 days). It was concluded that i-PRF has the potential to enhance the stability of teeth after orthodontic tooth movement and could have the ability to reduce relapse, probably by increasing the alveolar bone density.

This in vivo study was conducted in the Department of Orthodontic & Dentofacial Orthopedics, Babu Banarasi Das College of Dental Sciences, Lucknow with the aim to evaluate the role of growth factors (Advanced Platelet Rich Fibrin- APRF) in Orthodontic tooth movement in patients who were undergoing fixed Orthodontic treatment following extraction of all 1st premolar. Sample for this study consisted of 32 extraction socket of 8 patient with age range of 15-25 (mean age 19 ± 2.4 years) of both male and female(Table 1) who are undergoing fixed orthodontic treatment. Split mouth technique was followed to divide samples into two groups as control group (16 extraction socket) left side (Group I) and experimental group (16 extraction socket) right side(Group II). The tooth movement was done by using NiTi closed coil spring and anchorage was taken using Temporary Anchorage Devices (TADs) (miniscrew S K surgical) which was in different groups placed in the inter-radicular area between 2nd premolar and 1st molar.

Table 1 : Sample size distribution at different time interval

Group	**Side (right/left)**	**No. of sample (Extraction socket)**	**Age (mean ± S.D.)**
Group I (Control side)	Left side	16	19 ± 2.4 years
Group II (Experimental side)	Right side	16	19 ± 2.4 years

Criteria for sample selection: Following inclusion and exclusion criteria was taken for sample selection.

Inclusion criteria:

1. Bi-maxillary protusion and required fixed orthodontic treatment with extraction of all 1st premolar.
2. Age range 15-25 years.
3. Good oral hygiene
4. Willing for fixed Orthodontic treatment

Exclusion criteria:

1. Bone and blood disorders, any genetic disorder and any systemic illness.
2. Undergone any surgical procedure in orofacial region.
3. History of trauma.
4. Undergone Orthodontic treatment previously
5. History of hypersensitivity to any product used in the study.

Written informed consent was obtained from the selected subjects participating in this study before beginning of the study and was explained about study. Approval was taken from Ethical Committee of BBDCODS, BBDU, Lucknow prior to the start of the present study

SAMPLE SIZE ESTIMATION

Sample size estimation was done by using **GPower software (version 3.0).** Sample size was estimated for t test.

A minimum total sample size of 27 was found to be sufficient for an alpha of 0.05, power of 95 %, 0.66 as effect size (assessed from a similar study).

t tests - Means: Difference between two dependent means (matched pairs)

Analysis: A priori: Compute required sample size

Input:	Tail(s)	=	One
	Effect size dz	=	0.6632837
	α err prob	=	0.05
	Power (1-β err prob)	=	0.95
Output:	Noncentrality parameter δ	=	3.4465232
	Critical t	=	1.7056179
	Df	=	26
	Total sample size	=	27
	Actual power	=	0.9563612

Estimated sample 27 considering the attrition of sample in future, sample size was rounded off to 32.

MATERIALS AND EQUIPMENTS:

1. Materials used for fixed Orthodontic treatment. (Figure 1)

a) Mouth mirror

b) Explorer

c) Tweezer

d) MBT priscription (0.22 slot SS) (3M unitek)

e) Cheek retractor

f) Bonding material (Orthofix)

g) Bracket positioning tweezer

h) MBT gauge (GDC)

i) Light cure gun (woodpecker)

j) Arch wire Niti and SS (Round and Rectangular)

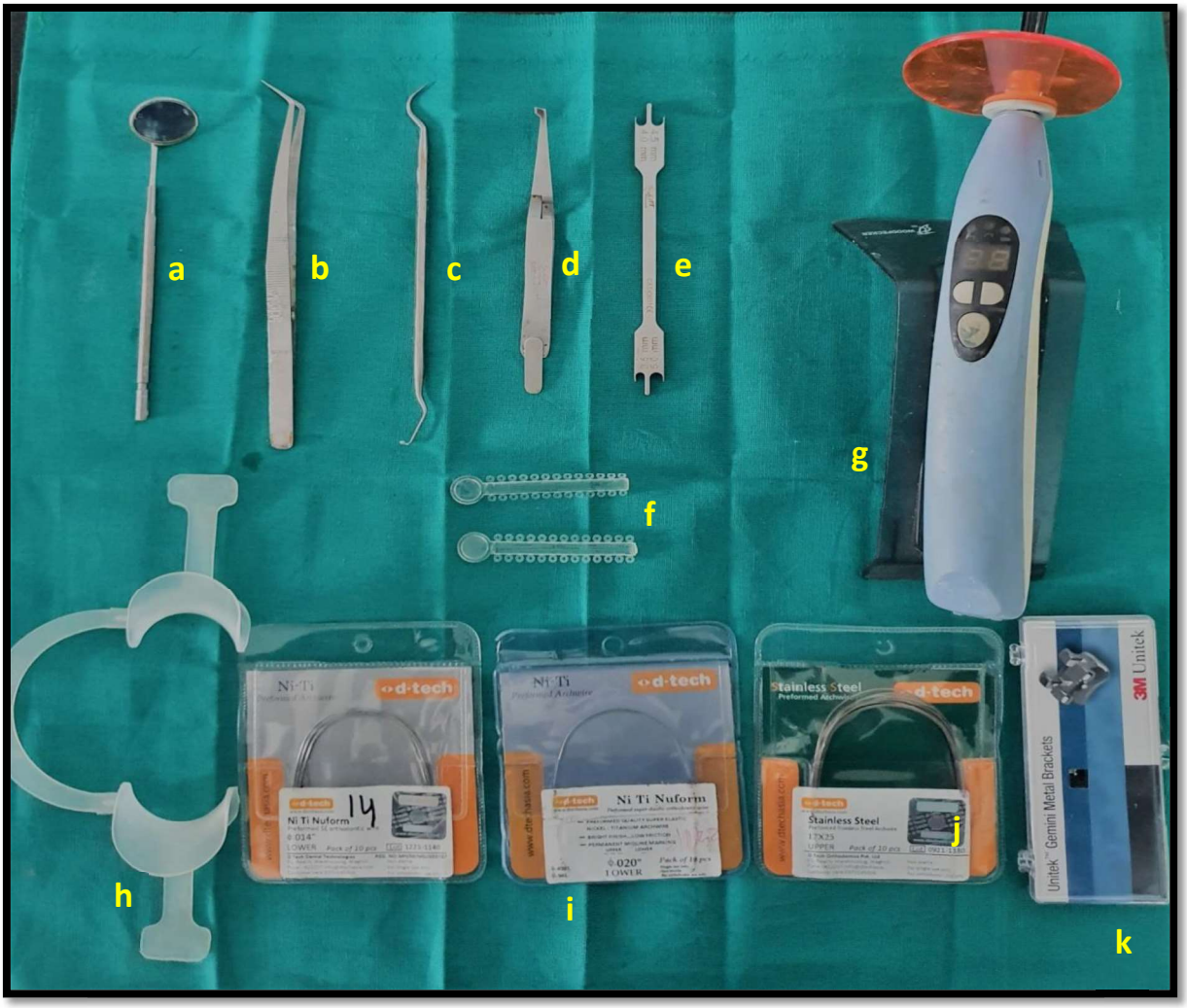

Figure 1: Materials used for fixed Orthodontic treatment: (a) Mouth mirror,(b)Tweezer,(c) Explorer,(d) Bracket positioning tweezer,(e) MBT gauge (GDC),(f) Modules,(g) Light cure gun,(h) Cheek retractor,(i) Niti Arch wire(j) SS-Arch wire,(k) MBT priscription(0.22 slot)

2. Materials used for placement of miniscrew for Anchorage (Figure 2)

a) Screw driver

b) Miniscrew (S.K surgical) of length form maxilla (1.3X11 mm) and for mnadibe (1.3X8 mm)

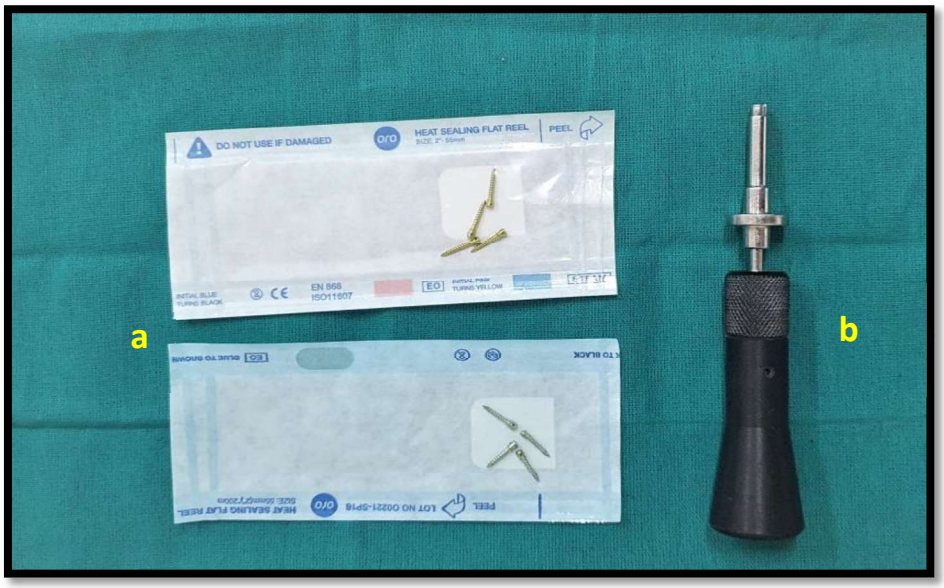

Figure 2: Material used for anchorage, (a) TAD (miniscrew S.K. surgical), (b)Driver,

3. Materials used for withdrawl of blood (Figure 3)

a) Torniquet

b) Butterfly needle

c) Vacutainer

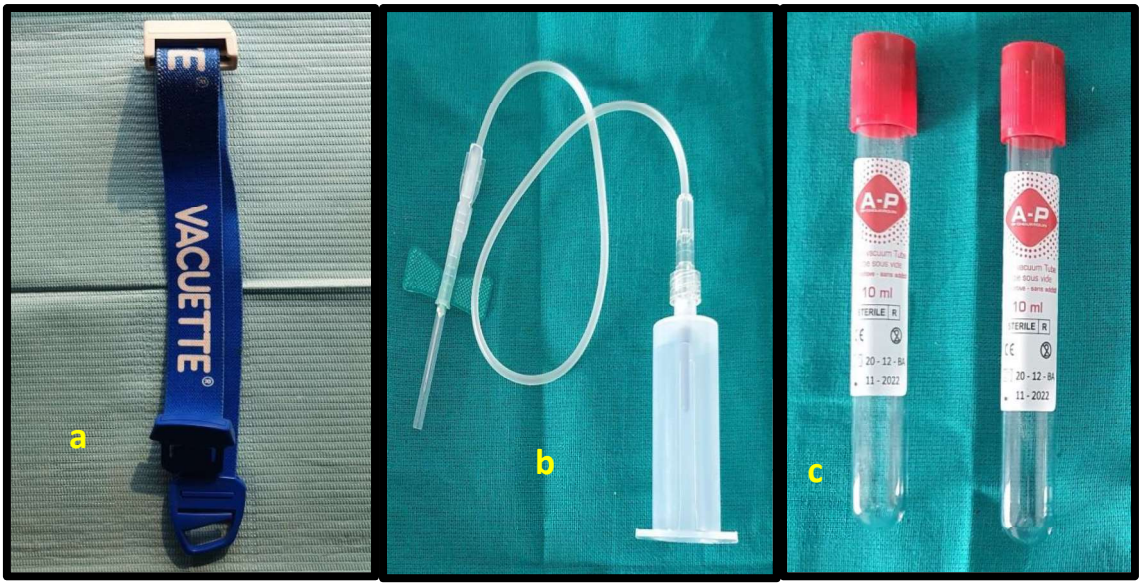

Fig 3 Materials used for withdrawl of blood, (a) Torniquet,(b) Butterfly needle, (c) vacutainer

4. Materials used for preparation of APRF gel (Figure 4)

(a) Centrifugation machine **(Figure 4 a)**

(b) APRF box **(Figure 4 b)**

Figure 4 (a) Centrifugation machine (b) ARPF box

5. Materials used for canine retraction (Figure 5)

a) NiTi closed coil spring (6mm)

b) Ligature wire (0.009”SS)

c) Dontrix gauge (Morelli)

d) 0.017X25 S.S archwire

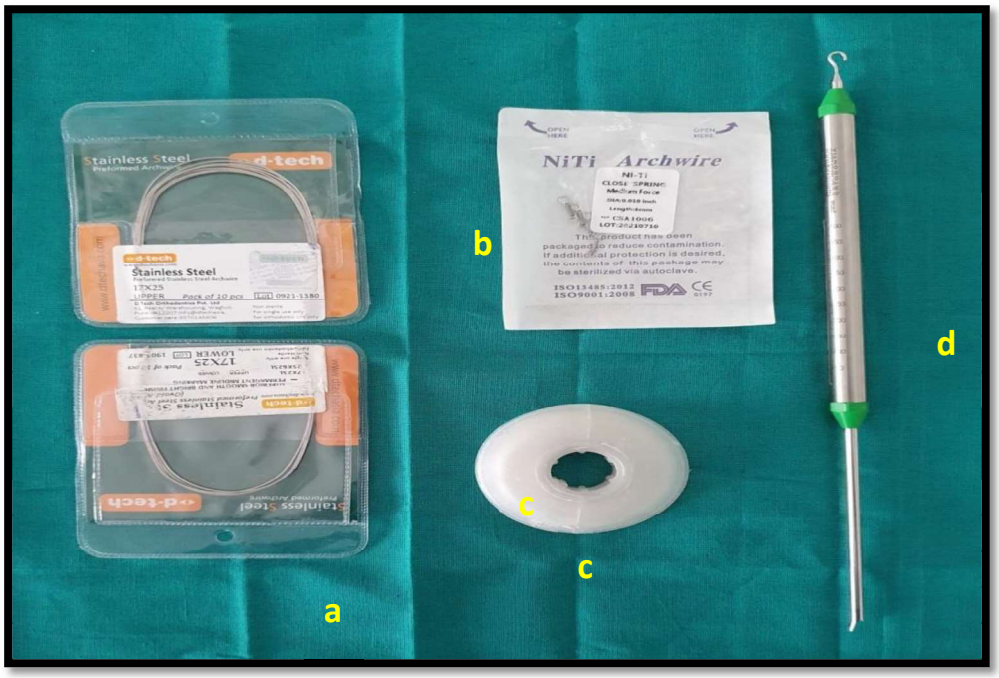

Figure 5 Materials used for canine retraction (a) 0.017X25 S.S archwire,(b) NiTi closed coil spring, (c) Ligature wire (0.009"SS),(d) Dontrix gauge.

6. Materials used for making study model (Figure 6)

a) Alginate impression material (Neoalgin)

b) Bowl

c) Spatula

d) Impression tray (Rim lock perforated tray)

e) Dental stone

f) 3% hypochlorite

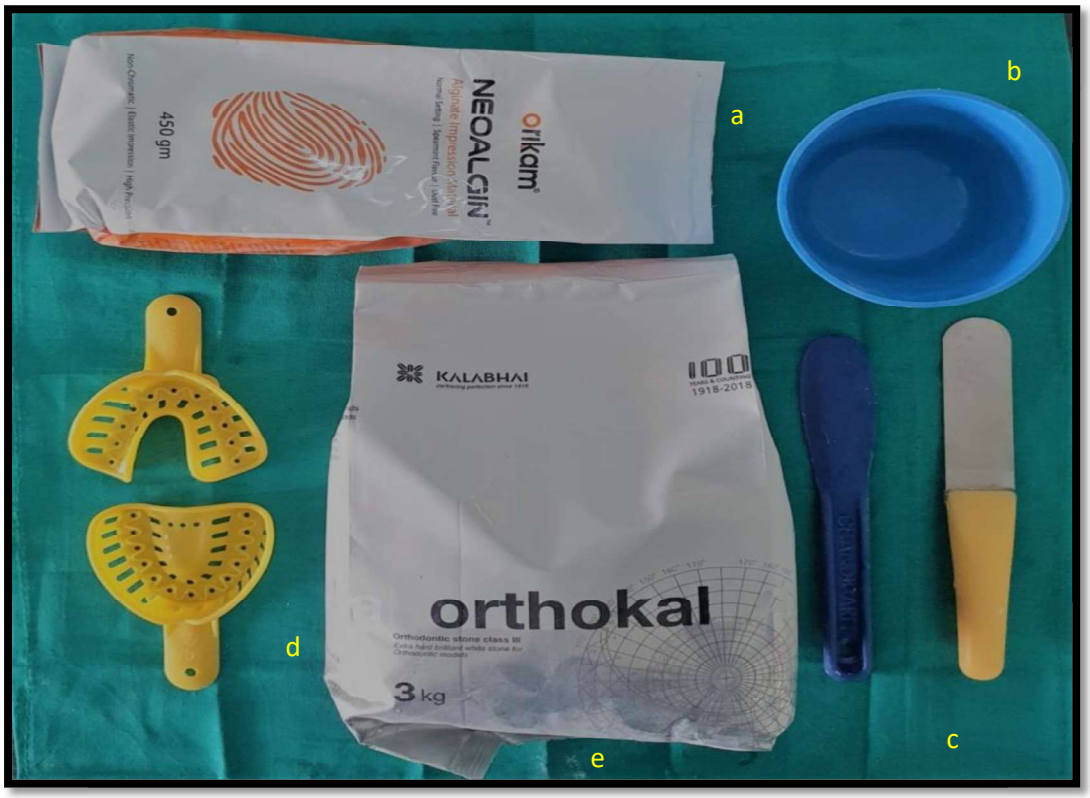

Figure 6 Materials used for making study model (a) Alginate, (b) Bowl, (c) Spatula, (d) Impression trays, (e) Dental stone

7. Material used for measurement on study model (Figure 7)

a) Digital vernier caliper

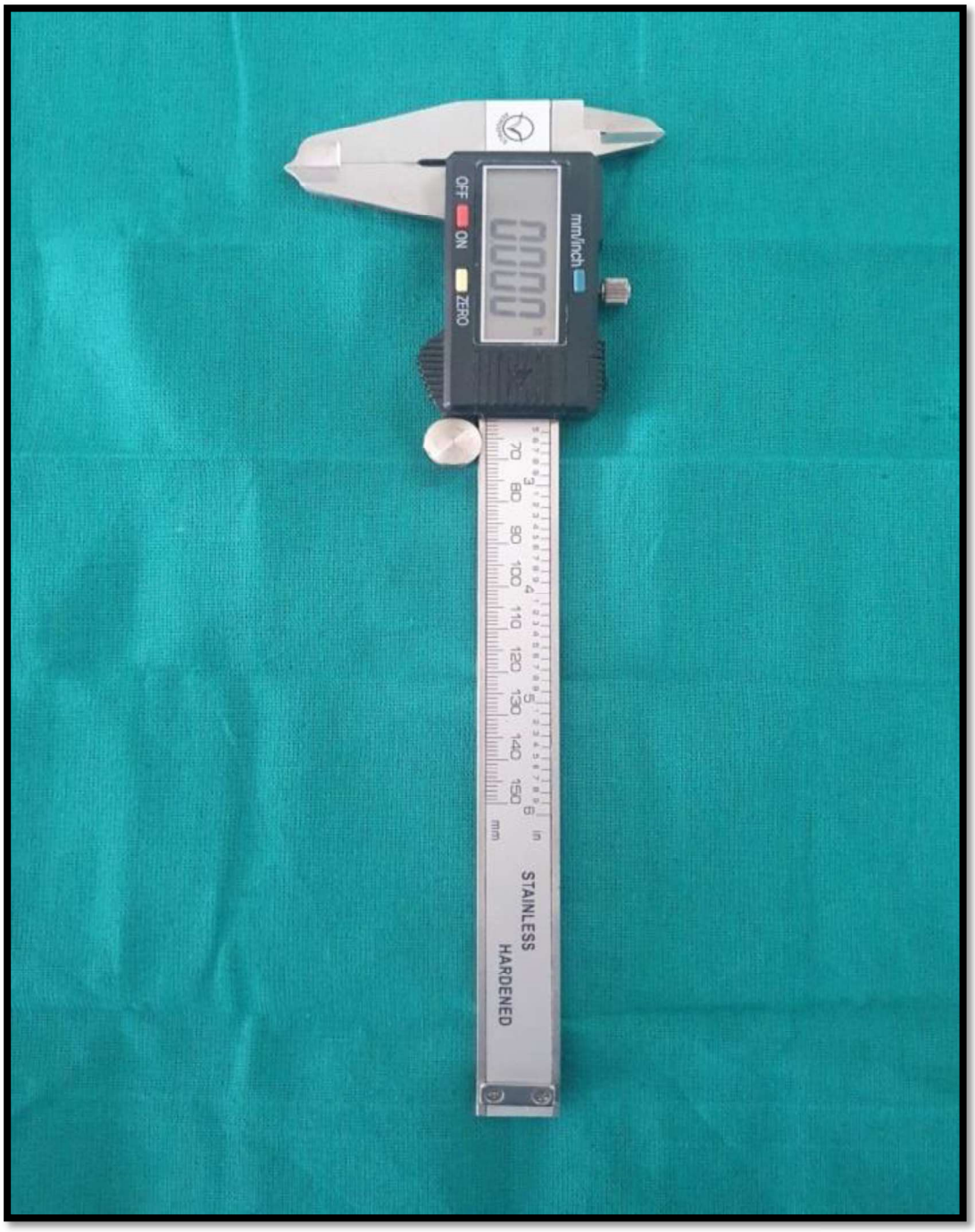

Figure 7: Digital vernier caliper

METHODOLOGY :

Pre-treatment records (lateral cephalograph, orthopentomogram, study models, extra oral and intra oral photographs) and demographic data of all patient was taken.

After case analysis, MBT priscription (0.022 slot SS) (3m unitek) was placed on selected cases of Angle's class I Bi-maxillary protusion who need extraction of all 1st premolar. Alignment and levelling was done using preformed NiTi arch wire. For anchorage TADs (miniscrew S K surgical) were placed in both maxillary and mandibular arch. TADs of appropriate length and diameter i.e 1.3 X 11mm in maxillary and 1.3 X 8mm in mandibular arch was placed in the inter-radicular area between second premolar and first molar.

Atraumatic extraction of maxillary and mandibular 1st premolar was done. At the time of premolar extraction APRF was prepared by 10 ml Blood drawn from the patients antecubital fossa and centrifugation was done for 14 minutes at 1500rpm (Figure 8 a,b,c). One centrifugation resulted in the formation of three layers: the top layer is platelet poor plasma (PPP), the intermediate layer is A-PRF and the deep layer, contain red blood cells (RBC). The APRF was removed from the tube and attached red blood cells were scraped and removed. In order to obtain plugs, the APRF has been introduced into the special cylinders of A-PRF Box and compressed with the help the piston. APRF (Figure9a, b, c) was obtained and placed in extraction socket on experimental side(right side) only and suture was placed on the same side.

Figure 8: method of blood collection and centrifugation (a) transfer of blood to vacutainer (b) vacutainer in centrifugation machine (c) APRF obtained after centrifugation

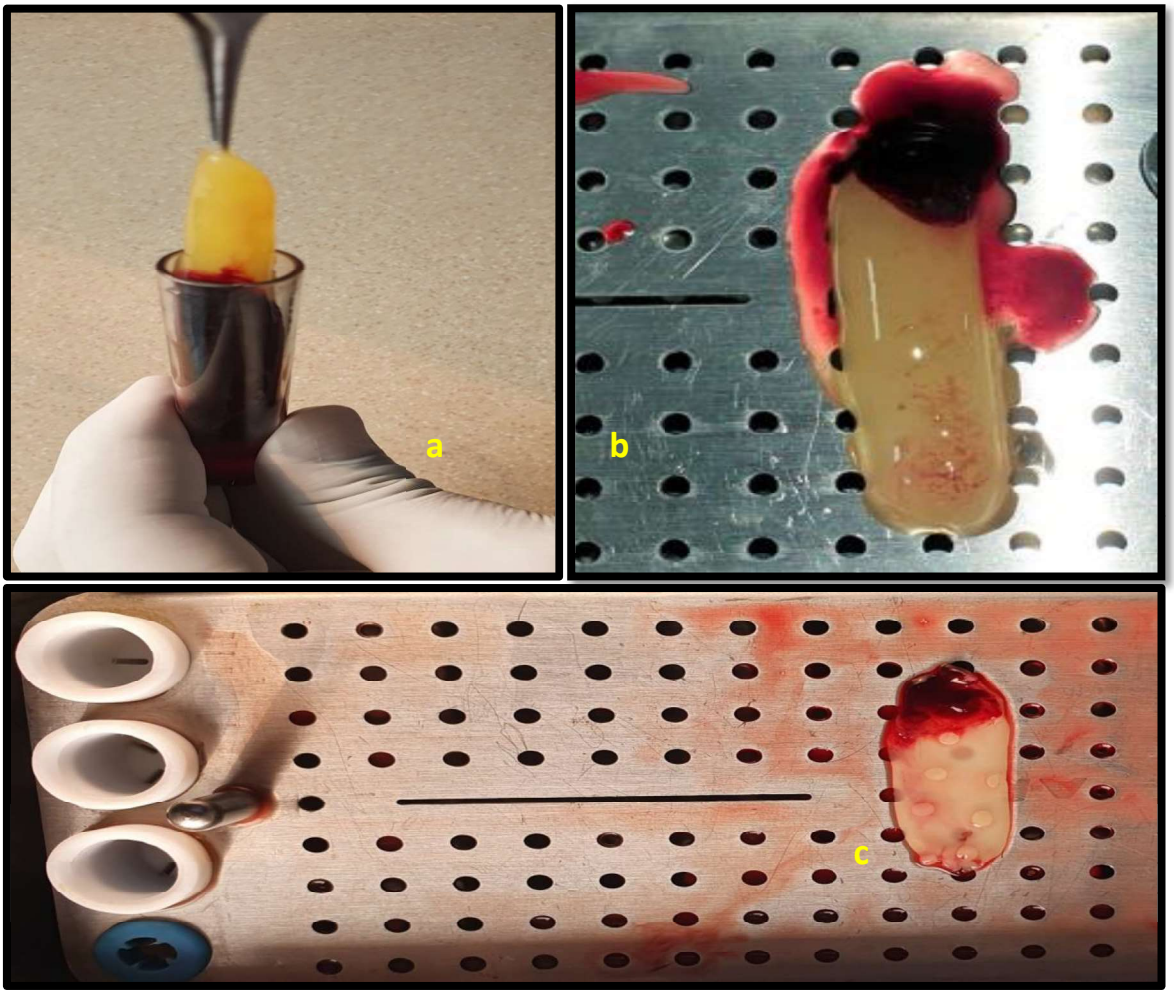

Figure 9: **method of preparation of APRF gel for final placement** (a) collection of APRF clot, (b): placement of APRF in APRF box, (c) APRF gel obtained after compression

Atraumatic extraction of maxillary and mandibular 1st premolar was done for left side. After a gap of three day atraumatic extraction of 1st premolar of right side was done. At the same time APRF was obtained from the blood drawn from patient antecubital fossa as per the protocol. APRF thus obtained was placed in extraction socket of maxillary and mandibular premolar of right side (Group II) and suture was placed and 0.017X0.025 SS wire was placed. Canine retraction was started using closed coil spring of 6mm from miniscrew to canine hook after gap of four days and force was standardized to 150 grams using Dontrix gauge (Figure 10 a,b). At the same time baseline study model was prepared. For study model preparation impressions were made using alginate impression (Neoalgin) material, washed under running water and disinfected by using 3% sodium hypochlorite and poured immediately with dental stone. (T0).

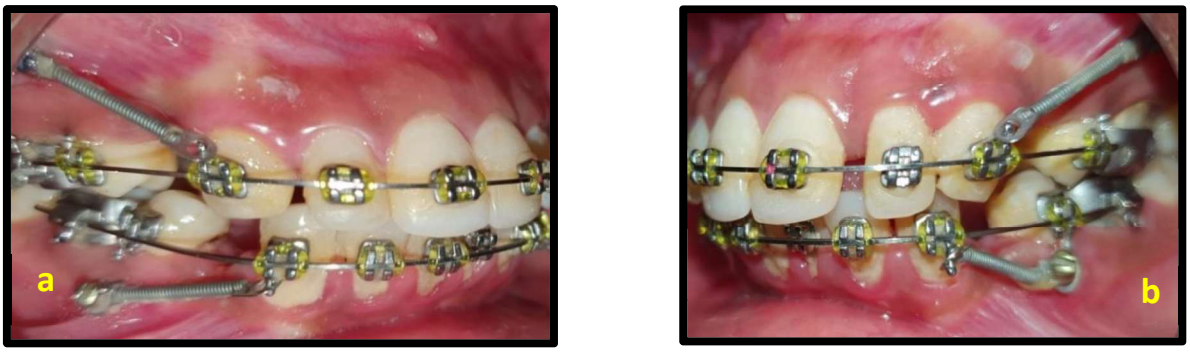

Figure 10 Canine retraction in one of the sample of study : (a) Right side , (b) Left side

Patients were recall every month for a period of three months and study model was prepared to measure the amount of tooth movement that is after 1 month (T1), after 2 month (T2) and after 3 month (T3). Different time interval are –

T0- At commencement of tooth movement after extraction

T1- Time of 1st month elapsed after T0

T2- Time of 2nd month elapsed after T1

T3- Time of 3rd month elapsed after T2

At each visit NiTi coil spring was activated by stretching the coil spring so that 150 gm of force is delivered (measured by Dontrix gauge) for canine retraction. 150 gm of force was maintained throught the period of retraction.

For assessing the Orthodontic tooth movement digital vernier caliper was used and the space between the canine and second premolar was measured at different time intervals on all the casts. The two beaks of the digital vernier caliper were placed on the distal contact surface of canine and mesial contact surface of premolar.(Figure 11)

All measurements was done by same operator to avoid any inter-operator error.

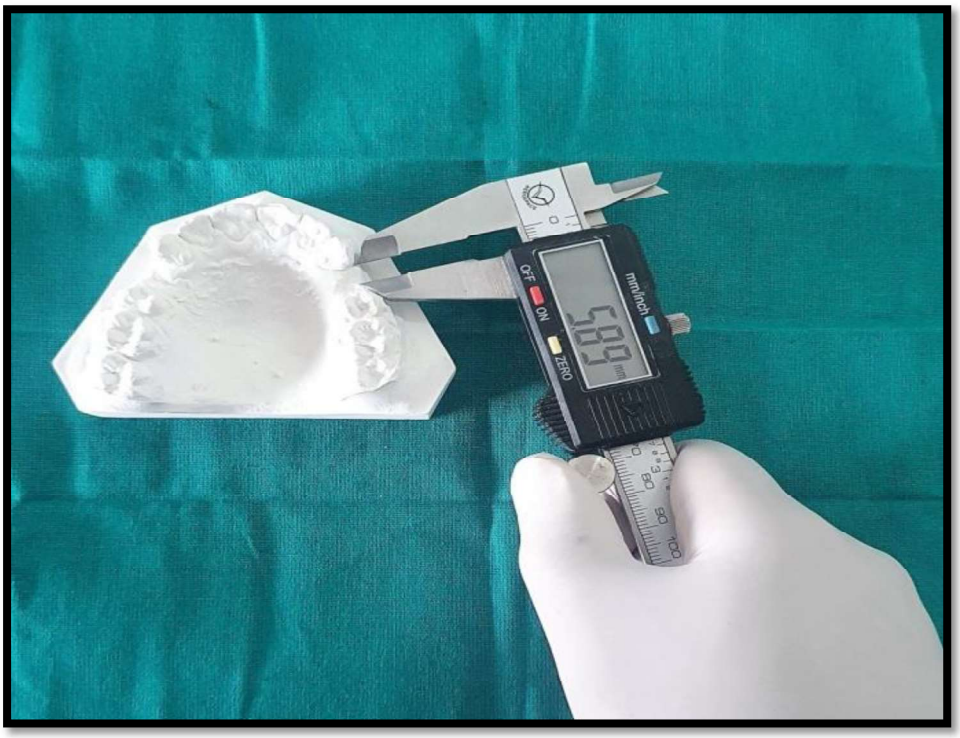

Figure 11: Measurement of tooth movement

Amount of tooth movement at different time interval was measured as difference in distance between canine and second premolar at each consecutive time interval (Table 2)

1) Tooth movement in 1st month

= (difference in extraction space between canine and second premolar from T0 to T-1)

2) Tooth movement in 2nd month

= (difference in extraction space between canine and second premolar from T1 to T2)

3) Tooth movement in 3rd month

= (difference in extraction space between canine and second premolar from T2 to T3)

Table 2 : Amount of tooth movement at different time interval

Amount of tooth movement	**Tooth movement in 1st month**	**Tooth movement in 2nd month**	**Tooth movement in 3rd month**
Measurement in mm	T0-T1	T1-T2	T2-T3

All the data was obtained and compiled on a Microsoft excel datasheet and statistical analysis was done.

DATA ANALYSIS

Data was entered into Microsoft Excel spreadsheet and was checked for any discrepancies. Summarized data was presented using Tables and Graphs. The data was analysed by SPSS (21.0 version). Shapiro Wilk test was used to check which all variables were following normal distribution. Data was normally distributed therefore, bivariate analyses were performed using the parametric tests i.e Paired t test. Level of statistical significance was set at p-value less than 0.05

STATISTICAL ANALYSIS

Formula used for the analysis

A. The Arithmetic Mean

The most widely used measure of central tendency is arithmetic mean, usually referred to simply as the mean, calculated as

$$\bar{X} = \frac{\sum_{i=1}^{n} X_i}{n}$$

B. The Standard Deviation

The standard deviation (SD) is the positive square root of the variance, and calculated as

$$SD = \sqrt{\frac{\sum X_i^2 - \frac{(\sum X_i)^2}{n}}{n-1}}$$

where, n= no. of observations

and also denoted by subtracting minimum value from maximum value as below

C. Tests of significance

Test of significance are used to estimate the probability that the relationship observed in the data occurred purely by chance was there a relationship between the variables. They are used to test the hypothesis proposed at the start of the study.

In this study Parametric tests were used

a) The data was normally distributed

b) The data was obtained from the sample which is randomly selected

c) The data was quantitative data

I. Srudent T TEST.

T tests are based on the t distribution which is a symmetrical, bell-shaped curve like the normal distribution, but having different area and probability properties.

T distribution is a family of curves which are differentiated by their degrees of freedom.

With increasing sample sizes, the t distribution assumes the shape of the normal distribution. 2 A sample size of 100 is often chosen as the cut-off point for deciding when to apply For t or z.

TYPES OF T TESTS INDICATIONS.

a) Paired T Test

The paired t test is used to decide whether the differences between variables measured on the same or similarly matched individual are on average zero. As the data are matched there must be an equal number of observations in each sample.

Assumption. The paired t-test assumes that the differences in scores between pairs are approximately normally distributed, although the two sets of data under scrutiny do not need to be normally distributed.

b) Unpaired or two-sample t test (equal variance assumed)

The unpaired t test is used for comparing two independent groups of observations when no suitable pairing of the observations is possible. The samples do not need to be of equal sizes.

Assumptions. The test requires the populations to be normally distributed with equal variance, though the test is relatively robust to deviations from these assumptions. Unpaired t test or two-sample t test (unequal variance)

When the variances of the two groups differ and transformation does not produce equal variance, the calculation of the t test becomes more complex. Instead of using the pooled variance, estimates of the individual population variances are used

FORMULA:

$$t = \frac{M_x - M_y}{\sqrt{\frac{S_x^2}{n_x} + \frac{S_y^2}{n_y}}}$$

M =mean

n = number of scores per group

$$S^2 = \frac{\sum (x - M)^2}{n - 1}$$

x = individual scores

M = mean

n= number of scores in group

- Define the problem
- State null hypthesis(H_0) & alternate hypothesis(H_1)
- Find t value, Find (X_1 - X_2)
- Calculate SE of difference between two means

SE = $\sigma\sqrt{1/n_1+1/n_2}$ or

t = (X_1 - X_2) / SE

- Calculate degree of freedom = n_1 + n_2 - 2
- Fix the level of significance (0.05)
- Compare calculated value with table value at corresponding degrees of freedom and significance level
- If observed t value is greater than theoritical t value, t is significant, reject null hypothesis and accept alternate hypothesis

Statistical significance

Level of significance "p" is level of significance signifies as below:

p > 0.05 Not significant (ns)

p <0.05 significant (*)

Measurement of reliability:

To determine intraoperator measurement reliability, measurements of 5 randomly selected study models were done after 10 days by single investigator. All the measurement were recorded on Microsoft excel. Paired t-test was used to determine whether there was any significant difference between the two readings. It was found that there was no statistical significant difference amongst the two readings, hence measurement were found to ne reliable. (Table 3)

Table 3 : Measurement of reliability for amount of tooth movement.

Observation	**Sample size (N)**	**Amount of tooth movement (in mm)**	**Std. Error**	**P value**
Reading 1	5	0.85±0.33	.10588	0.390
Reading 2	5	0.87± 0.36	.11462	

P > 0.05 non significant;* P < 0.05 just significant ; **P < 0.01 significant ; ***P < 0.001 highly significant.

The present study was conducted in the department of Orthodontic & dentofacial Orthopedics, Babu Banarasi Das College of Dental Sciences, Lucknow to evaluate the role of growth factors (Advanced Platelet Rich Fibrin- APRF) in Orthodontic tooth movement. The sample for this split mouth study design consisted of 32 extraction socket of 8 patient with age range of 15-25 years (mean age 19 ± 2.4 years). Sample was divided into two groups, left side served as Control group (Group I- 16 extraction socket) and right side served as Experimental group (Group II – 16 extraction socket) which receives APRF in the extracrion socket just after tooth extraction. Study model was prepared five days after the extraction of 1st premolar (T0) and canine retraction was initiated. Patients were recall at every month interval for a period of three months and study model was prepared to measure the amount of tooth movement that is after 1 month (T1), after 2 month (T2) and after 3 month (T3). For assessing the Orthodontic tooth movement digital vernier caliper was used and the space between the canine and second premolar was measured at different time intervals on all the study model

Tooth movement was measured at different time as follows:

T0- At commencement of tooth movement after extraction

T1- Time of 1st month elapsed after T0

T2- Time of 2nd month elapsed after T1

T3- Time of 3rd month elapsed after T2

Amount of tooth movement was measured at different times interval as follow:

T0-T1= Tooth movement in 1st month

T1-T2= Tooth movement in 2nd month

T2-T3= Tooth movement in 3rd month

Results of the study were summarized in the tables as follows

1. Measurement of mean and S.D values of tooth movement for Group I and Group II at different time interval. **(Table 4)**
2. Comparison between Group I and Group II for each time interval using Paired t-test. **(Table 5)**
3. Intragroup comparison of tooth movement in Group I. **(Table 6)**
4. Intragroup comparison of tooth movement in Group II.**(Table 7)**
5. Comparison of overall tooth movement. **(Table 8)**

Table 4: Descriptive statistics for amount of tooth movement at various time intervals for Group I and Group II

TIME INTERVAL	TOOTH MOVEMENT IN GROUP I (mean±S.D mm)	TOOTH MOVEMENT IN GROUP II (mean±S.D mm)
T0-T1 (tooth movement in 1st month)	0.54 ± 0.16	0.81 ± 0.32
T1-T2 (tooth movement in 2nd month)	0.69 ± 0.29	0.78 ± 0.30
T2-T3 (tooth movement in 3rd month)	0.70 ± 0.20	0.84± 0.23

Table 5 : Comparative statistics of tooth movement between Group I and Group II for each time interval using Paired t- test

TIME INTERVAL	TOOTH MOVEMENT IN GROUP I (mean±S.D mm)	TOOTH MOVEMENT IN GROUP II (mean±S.D mm)	MEAN DIFFERENCE	t value	P VALUE
T0-T1	0.54 ± 0.16	0.81 ± 0.32	0.26	4.71	**0.001*** **
T1-T2	0.69 ± 0.29	0.78 ± 0.30	0.08	1.2	0.247
T2-T3	0.70 ± 0.20	0.84± 0.23	0.13	3.6	**0.002****

P > 0.05 non significant;* P < 0.05 just significant ; **P < 0.01 significant ; ***P < 0.001 highly significant.

For Group I maximum amount of tooth movement was seen in 3rd month (T2-T3) (0.70 ± 0.20mm) followed by 2nd month (T1-T2) (0.69 ± 0.29mm) and then by 1st month (T0-T1) (0.54 ± 0.16mm) (T2-T3>T1-T2>T0-T1) (Table 4).

For Group II maximum amount of tooth movement was seen in 3rd month (T2-T3) (0.84± 0.23mm) followed by 1st month (T0-T1) (0.81 ± 0.32mm) and then by 2nd month (T1-T2) (0.78 ± 0.30mm) (T2-T3>T0-T1>T1-T2) (Table 4).

The mean value for amount of tooth movement at **first month** for Group II was more (T0-T1 = 0.81±0.32mm) when compared to the mean tooth movement for Group I (T0-T1 =0.54±0.16mm). The difference between the two groups was statistically highly significant ($p<0.001$). (Table 5)

The mean value for amount of tooth movement during **second month** for Group II was more (T1-T2= 0.78±0.30mm) when compared to the mean tooth movement for Group I (T1-T2=0.62±0.29 mm). The difference between the two groups was statistically non-significant. ($P>0.05$) (Table 5)

The mean value for amount of tooth movement at **third month** for Group II was more (T2-T3 =0.84±0.23mm) when compared to mean tooth movement for Group I (T2-T3 = 0.70±0.20 mm). The difference between the two groups was statistically significant ($p<0.01$). (Table 5)

Table 6 : Intragroup comparison of tooth movement in Group I at different time interval

TIME INTERVAL	Tooth movement (mean±S.D mm)	Std. Error Mean	95% Confidence Interval of the Difference		T	df	P value
			Lower	Upper			
T0-T1 vs T1-T2	0.14±0.36	.09167	-.34101	.04976	-1.589	15	.133
T1-T2 vs T2-T3	0.02±0.35	.08812	-.20594	.16969	-.206	15	.840
T0-T1 vs T2-T3	0.16±0.21	.05334	-.27744	-.05006	-3.070	15	.008

P > 0.05 non significant;* P < 0.05 just significant ; **P < 0.01 significant ; ***P < 0.001 highly significant.

Table 7 : Intragroup comparison of tooth movement in Group II at different time interval

Time interval	Paired Differences				t	df	P value
	Mean	Std. Error Mean	95% Confidence Interval of the Difference				
			Lower	Upper			
T0-T1 vs T1-T2	0.03±0.48	.12061	-.22269	.29144	.285	15	.780
T1-T2 vs T2-T3	0.03±0.36	.09086	-.22617	.16117	-.358	15	.726
T0-T1 vs T2-T3	0.06±0.41	.10375	-.28802	.15427	-.645	15	.529

P > 0.05 non significant;* P < 0.05 just significant ; **P < 0.01 significant ; ***P < 0.001 highly significant.

Intragroup comparison for **Group I** showed that amount of tooth movement was more in second month (T1-T2) as compared to first month (T0-T1) and the mean difference was 0.14±0.36mm but the difference was statistically non significant (P>0.05) (Table 6).

On comparing the amount of tooth movement occured between second (T1-T2) and third (T2-T3) month. Slightly more tooth movement (0.02±0.35mm) was in third month (T2-T3) as compared to second month (T1-T2) but the difference was statistically non significant (P>0.05) (Table 6)

On comparing the amount of tooth movement between first (T0-T1) and third month (T2-T3) more amount of tooth movement (0.16±0.20mm) was found in third month (T2-T3) in comparison to first month (T0-T1) but the difference was again statistically non significant (P>0.05). (Table 6)

Intragroup comparison for **Group II** showed that amount of tooth movement was more in second month (T1-T2) as compared to first month (T0-T1) and the mean difference was 0.03±0.48mm but the difference was statistically non significant (P>0.05) (Table 7)

On comparing the amount of tooth movement between first (T0-T1) and third month (T2-T3) more amount of tooth movement (0.03±0.36mm) was found in third month (T2-T3) in comparison to first month (T0-T1) but the difference was again statistically non significant (P>0.05). (Table 7)

On comparing the amount of tooth movement between first (T0-T1) and third month (T2-T3) more amount of tooth movement (0.06±0.41mm) was found in third month (T2-T3) in comparison to first month (T0-T1) but the difference was again statistically non significant (P>0.05). (Table 7)

Table 8 : Comparison of overall tooth movement in Group I and Group II

Time interval		Mean±S.D (Tooth movement in mm)	Std. Error Mean	Mean difference	Std deviation	t value	P value
Overall measurement	Group I	1.94±0.40	.10058	-.49688	.37840	5.2	**0.001*** **
	Group II	2.44±0.46	.11534				

P > 0.05 non significant;* P < 0.05 just significant ; **P < 0.01 significant ; ***P < 0.001 highly significant.

On overall comparison of tooth movement but Group I and Group II more tooth movement was found in Group II (2.44±0.46mm) as compared to Group I (1.94±0.40mm) (Table 8).

The aim of Orthodontic treatment is to improve the functional efficiency, structural balance and esthetic harmony by moving teeth to their desirable and stable position. Tooth movement by Orthodontic force application is accompanied by remodelling changes in paradental and dental tissues including alveolar bone, periodontal ligament, pulp and gingiva. Macroscopic and microscopic changes were seen in tissues when exposed to Orthodontic forces of various magnitude, frequency, duration. Mechanical forces enhance vascularity and blood flow and induce strain in periodontal ligament resulting in release of various molecules such as cytokines, neurotransmitter, colony-stimulating factor (CSF) growth factors and arachidonic acid metabolites. These molecules evoke cellular responses by various cell types in and around the teeth, providing an environment for bone resorption and deposition at the site of periodontal ligament tension and compression, resulting in Orthodontic tooth movement.

The long duration of treatment with fixed mechanotherapy is one of the major challenges in Orthodontics and this act major constraint in pursuing treatment, also, if the treatment time prolongs, patient oral hygiene and patient co-operation declines, causing poor oral health.

Acceleration of Orthodontic tooth movement in such cases would be beneficial in terms of treatment duration and patient compliance. Different types of techniques are used in Orthodontics to accelerate tooth movement like mechanical stimulation methods, pharmacological method, low level laser therapy (LLLT) by soft tissue LASERS and surgical methods. Drugs used for Orthodontic tooth movement for fasten tooth movement, had been associated with side effects. LASER procedure need multiple visit and costly equipment. Surgical method used for Orthodontic tooth movement are corticotomy (by Heinrich Kole[11]), piezosurgery, fiberotomy, Wilkodontics, microosteoperforation etc.

Recently , local use of growth factors to promote regeneration and repair had been advocated in tooth extraction socket, sinus agumentation and surgical implant placement for better tissue

healing. Growth factors have the potential to improve wound healing by means of several mechanisms like they have chemotactic activities which attract the inflammatory cell and fibroblasts into the wound, stimulate angiogenesis, and the ingrowth of new blood vessels, stimulate cellular proliferation, and Influence the synthesis of cytokine[16].

Orthodontic tooth movement also requires good vascularity with increased proliferation of various inflammatory cell and fibroblast. As growth factors enhance this process, hence it was anticipated that these will accelerate Orthodontic tooth movement as well.

Platelet-rich fibrin (PRF) was first developed by Choukroun[16] in France which is a second generation platelet concentrate, because the natural concentrate is produced without any anticoagulant agents. After the centrifugation (at 3000 RPM for 1 min) is done three layers had been formed acellular plasma top layer, PRF clot in the middle and the RBC base layer. The PRF clot forms a strong fibrin matrix with a complex three-dimensional architecture, in which most of the platelets from harvested blood are concentrated. Choukroun[16] further modified PRF to Advanced platelet-rich-fibrin (APRF) and Injectable platelet-rich-fibrin (IPRF) , IPRF is a injectable form of PRF obtained at similar speed as PRF but at lesser time (1 min). the protocol of obtaining APRF is using centrifugation speed at 1500 RPM for 14 min. In APRF there was a sustained release of Platelet derived growth factor (PDGF), Transforming growth factor (TGF-β-1), Vascular endothelial growth factor (VEGF), Epidermal growth factor (EGF), Platelet derived endothelial growth factor (PDEGF) and the presence of monocytes/macrophages which further facilitated tissue regeneration and wound healing. APRF is used in implant surgery, periodontal reconstructive surgery, sinus lift, and is furthermore used with freeze-dried bone allograft for improving bone osteogenesis and alveolar stability at the site of implants. Mitrea et al[62], used A-PRF for bone defect resulting from a periapical cyst enucleation. The time of healing of the cystic cavity is 6 months to 1 year, but when the cystic cavity was filled with A-PRF, the healing was accelerated and

period of healing was decreased to three months. Calin et al[40], used mixture of A-PRF and Cerabone for sinus lift for insertion of implant and found that combination of A-PRF and Cerabone in sinus lift technique speed healing time by 50%, thus favoured implant osseointegration. Alhasyim et al[21], used carbonated hydroxyapettite – incorporated APRF in rabbits for post orthodontic tooth stability it was found that Intrasulcular injection of hydrogel Carbonated Apatite Hydrogel (CHA) incorporated APRF can locally reduce orthodontic relapse in rabbits. Locally injected IPRF had been found to be effective in accelerating tooth movement so it was decided to evaluate OTM by placement of APRF in extraction socket (1st premolar extraction socket) and retraction of canine by using NiTi coil spring.

Ghannati et al[34], compared standard PRF (SPRF) and APRF and found that SPRF had dense fibrin clot, minimal interfibnous than APRF that had loose structure and mere inter fibrnous space and cell. They found significantly greater number of neutrophillic granulotcytes and platelet in APRF than SPRF.

Platelets besides releasing molecules like von- willebrand factor, vascular endothelial growth factor (VEGF), platelet derived endothelial growth factor (PDEGF), fibronectin, have the ability to modulate inflammatory response by activating neutrophils and monocyte, lymphocyte. Neutrophil granocytes facilitate movEment of monocyte at surgical site and secrete Matrix metallopeptidase 9 (MMP9).Vascular endothelial growth factor A(VEGF A) that promotes neovascularisation and repair of soft tissues.

The present study was conducted in the Department of Orthodontic and Dentofacial Orthopedics, Babu Banarasi Das College of Dental Sciences, Lucknow with an aim to evaluate the role of growth factors (Advanced Platelet Rich Fibrin- APRF) in Orthodontic tooth movement in patients who had undergone extraction of all 1st premolar. The sample of

this study consisted of 32 extraction sockets of 8 patient with age range of 15-25 (mean age 19 ± 2.4 years). Split mouth study technique was followed were sample was divided into two groups, left side served as Control group (Group I N= 16 extraction sockets) and right side served as Experimental group (Group II N=16 extraction sockets) which received APRF in the extracrion socket just after tooth extraction. MBT priscription (0.022 slot SS) was placed on cases of Angle's class I Bi-maxillary protusion who needed extraction of all 1st premolars. Alignment and levelling was done using preformed NiTi arch wire, followed by 0.016 NiTi, 0.016X0.022 NiTi, 0.017X0.022 NiTi and 0.017X25 SS wire. For anchorage miniscrew were used as in term of anchorage device (TADs, SK surgical) in both maxillary and mandibular arch. Miniscrew of appropriate length and diameter were placed in the inter-radicular area between second premolar and first molar in maxillary and in mandibular arch. Atraumatic extraction of maxillary and mandibular 1st premolar was done for left side.

After a gap of three day atraumatic extraction of 1st premolar of right side was done. At the same time APRF was obtained from the blood drawn from patient antecubital fossa. The blood was collected in Vacutainer and then centrifuged for 14 minute for 1500 rpm. APRF thus obtained time of 1st premolar was placed in extraction socket of maxillary and mandibular premolar of right side (Group II) and suture was placed and 0.017X0.025 SS wire was placed. Canine retraction was started using closed coil spring of 6mm from miniscrew to canine hook and force was standardized to 150 grams using Dontrix gauge. Patients was recalled for 3 consecutive months at one month(T1), two month(T2) and third month(T3) and study model were made. Study model was taken just before extraction and was termed as T0. The study models were used to measured the amount of tooth movement at different time interval (T1,T2 and T3). For assessing the Orthodontic tooth movement digital vernier caliper was used and the space between the canine and second premolar was measured at different time intervals on all the casts. The two beaks of the digital vernier caliper were placed on the

distal contact surface of canine and mesial contact surface of premolar. Data was tabulated and adequate intergroup and intragroup comparison were made.

The result of the present study suggested that APRF significantly accelerated tooth movement in experimental group (Group II) in comparison to control group (Group I). For Group I maximum amount of tooth movement was seen in 3rd month (T2-T3) (0.70 ± 0.20mm) followed by 2nd month (T1-T2) (0.69 ± 0.29mm) and then by 1st month (T0-T1) (0.54 ± 0.16mm) (T2-T3>T1-T2>T0-T1).

For Group II maximum amount of tooth movement was seen in 3rd month (T2-T3) (0.84± 0.23mm) followed by 1st month (T0-T1) (0.81 ± 0.32mm) and then by 2nd month (T1-T2) (0.78 ± 0.30mm) (T2-T3>T0-T1>T1-T2).

On intergroup comparison, the amount of tooth movement at each interval was more in Group II than Group I, however difference was statistical only for T0-T1 and T2-T3.

On intragroup comparison for Group I amount of tooth movement was T1-T2>T0-T1, T2-T3>T1-T2, T2-T3>T0-T1, however difference was statistically non significant.

On comparison for Group II, amount of tooth movement was T0-T1>T1-T2, T2-T3>T1-T2, T2-T3>T0-T1, however difference was statistically non significant.

On overall comparison amount of tooth movement was found significantly more in Group II than Group I.

Previous animal based research investigation and limited clinical studies have shown the effectiveness of platelet based preparation for accelerating tooth movement. The efficacy of PRP and PRF on orthodontic tooth movement has been tested on experimental animals prior to its use on humans including by Rashid et al[1] (dogs), by Gulec et al[18] (rats), by Akbulut et al[43] (male albino rats), by Nakornnoi et al[44] and Alhasyimi et al[21] (on rabbits).

The effect of growth factors on the rate of Orthodontic tooth movement in humans by Timamy et al[46], Mathur et al[55], Erdur et al[51], Zeitounlouian et al[54], Rokia et al[50], Karci et al[53], Pacheco et al[47] and Barhate et al[56]. The result of present study would be compared with previous studies that also assessed effect of on the rate of tooth movement in humans

Timamy et al[46], investigated the effect of local injection of platelet-rich plasma (PRP) on the rate of orthodontic tooth movement on sixteen female patient. In this split mouth study the intervention side received PRP injections with CaCl2 at 0, 3 and 6 weeks while the control side received CaCl2 injection only and the tooth movement was measured for four months from the baseline. Similar to the result of the present study they also found significantly more tooth movement in experimental group (1.55±0.63 mm) as compared to the control group (1.35±0.62 mm) during 1st month. Similar trend was seen for second month (experimental group 1.33±0.87 > control group 1.27±0.04) with statistically non significant difference. For third month, trend was different from present study i.e experimental group (0.59±0.96 mm) < control group (1.01±0.63 mm) with statistical significant difference.The result for overall comparison were contradictory to present study in term of statistical significant difference.

The variation could be attributed to difference in method of obtaining and mode of administration of PRP. Despite of multiple injection at different time interval in their study tooth movement did not show statistical significant amount of tooth movement in experimental group. According to author there is negative feedback mechanism in growth factors which is similar to hormonal negative feedback which occur in relation in increased blood and tissue concentration. Therefore increasing in tissue concentration of growth factors which is incidental to local injection of PRP have affected the production of growth factors during Orthodontic tooth movement.

Mathur et al[55], compared tooth movement using platelet-rich plasma (PRP) in patients with moderate crowding during the leveling and aligning phase using Split-mouth study design. They evaluated tooth movement three times at an interval of 21 days. Similar to present study they found that total tooth movement was more on the experimental side (1.81±0.24 mm) than on control side (1.47±0.24 mm) but they did not make any statistical comparison. Similar to present study amount of tooth movement was significantly more on experimental side (1.04±0.16 mm) than on control side (0.72±0.18 mm) during first time interval. The second and third time interval could be corroborated to second month of measurement in present study which showed statistical insignificant difference in amount of tooth movement between experimental and control group.

Erdur et al[51] , evaluated the efficiency of i-PRF in accelerating canine tooth movement at five time points before tooth extraction (T0), first week (T1), fourth week (T2), eighth week (T3), and 12th week (T4) and they also examined levels of the matrix metalloproteinase-8 (MMP-8), interleukin-1b (IL-1b), receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells ligand (RANKL), and osteoprotegerin (OPG) in the gingival crevicular fluid collected thrice, before extraction (T0), first week (T1), and at the fourth week (T2). In his split mouth design the study group received i-PRF two times, with a 2-week interval and the contralateral side served as the control group and did not receive i-PRF. Overall tooth movement for experimeantal group (6.06 ± 0.29) was significantly more than control group (3.89 ± 0.34) ($P<0.001$). The tooth movement was significantly higher in experimental group than control group for all time interval ($P<0.001$). In the study group, the mean IL-1b, MMP-8, and RANKL values were significantly higher ($P <0.001$), while the mean OPG values were significantly lower ($P <0 .05$). These values of inflammatory markers suggest the underlying mechanism of accelerated tooth movement in experimental group in comparison to control group IL-1b, MMP-8 AND RANKL whereas OPG inhibits osteoclast differentiation by

binding to RANKL. These inflammatory marker play significant roles in reinforcing and activating osteoclast precursor cells. Increased release of these factors is accompanied by higher osteoclast activation and therefore a higher rate of tooth movement was observed.

Zeitounlouian et al[54] , investigate the effectiveness of i-PRF in accelerating maxillary canine retraction in 21 participant with split mouth design.They evaluated tooth movement at 1 month interval for 5 consecutive months. They also evaluated anchorage loss and canine rotation . The i-PRF was injected into the sub mucosa on the buccal and palatal side on the intervention sides through attached gingiva and injection was repeated one month later. Similar to the result of the present study the rate of tooth movement was found more in experimental group (1^{st} month 0.92 ± 0.56mm, 2^{nd} month 1.40 ± 0.83mm, 3^{rd} month 1.46 0.56mm, 4^{th} month 1.14 ± 0.87mm and 5^{th} month 0.68 ± 0.55mm) than control group (1^{st} month 1.25 ± 0.99mm, 2^{nd} month 0.97 ± 0.61mm, 3^{rd} month 1.13 ± 0.60mm, 4^{th} month 0.86 ± 0.71mm and 5^{th} month 1.23 ± 0.31mm) however contrary to present study they found statistical significant difference of second month (P=0.018) of tooth movement whereas it was significant difference in first and third month in the present study. The significant increased in rate in canine retraction observed at second month was nearly 1.5 times greater than on the control side. According to author this acceleration was might be due to cumulative effect of the sequential i-PRF injections performed at T0 and T1. The boost injection further activating a transient acceleratory effect of growth factors and cytokines concentrated in the region.

Pacheco et al[47], conducted a randomized controlled clinical split mouth trial to evaluate the distilization rate and changes in inclination of maxillary canine. The experimental side was treated with L-PRF membrane and other side was control side. The disitlization rate was assessed monthly for 5 months. Contrary to the result of the present study he found that distalization rate of the canines were greater on the control side (0.909 mm) than on the side

treated with L-PRF (0.668 mm) (P<0.05). Difference in the result may be attributed to the variation in clinical technique and use of LPRF as APRF is used in present study.

Karci et al[53] , evaluated and compared the effects of two method of accelerating tooth movement PRF injection and piezocision on twenty-four patients study models were taken at time interval of 2 weeks for 12 weeks. The results would be compared to PRF group and control group. Similar to present study canine distal movement in PRF group (2.83±0.21mm) was significant more than control group (2.04±0.22mm). On comparison at each interval, different was statistical significant for first interval (2 week) only. This result is contrary to our study as we found statistical significant difference for first month and third month as well.

Similar result were found by Barhate et al[56],who evaluated the effect of L-PRF on the rate of maxillary canine retraction in fifteen patient at 1-week (T_1), 2-weeks (T_2), 4-weeks (T_3), and 8-weeks (T_4). Total canine retraction obtained by them was statistically greater in experimental sides (2.43 ± 0.46 mm) than control sides (2.08 ± 0.28 mm) (P = 0.001). However they found significant difference in tooth movement at each time interval T0-T1 (P=0.38), T1-T2 (P=0.002) and T2-T3(P=0.011) in comparison to our result where we found significant difference at first and third month only.

Rokia et al [50], evaluated the effect of i- PRF to accelerate alignment and levelling of the upper anterior teeth and reduce the time required for treatment in 16 patients undergoing Orthodontic treatment at 3-time stages that is after 1st month (T1) after 2nd month (T2) and after completion of levelling and alignment (T3). Patients were divided into two 2 groups: the experimental group received i-PRF and a control group for which only brackets would be applied He found that i-PRF was ineffective in accelerating the alignment and the levelling process (P>0.05) as well as in reducing the time required for treatment (P >0.05). In the

present study overall tooth movement was more on experimental group as compared to control group

The result of animals studies (by Rashid et al[1], by Gulec et al[18], by Akbulut et al[43], Nakornnoi et al[44] and by Alhasyimi et al[21]) also demonstrated acceleration of tooth movement on experimental side in comparison to control.

Rashid et al[1], evaluated the effect of PRP on rate of Orthodontic tooth movement on six skeletally mature male mongrel dogs in whom maxillary second premolar was extracted bilaterally. PRP was injected around the first premolar in one randomly selected maxillary quadrant while the other quadrant served as the control. He found that tooth movement was faster on experiment group during 1st month (6.34±0.66mm) as compared to control group (3.63±0.51mm) whereas, during 2nd month tooth movement was faster in experimental group (15.60±1.74 mm) as compared to control group (9.46±1.23 mm). which was contrary to our study as the movement decreased on 2nd month in present study.

Gulec et al[18], evaluated the effects of different concentrations of PRP on alveolar bone density and Orthodontic tooth movement on seventy six rats. He divided the two groups right side is high concentration PRP (hPRP) and moderate concentration PRP (mPRP) (experimental group) and left side is high conceration PRP control side (hPRP-C) and moderate concentration PRP control side(hPRP-C) . Alveolar bone density was decreased in the experimental groups compared with the control groups (P = 0.0001) whereas, Orthodontic tooth movement in the high-concentration experimental group were 1.7 times greater than in the high-concentration control group and 1.4 times greater than in the moderate-concentration experimental group (P =0.001) on day 21.

Contrary to present study, Akbulut et al[43], evaluated the effects of platelet-rich plasma on orthodontic tooth movement in Wistar male albino rats. He found that the rats in the platelet-

rich plasma group(0.287 ± 0.17mm) showed less tooth movement than those in the control group(0.625 + 0.028) at day 3.

Nakornnoi et al[44], investigated the effects of a local injection of leukocyte-platelet rich plasma (L-PRP) on orthodontic tooth movement in twenty-three male New Zealand white rabbits. He found that significantly higher rate of tooth movement was observed in the experimental side only on days 0–7 (1.04 ± 0.05 mm vs. 0.94 ± 0.09 mm) and 7–14 days (0.58 ± 0.09 mm vs. 0.45 ± 0.12mm). However, the rate of tooth movement between the 2 groups was not significantly different at the intervals of 14–21 days and 21–28 days.

Alhasyimi et al[21], evaluated the effect of carbonated hydroxyapatite(CHA)-incorporated A-PRF on relapse in rabbits. He found that relapse rate of CHA-A-PRF group was lower than that of the other groups, and the relapse distances were significantly lower on days 14 and 21 ($P < .05$).

Other studies that evaluated acceleration of tooth movement using surgical or non surgical methods also showed that tooth movement accelerates but extent was different in different studies.

Khanna et al[63], evaluated the amount of canine retraction with Periodontal Distraction using miniscrew implants and NiTi coil spring in twenty five patients. For each patient left side served as control side (Group I) and right side served as experimental side (Group II). He found significantly higher amount of tooth movement from T0-T1 in Group II than in Group I. No significant difference in amount of tooth movement was observed for T2-T3.

Alikhani et al[64], evaluated the effect of micro-osteoperforation on the rate of toth movement. Maxillary canine were retracted by NiTi coil spring 100 gms force, and movement was measured after 28 days. It was found that canine retraction after first month on experimental

side was 1.1±0.2 mm and on control side was 0.5±0.2 mm and difference was statistically significant.

Bustani et al[65], evaluated maxillary canine retraction with corticotomy-facilitated orthodontics. Surgical holes were made mesially and distally on the experimental side. Canine retraction was done by power chain applying 200 gms of force per side. Rate of canine movement and potential molar anchorage loss were measured after one month using study model. Canine retraction after one month on control side 1.22±0.40 mm was slower than on experimental side 1.74±0.47 mm and difference was statistically significant.

Garg et al[66], evaluated the effectiveness of vibratory stimulation from powered toothbrush as a method of accelerating individual canine retraction in 24 patients undergoing fixed Orthodontic treatment with right side served as a experimental side where patients were asked to apply the vibratory stimulus through powered tooth brush and left side served as control. He found that statistically significant increase in canine movement was seen for total canine movement on right side from (T0-T3) (3.229 ± 1.375 mm), movement from T0-T1 (1.124 ± 0.806 mm) and from T2-T3 (0.990 ± 0.523 mm) as compared to control group total canine movement from (T0-T3) (2.406±1.303 mm), movement from T0-T1 (0.831±0.589 mm) and from T2-T3 (0.755±0.537 mm)

Pavlin et al[4], observed that low-level cyclic loading with AcceleDent increased the rate of orthodontic movement on forty five patient. The subjects were randomized in two groups, vibration group and control group. Cyclic loading was applied to the vibration group for 20 minutes per day using the AcceleDent device. It was found that the mean rate of tooth movement was significantly higher for the AcceleDent group with 1.16 mm/month compared to 0.79 mm/month in the control group, with the mean difference of 0.37 mm/month (P = 0.05).

Shaikh et al[67], evaluated the efficacy of low – intensity laser therapy (LILT) on acceleration of Orthodontic tooth movement and also measured the levels of IL-6 and TNF-α in GCF on twenty patients which divided into experimental (LILT) and control group. It was observed that statistical significance in the rate of tooth movement in the experimental group as compared to control group. Also there was increased in level of IL-6 and TNF-α on experimental side as compared to control side.

Collins et al[9] , evaluated the rate and amount of orthodontic tooth movement by the injection of a vitamin D metabolite 1,25dihydroxycholecalciferol (1,25D) into the periodontal ligament in cats. After 21 days of canine retraction the teeth that had received weekly intraligamentous injections of a solution of 1,25dihydroxycholecalciferol (1,25D) had moved 60% on experimental than control teeth ($P < 0.05$).

Kyrkanides et al[68], evaluated the effect of Nonsteroidal anti-inflammatory drugs in orthodontic tooth movement in rats. It was observed that the use of over-the-counter nonsteroidal anti-inflammatory drugs during tooth movement may result in aberrant remodeling of periodontal vasculature and other structures, which ultimately effect the orthodontic treatment.

The acceleration of tooth movement in APRF group in present study during 1st month could be understood on the basis of its underlying mechanism Orthodontic tooth movement causes mechanical stress to direct osteoblastic and osteoclastic activities which modify bone metabolism. Bone metabolism is regulated by other factors that regulate osteoblastic and osteoclastic activity (e.g inflammatory cytokines , hormones and growth factors). Also surgical intervention because of extraction can induce Regional acceleratory phenomenon[69] (RAP) which also release various inflammatory markers. APRF rich in protein and growth factors (inflammatory marker IL-1b, RANKL and MMP8) and had been used as bioactive

surgical additives in the extraction socket on experimental side as well as presence of RAP accelerated Orthodontic tooth movement during first month in the present study. We observed lesser Orthodontic tooth movement during second month in comparison to first month, this might be attributed to the fact that rapid increase of inflammatory markers during first month resulted in initiation of negative feedback mechanism, to decrease level of cytokines resulting in decreased Orthodontic tooth movement with corresponding activation of OPG during second month. During third month, tooth movement again showed minor increase in comparison to second month that probably due to continuation of normal Orthodontic tooth movement due to removal of negative feedback mechanism and restoration to normal Orthodontic tooth movement in absence of additional growth factors.

The clinical application of the present study suggests APRF can be effective in decrease the overall time duration of treatment. It can be used with conventional Orthodontic treatment routinely to accelerate Orthodontic tooth movement.. It can be good alternative surgical invasive procedure (corticotomy/osteotomy) in adult patients especially when they have specific treatment time goals.

The limitation of this study could be it is invasive procedure that required an additional needle prick for collecting the blood for preparation of APRF . Patients who have phobia of needle (trypan phobia) this procedure would not be tolerated and likely reject the procedure.

Further in- vivo studies are required to assess the effect of APRF on accelerating tooth movement on larger sample size using randomized controlled study design. Effect of APRF can also be evaluated for enmass retraction of anterior teeth using friction or frictionless mechanism.

Following conclusion are drawn from the present study conducted with an aim to evaluate the role of growth factors in Orthodontic tooth movement:

1. Overall tooth movement was significantly higher for Group II than Group I.
2. The amount of tooth movement was significantly higher in Group II than in Group I during first month and third month of observation, similar trend was seen for second month of observation however difference was statisticaly non significant.
3. For both the groups, amount of tooth movement between different time intervals first, second and third months showed statistically non significant difference.

With in the limitation of present study it can be stated that use of APRF can accelerate the tooth movement on experimental side in comparison to control side.

Further studies should aim at conducting the studies on larger sample size or using randomized control study design. Also effect of other growth factors must be assessed or comparison must be done on non surgical method of accelerating tooth movement.

Tooth movement by Orthodontic force application is accompanied by remodelling changes in paradental and dental tissues including alveolar bone, periodontal ligament, pulp and gingiva.The long duration of treatment with fixed mechanotherapy is one of the major challenges in Orthodontics and this act major constraint in pursuing treatment, also, if the treatment time prolongs, patient oral hygiene and patient co-operation declines, causing poor oral health.

Acceleration of Orthodontic tooth movement in such cases would be beneficial in terms of treatment duration and patient compliance. Different types of techniques are used in Orthodontics to accelerate tooth movement like mechanical stimulation methods (Acceledent/ Vibratory tooth brush), pharmacological method, low level laser therapy (LLLT) by soft tissue LASERS and surgical methods (Corticotomy/ Wilckodontics) addition of biological additives like PRP, PRF etc. The evolution from PRP to PRF to APRF for tissue regeneration and repair was based on differentiation of centrifugation speed and time. PRF was platelet rich concentration and anticoagulant.

In APRF there was a sustained release of Platelet derived growth factor (PDGF), Transforming growth factor (TGF-β-1), Vascular endothelial growth factor (VEGF), Epidermal growth factor (EGF), Platelet derived endothelial growth factor (PDEGF) and the presence of monocytes/macrophages which further facilitated tissue regeneration and wound healing. As APRF had greater number of neutrophilic granulocytes and platelet than PRF, it was decided to use same in the present study for accelerating tooth movement.

The present study was conducted in the Department of Orthodontic and Dentofacial Orthopedics, Babu Banarasi Das College of Dental Sciences, Lucknow with an aim to evaluate the role of growth factors (Advanced Platelet Rich Fibrin- APRF) in Orthodontic tooth movement in patients who had undergone extraction of all 1st premolar. The sample of this

study consisted of 32 extraction sockets of 8 patient with age range of 15-25 (mean age 19 ± 2.4 years). Split mouth study technique was followed were sample was divided into two groups, left side served as Control group (Group I N= 16 extraction sockets) and right side served as Experimental group (Group II N=16 extraction sockets) which received APRF in the extracrion socket just after tooth extraction. MBT priscription (0.022 slot SS) was placed on cases of Angle's class I Bi-maxillary protusion who needed extraction of all 1st premolars. Alignment and levelling was done using preformed NiTi arch wire, followed by 0.016 NiTi, 0.016X0.022 NiTi, 0.017X0.022 NiTi and 0.017X25 SS wire. For anchorage miniscrew were used as in term of anchorage device (TADs, SK surgical) in both maxillary and mandibular arch. Miniscrew of appropriate length and diameter were placed in the inter-radicular area between second premolar and first molar in maxillary and in mandibular arch. Atraumatic extraction of maxillary and mandibular 1st premolar was done for left side.

After a gap of three day atraumatic extraction of 1st premolar of right side was done. At the same time APRF was obtained from the blood drawn from patient antecubital fossa. The blood was collected in Vacutainer and then centrifuged for 14 minute for 1500 rpm. APRF thus obtained time of 1st premolar was placed in extraction socket of maxillary and mandibular premolar of right side (Group II) and suture was placed and 0.017X0.025 SS wire was placed. Canine retraction was started using closed coil spring of 6mm from miniscrew to canine hook and force was standardized to 150 grams using Dontrix gauge. Patients was recalled for 3 consecutive months at one month(T1), two month(T2) and third month(T3) and study model were made. Study model was taken just before extraction and was termed as T0. The study models were used to measured the amount of tooth movement at different time interval (T1,T2 and T3). For assessing the Orthodontic tooth movement digital vernier caliper was used and the space between the canine and second premolar was measured at different time intervals on all the casts. The two beaks of the digital vernier caliper were placed on the distal contact surface

of canine and mesial contact surface of premolar. Amount of tooth movement was calculated as difference between amount of extraction space between consecutive time intervals. Data was tabulated and adequate intergroup and intragroup comparison were made

Following conclusion can be drawn from the present study :

- There was significant increased in amount of tooth movement on the experimental group (Right side) as compared to control group (left side) at overall period of time (T0-T3)
- Significant amount of tooth movement was observed on experimental side (right side) as compared to left side at 1st month (T0-T1) and 3rd month (T2-T3).
- Amount of tooth movement was higher in experimental group (Right side) as compared to control side (left side) at 2nd month (T1-T2) but difference was not statistical significant.

The decrease in overall duration of treatment might be attempted using APRF, especially in adult patients who has specific treatment time goals

Further in- vivo studies are required to assess the effect of APRF on accelerating tooth movement on larger sample size using randomized controlled study design. Effect of APRF can also be evaluated for enmass retraction of anterior teeth using friction or frictionless mechanism.

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APPENDIX-I

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES (FACULTY OF BBD UNIVERSITY), LUCKNOW

INSTITUTIONAL RESEARCH COMMITTEE APPROVAL

The project titled "**Role of Growth Factors in Orthodontic Tooth Movement**" submitted by **Dr Kamran Javaid** Post graduate student from the **Department of Orthodontics and Dentofacial Orthopaedics** as part of MDS Curriculum for the academic year 2020-2023 with the accompanying proforma was reviewed by the Institutional Research Committee present on **12th October 2021** at BBDCODS.

The Committee has granted approval on the scientific content of the project. The proposal may now be reviewed by the Institutional Ethics Committee for granting ethical approval.

Prof. Vandana A Pant
Co-Chairperson

Prof. B. Rajkumar
Chairperson

APPENDIX-II

Babu Banarasi Das University
Babu Banarasi Das College of Dental Sciences,
BBD City, Faizabad Road, Lucknow – 226028 (INDIA)

Dr. Lakshmi Bala
Professor and Head Biochemistry and
Member-Secretary, Institutional Ethics Committee

Communication of the Decision of the IXth Institutional Ethics Sub-Committee

IEC Code: 02 **BBDCODS/04/2022**

Title of the Project: Role of Growth Factors in Orthodontic Tooth Movement.

Principal Investigator: Dr Kamran Javaid **Department:** Orthodontics & Dentofacial Orthopaedics

Name and Address of the Institution: BBD College of Dental Sciences Lucknow.

Type of Submission: New, MDS Project Protocol

Dear Dr Kamran Javaid,

The Institutional Ethics Sub-Committee meeting comprising following four members was held on 07th April, 2022.

1.	Dr. Lakshmi Bala Member Secretary	Prof. and Head, Department of Biochemistry, BBDCODS, Lucknow
2.	Dr. Amrit Tandan Member	Prof. & Head, Department of Prosthodontics and Crown & Bridge, BBDCODS, Lucknow
3.	Dr. Rana Pratap Maurya Member	Reader, Department of Orthodontics, BBDCODS, Lucknow
4.	Dr. Akanksha Bhatt Member	Reader, Department of Conservative Dentistry & Endodontics, BBDCODS, Lucknow

The committee reviewed and discussed your submitted documents of the current MDS Project Protocol in the meeting.
The comments were communicated to PI thereafter it was revised.

Decisions: The committee approved the above protocol from ethics point of view.

Forwarded by:

Lakshmi Bala

(Dr. Lakshmi Bala)
Member-Secretary
IEC

Member-Secretary
Institutional Ethic Committee
BBD College of Dental Sciences
BBD University
Faizabad Road, Lucknow-226028

(Dr. Puneet Ahuja)
Principal
BBDCODS

PRINCIPAL
Babu Banarasi Das College of Dental Sciences
(Babu Banarasi Das University)
BBD City, Faizabad Road, Lucknow-226028

Consent Form (English)

Title of the Study: Role of Growth factors in Orthodontic tooth movement.

Study Number……..
Subject's Full Name…….
Date of Birth/Age ……
Address of the Subject…….
Phone no. and e-mail address……
Qualification ……
Occupation: Student / Self Employed / Service / Housewife/
Other (Please tick as appropriate)
Annual income of the Subject……
Name and of the nominees(s) and his relation to the subject…… (For the purpose of compensation in case of trial related death).

1. I confirm that I have read and understood the Participant Information Document dated ……..for the above study and have had the opportunity to ask questions. **OR** I have been explained the nature of the study by the Investigator and had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and given with free will without any duress and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
3. I understand that the sponsor of the project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.
4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
5. I permit the use of stored samples (tooth/tissue/blood) for future research. **Yes [ ] No [ ] Not Applicable [ ]**
6. I agree to participate in the above study. I have been explained about the complications and side effects, if any, and have fully understood them. I have also read and understood the participant/volunteer's information document given to me.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:……..
Signatory's Name……. Date …….
Signature of the Investigator…… Date……..

Study Investigator's Name..... Date……..
Signature of the witness…… Date……..
Name of the witness……
Received a signed copy of the PID and duly filled consent form
Signature/thumb impression of the subject or legally Date……..
Acceptable representative

सहमति पत्र

अध्ययन का शीर्षक :- ऑर्थोडोंटिक टूथ मूवमेंट में वृद्धि कारकों की भूमिका।

अध्ययन संख्या ....
तिर्य का पूरा नाम .....
ज□ की ि◌ारीख / आयु .....
तिर्य का पिा .....
फोन नंबर। और ई-मेल पिा .....
योग्यिा .....
व्यिसाय: छात्र / स्वयं कायषरि / सेि◌ा / गृतहणी / अन्म (कृपया उतिि◌ के रूप में तितिि◌ करें)

तिर्य की ि◌ातर्षक आय .....

नाम और नामांतकि व्यक्ति (नाम) और उनके तिर्य के संबंध में ..... (प्रयोजन के तलए मुकदमा संबंतधि मौि◌ के मामले में मुआिजे)

1. मैं पुति करिा हं तक मैंने प्रतिभागी सूि◌ना दस्ताि◌ेज को पढ़ तलया है और समझ तलया है .... इसके बाद के अध्ययन के तलए और सिाल पूछने का अिसर तमला है। या मुझे अन्वेर्क द्वारा अध्ययन की प्रकृति समझाई गई है और सिाल पूछने का अिसर तमला है।

2. मैं समझिा हं तक अध्ययन में मेरी भागीदारी स्वैक्तिक है और तबना तकसी दबाि◌ के स्विंत्र इि◌ के साथ दी गई है और तकसी भी कारण के तबना तकसी भी समय तबना तकसी मेतिकल देखभाल या कानूनी अतधकारों को प्रभातिि◌ तकए तबना तकसी भी समय मैं ि◌ापस लेने के तलए स्विंत्र हं।

3. मैं समझिा हं तक इस पररयोजना के प्रायोजक, प्रायोजक की ओर से काम करने ि◌ाले अन्म लोग, एतथक्स कमेरी और तनयामक प्रातधकरणों को मेरे मौजूदा अध्ययन के संबंध में अपने स्वास्थ्य के ररकाि◌ष को देखने की मेरी अनुमति की आिश्यकिा नहीं है और आगे की शोध इसके संबंध में आयोतजि तकया जा सकिा है, भले ही मैं परीक्षण से ि◌ापस ले जाऊं। हालांतक, मैं समझिा हं तक मेरी पहिान ि◌ीसरी पारी के तलए जारी तकसी भी जानकारी या प्रकातशि में प्रकर नहीं होगी।

4. मैं इस अध्ययन से उत्पन्न तकसी भी ि◌ेरा या पररणामों के उपयोग को प्रतिबंतधि करने के तलए सहमि नहीं हं एक प्रयोग केि◌ल ि◌ैज्ञातनक उद्देश्य (प्रयोजनों) के तलए ह

5. भतिष्य के अनुसंधान के तलए मैं संग्रहीि◌ नमूने (दांि◌ / ऊिक / रि) का उपयोग करने की अनुमति देि◌ा हं हा◌ॅ ◌ॅं नही [ ]

6. मैं उपरोि◌ अध्ययन में भाग लेने के तलए सहमि हं। मुझे जतरलिाओं और साइि इफेक्ट्स, यतद कोई हो, के बारे में समझाया गया है और उन्हें पूरी ि◌रह से समझा है। मैंने प्रतिभागी /स्वयंसेि◌क के सूि◌ना दस्ताि◌ेज को भी पढ़ा और समझ तलया है

प्रतितनतध: ....

हस्ताक्षरकिाष का नाम ..... िारीख .....।

अन्वेर्क के हस्ताक्षर ..... तदनांक ....

अध्ययन अन्वेर्क का नाम ..... तदनांक ....

गिाह के हस्ताक्षर ..... तदनांक ....

गिाह का नाम .....

पीआइी की एक हस्ताक्षररि प्रति और तितधिि भरी सहमति फॉमष प्राप्त तकया

तिर्य के हस्ताक्षर / अंगूठे का प्रभाि या कानूनी िौर पर तदनांक .... स्वीकायष प्रतितनतध

Babu Banarasi Das College of Dental Sciences

(Babu Banarasi Das University)
BBD City, Faizabad Road, Lucknow – 227105
(INDIA)

Guidelines for Devising a Participant / Legally Acceptable Representative InformationDocument (PID) in English

Guideline for preparation of the participant information document	
While submitting your project report to the Institutional Ethics Committee, ensure that you have included participant information document and an informed consent form that is prepared as per the guidelines for Good Clinical Practice-Centre for Drug Candidate Optimization (GCP-CDCO2001), International Conference on Hormonization-Good Clinical Practice (ICH – GCP), ICMR ethical guidelines 2006, and the Declaration of Helsinki. The document is important because it enables the participants to make an informed choice. It also has got to be unique because no two research projects are identical. **The participant information document (PID should include only those headings listedbelow which are relevant to that study. Any further information you wish to add, is your choice.**	
1.	Participant information document and an consent form **in English and Hindi** (otherlanguages if required)
2.	Font: Arial spacing of lines with 1.5
3.	Size: 12
4	All the consent forms must have Version No, Date, Page no **in the footer**
5.	In the case of participants with age≥ 18 yrs, PID and consent form should be attached while inthe case of participant's age≤ 18 yrs and ≥ 8 yrs the above along with information documentand assent form for children (minor) should be attached. In the case of ≤ 8 it will be signed by the guardian.

Potential recruits to your research/trial study must be given sufficient information to allow them to decide whether or not they want to take part. The Information Document should contain information under the headings given below, and preferably in the order specified. It should be written in simple, non-technical terms and be easily understood by a lay person. Use short words, sentences and paragraphs.

1. **Study Title**

Role of growth factors in orthodontic tooth movement.Invitation Paragraph

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research/study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your treating physician/family doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

2. **What is the purpose of the study?**

The purpose of this study is to evaluate and compare the rate of tooth movement by the use of growth factors.

3. **Why have I been chosen?**

As you fulfill the criteria needed for this study .

4. **Do I have to take part?**

It will be your decision after knowing the details of study.

5. **What will happen to me if I take part?**

You will not be harmed. For fixed orthodontic treatment you have to come for every month during that period the study will be completed.

6. **What do I have to do?**

You have to come to the given appointment.

7. **What is the procedure that is being tested?**

The procedure will involve to evaluate the role of growth factors in orthodontic tooth movement.

8. **What are the interventions for the study?**

For fixed orthodontic tooth movement growth factors will be injected after the extraction , in the socket of tooth through syringe.

9. What are the side effects of taking part?
There will be no side effects.

10. What are the possible disadvantages and risks of taking part?
There are no risk.

11. What are the possible benefits of taking part?

Orthodontic tooth movement might be fasten .

12. What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the research being studied. If this happens, your researcher will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your researcher/investigator will make arrangements for your withdrawal. If you decide to continue in the study, you may be asked to sign an updated consent form.

13. What happens when the research study stops?
If the study stops/finishes before the stipulated time, this will be explained to the patient/volunteer.

14. What if something goes wrong?
If any severe adverse event occurs, or something goes wrong during the study, the

complaints will be handled by reporting to the institution (s), and Institutional ethical

community.

15. Will my taking part in this study be kept confidential?

Yes

16. What will happen to the results of the research study?
The results of the study will be used to be compare the rate of tooth movement on the control side and the experimental side.

17. Who is organizing the research?

This research study is organized by the academic institution (BBDCODS).

18. Will the results of the study be made available after study is over?
Yes

19. Who has reviewed the study?

The study has been reviewed and approved by the Head of the Dept, and the IEC/IRC of
the institution.

20. Contact for further information

Dr. Kamran javaid
Department of Orthodontics and Dentofacial Orthopaedics
Babu Banarasi College of Dental Sciences.
Lucknow-227105

Mob- 7275419006

Dr. Rohit khanna (Professor)
Department of Orthodontics and Dentofacial Orthopaedics
Babu Banarasi College of Dental Sciences.
Lucknow-227105
Mob-9415037011

Dr. Tripti Tikku(HOD)
Department of Orthodontics and Dentofacial Orthopaedics
Babu Banarasi College of Dental Sciences.
Lucknow-227105
Mob-9554832799

Signature of PI.....

Name.....

Date.....

Babu Banarasi Das College of Dental Sciences

(Babu Banarasi Das University, Lucknow)

BBD City, Faizabad Road, Lucknow – 227105 (INDIA)

प्रतिभागी के लिए सूचना पत्र

1.अध्ययन शीर्षक

ऑर्थोडोंटिक टूथ मूवमेंट में वृद्धि कारकों की भूमिका।

2. निमंत्रण अनुच्छेद

आपको एक शोध अध्ययन में भाग लेने के लिए आमंत्रित किया जा रहा है। निर्णय लेने से पहले आपके लिए यह समझना महत्वपूर्ण है कि शोध/अध्ययन क्यों किया जा रहा है और इसमें क्या शामिल होगा। कृपया निम्नलिखित जानकारी को ध्यान से पढ़ने के लिए समय निकालें और यदि आप चाहें तो दोस्तों, रिश्तेदारों और अपने इलाज करने वाले चिकित्सक/पारिवारिक चिकित्सक के साथ इस पर चर्चा करें। हमसे पूछें कि क्या कुछ ऐसा है जो स्पष्ट नहीं है या यदि आप अधिक जानकारी चाहते हैं। यह तय करने के लिए समय निकालें कि आप भाग लेना चाहते हैं या नहीं।

3. अध्ययन का उद्देश्य क्या है ?

इस अध्ययन का उद्देश्य विकास कारकों के उपयोग द्वारा दांतों की गति की दर का मूल्यांकन और तुलना करना है ।

4. मुझे इस अध्ययन के लिए क्यों चुना गया है?

जैसा कि आप इस अध्ययन के लिए आवश्यक मानदंडों को पूरा करते हैं ।

5. क्या इसमें मुझे भाग लेना चाहिए ?

अध्ययन का विवरण जानने के बाद यह आपका निर्णय होगा।

6. मुझे क्या होगा यदि मैं इस अध्ययन में भाग लेता हूं।

आपको नुकसान नहीं होगा। निश्चित ओर्थोडोंटिक उपचार के लिए आपको हर महीने आना होगा उस अवधि के दौरान अध्ययन पूरा हो जाएगा ।

7. मुझे क्या करना है?

आपको दिए गए अपॉइंटमेंट पर आना होगा।

8. किस प्रक्रिया का अध्ययन किया जा रहा है?

प्रक्रिया में ऑर्थोडोंटिक टूथ मूवमेंट में वृद्धि कारकों की भूमिका का मूल्यांकन करना शामिल होग।

9. इस शोध में कौन से हस्तक्षेप दिए जाएंगे?

ऑर्थोडॉन्टिक दांत आंदोलन के लिए वृद्धि कारकों को निष्कर्षण के बाद इंजेक्ट किया जाएगा, सिरिंज के माध्यम से दांत के सॉकेट में।

10. इस अध्ययन में भाग लेने के क्या दुष्प्रभाव हैं ?

कोई नुकसान नहीं होगा ।

11. इस अध्ययन में भाग लेने के संभावित जोखिम और नुकसान क्या है?

कोई जोखिम नहीं होगा ।

12. अध्ययन में भाग लेने के संभावित लाभ क्या है?

ऑर्थोडॉन्टिक दांत गति तेज हो सकता है।

13. क्या होगा यदि कोई नई जानकारी उपलब्ध हो जाती है ?

कभी-कभी एक शोध परियोजना के दौरान, अध्ययन किए जा रहे शोध के बारे में नई जानकारी उपलब्ध हो जाती है। यदि ऐसा होता है, तो आपका शोधकर्ता आपको इसके बारे में बताएगा और आपसे चर्चा करेगा कि क्या आप अध्ययन जारी रखना चाहते हैं। यदि आप वापस लेने का निर्णय लेते हैं, तो आपका शोधकर्ता/अन्वेषक आपकी निकासी की व्यवस्था करेगा। यदि आप अध्ययन जारी रखने का निर्णय लेते हैं, तो आपको एक अद्यतन सहमति फॉर्म पर हस्ताक्षर करने के लिए कहा जा सकता है।

14. क्या होता है जब अध्ययन / शोध परीक्षण बंद हो जाता है।

यदि अध्ययन निर्धारित समय से पहले रुक जाता है / समाप्त हो जाता है, तो इसे समझाया जाएगा ।

15. क्या होगा अगर कुछ गलत हो जाता है?

यदि कोई गंभीर प्रतिकूल घटना होती है, या अध्ययन के दौरान कुछ गलत होता है, तो संस्थान (एस), और संस्थागत नैतिक समुदाय को रिपोर्ट करके शिकायतों को नियंत्रित किया जाएगा।

16. क्या इस अध्ययन में मेरा हिस्सा गोपनीय रखा जाएगा?

हां ।

17. अध्ययन / शोध परीक्षण के परिमाण का क्या होगा?

अध्ययन के परिणामों का उपयोग नियंत्रण पक्ष और प्रायोगिक पक्ष पर दांतों की गति की दर की तुलना करने के लिए किया जाएगा।

18. इस अध्ययन को कौन आयोजित कर रहा है और इस परीक्षण के लिए धन कहां से आएगा।

यह शोध अध्ययन शैक्षणिक संस्थान (बीबीडीसीओडीएस) द्वारा आयोजित किया जाता है।

19.क्या सेवाएं शोध खत्म हो जाने के बाद उपलब्ध रहेगी या नहीं?

हां।

20.अध्ययन की समीक्षा किसने की है?

अध्ययन की समीक्षा की गई है और विभाग के प्रमुख, और आईईसी/आईआरसी के द्वारा अनुमोदित किया गया है। निम्न लोगों से संपर्क करें

21.अधिक जानकारी के लिए संपर्क करें ।

डॉ कामरान जावेद
ऑर्थोडोंटिक्स और डेंटोफेशियल ऑर्थोपेडिक्स विभाग
बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज।
लखनऊ-227105

मोब- 7275419006

डॉ रोहित खन्ना (प्रोफेसर
ऑर्थोडोंटिक्स और डेंटोफेशियल ऑर्थोपेडिक्स विभाग
बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज।
लखनऊ-227105
मोब-9415037011

डॉ तृप्ति टिक्कू (एचओडी)

ऑर्थोडोंटिक्स और डेंटोफेशियल ऑर्थोपेडिक्स विभाग

बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज।

लखनऊ-227105

मोब-9554832799

bbdcods.iec@gmail.com

पीआईकाहस्ताक्षर .....

नाम .....

दिनांक.....

Measurement Chart

Sample	T0 Right	T0 Left	T1 Right	T0-T1 RIGHT	T1 Left	T0-T1 LEFT	T2 Right	T1-T2 RIGHT	T2 Left	T1-T2 LEFT	T3 Right	T2-T3 RIGHT	T3 LEFT	T2-T3 LEFT
1	7.2	7.1	6.05	1.15	6.52	0.58	5.07	0.98	5.7	0.82	4.57	0.5	5.04	0.66
	7.05	7.19	6.3	0.75	6.55	0.64	6	0.3	6.1	0.45	5.26	0.74	5.6	0.5
2	6.29	5.64	5.71	0.58	5.05	0.59	4.57	1.14	4.4	0.65	3.8	0.77	3.76	0.64
	6.82	6.89	6.61	0.21	6.72	0.17	5.42	1.19	6.1	0.62	4.5	0.92	5.4	0.7
3	7.1	6.64	6.01	1.09	6.08	0.56	5.6	0.41	5.71	0.37	4.38	1.22	4.98	0.73
	7.03	7.2	6.49	0.54	6.79	0.41	5.98	0.51	6.1	0.69	4.83	1.15	5.23	0.87
4	7.05	7.5	6.17	0.88	6.9	0.6	5.8	0.37	6.01	0.89	4.85	0.95	5.03	0.98
	7.16	7.04	6.01	1.15	6.36	0.68	5.03	0.98	5.55	0.81	3.7	1.33	4.3	1.25
5	7.39	7.16	6.26	1.13	6.55	0.61	5.7	0.56	6.05	0.5	4.77	0.93	5.36	0.69
	7.82	7.89	7.51	0.31	7.62	0.27	6.32	1.19	6.01	1.61	5.65	0.67	5.55	0.46
6	5.64	5.18	4.67	0.97	4.54	0.64	3.78	0.89	3.96	0.58	2.98	0.8	3.2	0.76
	5.58	5.15	4.32	1.26	4.6	0.55	3.44	0.88	3.98	0.62	2.8	0.64	3.32	0.66
7	7.17	6.83	6.25	0.92	6.13	0.7	5.31	0.94	5.53	0.6	4.47	0.84	4.76	0.77
	7.03	7.22	6.44	0.59	6.78	0.44	5.81	0.63	6.35	0.43	5.12	0.69	5.82	0.53
8	7.17	7.06	6.19	0.98	6.26	0.8	5.21	0.98	5.34	0.92	4.33	0.88	4.59	0.75
	7.01	7.1	6.48	0.53	6.61	0.49	5.94	0.54	6.11	0.5	5.41	0.53	5.71	0.4

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Introduction 2
Orthodontic tooth movement is caused by modelling and remodelling of supporting alveolar bone under the influence of various changes at cellular and molecular level in periodontal ligament (PDL). The oldest theory of Orthodontic tooth movement (OTM) that is pressure tension theory stated that side towards which tooth movement occurs undergoes resorption with compression of PDL fibres whereas on the opposite side, that is tension side deposition occur with stretching of PDL fibres. Signaling molecule involved in OTM are neurotransmitters, cytokines, growth factors, colony-stimulating factors, and arachidonic acid metabolites 1 .