Dear Editor and Reviewers,

We are re-submitting our revised manuscript entitled "Rescue of "Hopeless" Avulsed Teeth using Autologous Platelet-Rich-Fibrin following Delayed Reimplantation: Two Cases Report". We are grateful for your time, effort, thoughtful suggestions and insightful recommendations, which we believe have greatly improved our manuscript. We have read the comments and suggestions carefully and have made corresponding revisions as appropriate, which we hope will meet with your approval. Below, please find our replies (in blue text) to each of the points. The relevant modifications are highlighted in yellow in our revised manuscript.

To Reviewer 1

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Please do the correction according to the comments

Response： We thank the Reviewer for the kind suggestion.

To Reviewer 2

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The paper is very interesting, well wrriten. Images are adequate and very clear. The paper can be considered for publication after minor revisions, in particular some topics need to be addressed:

1. Which is the role of orthodontics in this cases? Please cite DOI 10.1177/1721727X1201000208

Response： Thank you for your advice. Since the two cases in our MS did not involve orthodontic treatment, I am sorry that I did not catch your meaning. The recommended reference by DOI 10.1177/1721727X1201000208 has been read carefully, but we failed to find the appropriate place to insert. A further explanation would be highly appreciated.

2. Which is the role of implantology without grafting? You should describe also a scale of evaluation and possible application in systemic (e.g. diabetes) patients. So you should cite DOI10.3390/ijerph191811735, DOI10.3390/app12136729, DOI10.3390/ijerph19095139 and DOI10.23805/JO.2018.10.04.04

Response： Thank you for your advice. Since the two cases in our MS did not involve implantation treatment, I am sorry that I did not catch your meaning. The recommended references by DOI10.3390 / ijerph191811735, DOI10.3390 /a pp12136729, DOI10.3390 / ijerph19095139 and DOI10.23805 / JO.2018.10.04.04 have been read carefully, but we failed to find the appropriate place to insert. A further explanation would be highly appreciated.

To Reviewer 3

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

1. It has been reported in the literature that periodontal healing can be achieved if the avulsed tooth is reimplanted within 5 minutes. If reimplantation is delayed for more than 1 hour after avulsion, then complete necrosis of the injured periodontal ligament tissue is expected [18]. your cases were avulsed for 18 and 2 hours do you have evidences that PDL could be vital in a contaminated environment and regain its vitality by PRF

Response： We appreciate the thorough reading by the reviewer. We agree that in the two cases in this study, all the lost teeth were dried and preserved outside the mouth for more than 1h, which could be considered as all the PDL on the tooth root surface had been necrotic. To further investigate the possible methods and mechanisms of promoting periodontal membrane healing after delayed reimplantation of the improperly preserved avulsed tooth, in our previously published work [*Zhao YH, et al. Biomaterials 2013; 34:5506-5520*], periodontal healing of avulsed teeth following tooth reimplantation were evaluated using animal models. Incisors of the dog were carefully extracted. Immediately after extraction, all teeth were cleaned with flowing physiological saline and kept dry on a metal tray at room temperature for 2 h . Before reimplantation, the root surfaces of the extracted teeth were cleaned and polished with sterile gauze and physiological saline to remove the necrotic tissues to simulate the delayed

reimplantation of dry-reserved avulsed teeth (Figure S1). In accordance with the random number table, the 36 dog incisors were randomly divided into four groups according to the adjuvant graft that was used: Group I, adjuvant use of the PDLSCs/PRF construct; Group II, adjuvant use of cell sheet fragments only; Group III, adjuvant use of the PRF granules only; and Group IV, without adjuvant graft (Figure S2). We found that there were a large number of BrdU-positive transplanted cells in Group I and II, suggesting that the transplanted PDLSCs were not only survive but also participated the repair and regeneration of new PDL tissues. Compared to Group I, the BrdU-negative cells, which might be derived from the remaining PDL within original alveolar socket or the circulating cells, also participated in the periodontal healing in Group II. The potential reason was that the proliferation of the transplanted PDLSCs in Group II was less effective than that was in Group I due to the lack of PRF. In such situation, the host stem cells were homing to the injury sites to facilitate regeneration. Second, the PRF can inhibit the osteogenic differentiation of PDLSCs, as demonstrated in cell culture, and hence reduces replacement resorption in vivo. Both the ECM and PRF predominantly consist of fibrins, which play the role of the isolator between the bone and the root and reduce the occurrence of ankylosis. In addition, the high density leukocytes in the PRF could produce an anti-inflammatory and immunoregulatory effect to promote healing and reduce inflammatory resorption. As a result, we observed that there were still PDL-like structures being observed in Group III (Figure S2 and S3)., suggesting that a few PDL tissues still remained in the alveolar socket after tooth avulsion, which would have contained PDL cells, including stem cells, thus supporting PDL formation. Furthermore, these circulating MSCs migrate to the local area through cell -homing in response to a variety of growth factors in natural proportions release by the PRF.

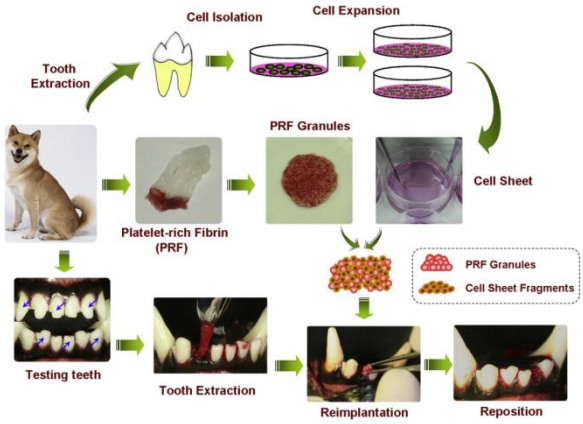

Figure S1. Animal model for delayed reimplantation of dry-reserved avulsed teeth.

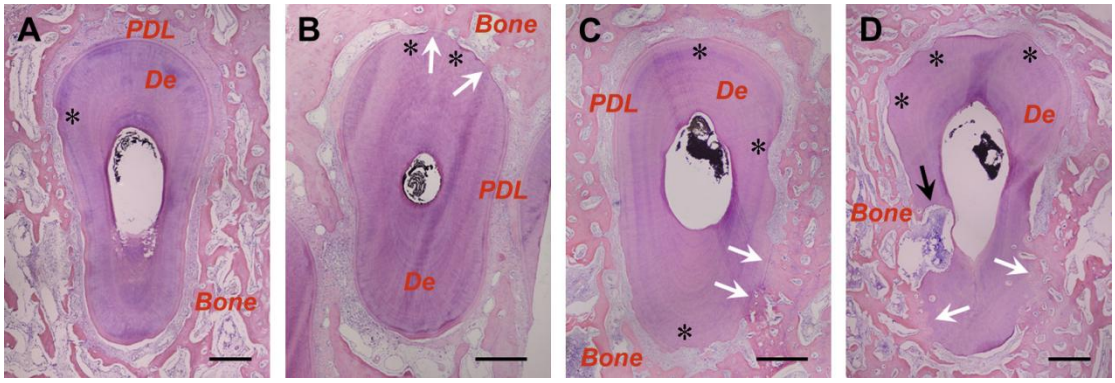

Figure S2. Representative panoramic images of periodontal healing in the different groups. (A) Group I: The ideal regeneration of periodontium was identified that manifested by the formation of well-organized periodontal ligament (PDL)-like tissues with very few places of pathologic resorptions (*); (B) Group II and (C) Group III: Small areas of ankylosis (white arrow) and surface resorption (*) of the tooth root could be found; (D) Group IV: The negative control group showed large areas of ankylosis (white arrow), surface resorption (*) of the tooth root, and severe inflammatory resorption (black arrow) (hematoxylin-eosin staining, magnification: 40 , scale bar ¼ 1 mm). Notes: PDL, periodontal ligament-like tissues; Bone, alveolar bone; De, dentine.

Groups	Treatment	New-born PDL-like tissues (%)	Replacement resorption (%)	Surface resorption (%)	Inflammatory resorption (%)
		$\bar{x}(\%) \pm$ s.d., X^*	$\bar{x}(\%) \pm$ s.d., X^*	$\bar{x}(\%) \pm$ s.d., X^*	$\bar{x}(\%) \pm$ s.d., X^*
I ($n = 9$)	PDLSCs/PRF	45.83 ± 8.84, 9^{d}	6.94 ± 9.08, 4^{c}	47.22 ± 8.33, 9	0^{b}
II ($n = 8$)	PDLSCs	35.94 ± 14.07, 8^{c}	14.06 ± 10.43, 6^{c}	39.06 ± 12.39, 8	10.94 ± 15.58, 3
III ($n = 7$)	PRF	30.36 ± 6.68, $7^{c,e}$	16.07 ± 9.45, 6^{b}	51.79 ± 13.36, 7	1.79 ± 4.72, 1^{b}
IV ($n = 7$)	control	12.50 ± 10.21, 5	30.36 ± 6.68, 7	39.29 ± 13.36, 7	17.86 ± 14.17, 4

Notes:
n = the number of teeth examined in each group.
$\bar{x}(\%)$ = the group pathology index mean value.
X^* = the number of teeth demonstrating a particular type of periodontal change.
[a] Statistical comparisons were performed by using the Kruskal–Wallis test and Mann–Whitney U test ($P = 0.05$); the percentage of each healing pattern was selected as index and the results were expressed as mean percentage ± standard deviation (s.d.).
[b] $P < 0.05$, in comparison to Group IV (control).
[c] $P < 0.01$, in comparison to Group IV (control).
[d] $P < 0.001$, in comparison to Group IV (control).
[e] $P < 0.01$ in comparison to Group I.

Figure S3. Histological evaluation of periodontal healing pattern for different groups

2. All of the available references including your reference did not include avulsed teeth with the PDL totally lost (did not mention the time and condition of reimplantation)

Response： We appreciate the reviewer's comments. IADT guidelines indicate that the activity of periodontal ligament cells (PDLCs) can be considered to be basically lost if the overall drying time for the avulsed tooth is longer than 1h [Ref. 22]. Previous studies also showed that PDLCs were considered to be basically alive if the drying time kept within 5 min; the PSLCs were considered to be partially necrotic if the drying time was less than 60 min; while they were considered to be almost necrotic if the drying time was longer than 60 min [Ref. 26]. In our previous animal experiments, the drying time of isolated teeth was 2h. The results showed that, compared with the control group, the probability of periodontal healing was significantly

promoted, indicating that a certain probability of periodontal healing could still be achieved with PRF replantation for dry-preserved teeth for more than 1h [Ref. 20]. In addition, there were also cases reported that PRF replantation combined with 5h avulsed teeth achieved good results [Ref. 31]. These documents have been cited and are listed in the **References** part.

3. Therefore, we used PRF together with replantation to reduce the probability of root resorption. (what is the mechanism behind that)

Response： We thank the reviewer for this helpful suggestion. As for the mechanism of PRF reducing root absorption of avulsed teeth, it is mainly believed that there are two reasons as follows. First, the periodontal ligament tissues remain within the original alveolar socket, which contains periodontal ligament cells and stem cells. During the tissue repair process, multiple growth factors are released by the PRF. Additionally, cell homing will occur, and host stem cells from the circulation will be recruited to the injury region by factors released by the PRF to promote their proliferation and induce their differentiation toward the periodontal membrane, facilitating the formation of periodontal membrane-like structures [20,32]. Second, we have shown that PRF consists of concentrated blood platelets, and the α-granules could be activated and degranulated. Thus, many growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) enable to released at least a week and up to 4 weeks which means that the PRF stimulates its environment for a significant time during remodeling [11,20,31,33-35]. These growth factors increase the mitotic activity of periodontal fibroblasts by 20%–37% [36], thereby improving the proliferation and periodontal differentiation of target cells and further promote periodontal healing of avulsed teeth [20]. Thanks for the pertinent suggestions from the Reviewer, we have added above-mentioned details into the 4th Paragraph of the Discussion part, as highlighted in yellow. Accordingly, the relative new references have been integrated into the References part of the revised MS.

4. It is not clear if the root surface obtain some treatment to get rid of necrotic periodontal tissues

Response： We appreciate the reviewer's comments. As for the treatment of the root surface of avulsed tooth, many scholars have done researches in the early stage, but the controversy existed. For example, some scholars found that removing the inactive periodontal tissue on the root surface of the avulsed tooth and using citric acid to decalcialize the root surface can significantly reduce the occurrence of pathological absorption. Some researchers believed that slight decalcification caused by 24% EDTA treatment for the tooth surface cannot promote the regeneration of collagen fibers in the periodontal tissue, nor can it prevent the root absorption of replanted teeth. In addition, some scholars applied enamel matrix protein (EMP) derivatives locally during the replantation of avulsed teeth, but the clinical effect still kept controversial. Iqbal et al. found that enamel matrix protein derivatives are beneficial to the recovery of periodontal tissue and can effectively reduce the occurrence of tooth root fixation. However, some scholars believed that Emdogain, a derivative of enamel matrix protein, did not significantly promote the periodontal healing of the replanted tooth. In brief, although several studies by using dexamethasone, ethylene diamine tetraacetic acid (EDTA), propolis, alendronate, steroids and fluoride for treating the root surface of the avulsed teeth immediately prior to replantation, there is currently no ideal solution having evidence-based proof or getting consistent recommendations to prevent from root resorption [Ref. 7-11]. The relative explanation highlighted in yellow has been added into the **Introduction** part of the revised MS.

5. These growth factors increase the proliferation and periodontal differentiation of target cells and further promote periodontal healing of avulsed teeth [15]. we do have debate in the literature regarding the effect of release of such group of GF together if their is an antagonistic or synergistic or no actions and if these concentrations are stimulatory

Response： We appreciate the thorough reading by the reviewer. PRF is indeed rich in a variety of growth factors, and the amount and continuous release of these growth factors have been detected in our previous animal experiments (Fig. S4). We agree with the Reviewer that the roles of different growth factors played in the process of regeneration and repair of the injuried tissues differed. For example, TGF-β has a very obvious role in promoting cell fibrosis, manifested by a large number of matrix synthesis such asWe appreciate the thorough reading by the reviewer type I collagen and fibronectin; PDGF can promote cell migration and proliferation. IGF can also

promote cell proliferation and differentiation. The above three growth factors all play important roles in the initial tissue healing by promoting cell migration and proliferation, inducing fibrin matrix remodeling, and promoting the secretion of collagen matrix. However, when a variety of growth factors act together, synergistic or even antagonistic effects among them cannot be ruled out. Therefore, the natural proportion of various growth factors is particularly important, which is just one of the important reasons why we choose PRF, which contains a large number of active growth factors. These factors are not only rich in content and variety in PRF, but also kept natural proportion under normal physiological conditions. Only by synergic effects of them, can they jointly maintain the balance of tissue environment, and plays an important role in regulating wound healing and tissue regeneration. We have added above-mentioned content into the 4th Paragraph of the Discussion part, as highlighted in yellow.

Samples	TGF-β1 (*pg*)	PDGF-AB (*pg*)	IGF-1 (*pg*)	VEGF (*pg*)	EGF (*pg*)
PRF releasate					
0–24 h	3521.57 ± 231.24	2210.35 ± 166.41	6754.60 ± 502.63	632.05 ± 57.66	1428.31 ± 124.01
24–48 h	2919.33 ± 159.21	696.21 ± 84.80	8855.51 ± 1122.25	211.71 ± 27.43	876.92 ± 74.86
48–72 h	1341.77 ± 107.11	263.97 ± 33.34	6640.87 ± 462.40	125.61 ± 15.39	860.53 ± 95.19
72–96 h	1382.99 ± 111.73	363.32 ± 43.14	5523.50 ± 635.71	112.71 ± 23.11	554.12 ± 47.13
96–120 h	1555.54 ± 121.58	341.89 ± 28.02	5189.12 ± 557.84	122.21 ± 19.11	355.61 ± 25.11

Abbreviations: PDGF-AB, platelet-derived growth factor; TGF-β1, transforming growth factor-β1; IGF-1, insulin-like growth factor-1; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor.

Figure S4. The amount of released growth factors from PRF membrane that derived from 10 mL blood for a serial of 5 days determined by enzyme linked immunosorbent assay.

6. Previous studies have shown that PRF can inhibit the osteogenic differentiation of periodontal ligament stem cells (PDLSCs) in vitro, which might contribute to reducing the possibility of ankylosis. please mention the suggested mechanism

Response： We appreciate the reviewer's comments. One essential reason for the occurrence of alternative resorption is that the extensive damage of the periodontal membrane caused by serious injury or improper storage stimulates the repair of bone stromal cells adjacent to the periodontal membrane, and then the direct contact between the root and alveolar bone is formed, that is, ankylosis occurs. Although we did not observe obvious ankylosis in the maxillary central incisor or the lateral incisor in these cases, it is a common finding in patients with avulsed teeth [Ref. 6,20,37,38]. Previous studies have shown that PRF can inhibit the osteogenic differentiation of periodontal ligament stem cells (PDLSCs) in vitro, which might contribute to reducing the

possibility of ankylosis. There may be three reasons. Firstly, PRF can promote cell proliferation and make the tissue repair with more seed cells instead of mobilizing bone stromal cells and bone-derived cells; Secondly, the main component of PRF is the collagen fiber mesh structure, which is placed in the periodontal membrane cavity and acts as a physical barrier, can avoid the direct contact between the tooth root and the inner wall of the alveolar socket, thus reducing the bone repair between them [Ref. 20]. Thirdly, PRF can inhibit the generation of osteoclasts by promoting osteoprotectin secretion and upregulating the expression of phosphorylated extracellular signal-regulatory protein kinases in osteoblast cultures. With the inhibition of osteoclast activity, the opportunity for external resorption can be suppressed to some extent [Ref. 31]. Thanks for the pertinent suggestions from the Reviewer, we have added above-mentioned details into the 5th paragraph of the Discussion part, as highlighted in yellow. Accordingly, the relative new references have been integrated into the References part of the revised MS.

7. We reason that this was related to highly aggregated leukocytes in the PRF, which may play anti-inflammatory and immunoregulatory roles to reduce inflammatory root resorption [15,29,30]. but you are not using L-PRF this explanation unrelated.

Response： We appreciate the reviewer's earnest reading. Indeed, L-PRF was not involved in our study. The relevant content has been deleted and the 5th paragraph of the Discussion part has been revised accordingly.

To Reviewer 4

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Good Case Report

Response： We thank the Reviewer for the comments.

To Reviewer 5

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors:

1. In the Abstract after immediately the background authors should present the aim of the study more clearly.

Response： We thank the Reviewer for the kind suggestion. The aim of this work is to improve the success rate of avulsed teeth after delayed reimplantation by adoption of autologous platelet-rich fibrin (PRF). The presented cases provide examples of PRF successfully reducing pathological root resorption of the avlused teeth, and the application of PRF may provide new healing opportunities for traditionally hopeless avulsed teeth. We have added above-mentioned details into the 5th paragraph of the Discussion part, as highlighted in yellow.

2. I have a serious concerns regarding the English. Sentences need major revision. Just for example "In case 2, a 17-year-old boy fell down 2 hours ago, with his left upper front tooth being completely out of the alveolar socket". What does it mean, that boy fell down 2 hours ago? Maybe authors need to write that after 2 hours the boy was hospitalized or something else? What mean left upper front tooth? Maybe left lateral incisor?

Response： We are awfully sorry for the unclear expressions, and appreciate the thorough reading and pertinent suggestion from the reviewer. What we're trying to convey is that "the patient suffered avulsion of left upper lateral incisor from an accident fall, and came to our hospital 2 hours later". The corresponding part of the article has been revised, as highlighted in yellow. Besides, the whole manuscript has been checked and re-edited by American Journal Expert.

3. Regarding tooth root external resorption type and possible treatment authors should add the following paper: Heboyan AG, Avetisyan AA, Margaryan MM, et al. Rare clinical case of tooth root external resorption as a delayed post-traumatic complication. The New Armenian Medical Journal 2018; 12: 93–98.

Response： We appreciate the reviewer's comments. Inflammation and replacement root resorption are the most common causes of failure of replanted avulsion teeth. The development of the lesion mainly depends on pulp vitality， when the root canal gets infected, microbial toxins can move to the resorption area through dentinal tubules, leading to the progression of inflammatory

resorption[Ref. 6, 23]. We have added the above-mentioned content about tooth root external resorption highlighted in yellow to the 1st paragraph of the Discussion part, and the relative new reference has been integrated into the References part of the revised MS.

4. Authors should include more recent studies in the Discussion section, here is one recommendation: Heboyan A, Avetisyan A, Karobari MI, et al. Tooth root resorption: A review. Science Progress. 2022;105(3). doi:10.1177/00368504221109217

Response： We appreciate the kind suggestion for the Reviewer. We have added the reative content about root resorption to the 1st paragraph of the Discussion part, and the relative new reference has been quoted in both Introduction and Discussion parts, and also integrated into the References part of the revised MS.

5. In the chief complaints, case 1: how much time was passed after trauma, when 14-year-old boy applied to clinic? Moreover, I could not understand what was the chief complaint of patients when applied to clinic? I think that at least they could have a pain (can be hemorrhage etc), but there is no any information regarding this.

Response： We appreciate the reviewer's comments. According to your suggestion, the complaint of the first case has been revised and highlighted in yellow in the revised MS.

6. Why the root canal therapy of the teeth 11 and 21 were started 2 weeks after the first visit?

Response： We appreciate the thorough reading by the reviewer. According the International Association of Dental Traumatology guidelines [22], root canal therapy of the avulsed teeth 21 should be started within 7-14 days. For fear that the influence of the treatment process may affect the periodontal healing of the replanted tooth, we generally chose to start the root canal treatment 2 weeks after the injury, when the avulsed periodontal membrane reached the initial healing. Therefore, the root canal therapy of the avulsed tooth 21 of case 1 were started 2 weeks after the first visit. As to the teeth 11, it was found negative dental pulp activity, sensitive to percussion, accompanied by small transmission shadow in apical region at return visit after 2 weeks. Root canal therapy of the laterally-dislocated tooth 11 and avulsed tooth 21 were performed 2 weeks after the first visit, with the calcium hydroxide paste as an intracanal medication sealing for 4

weeks. Then, bio-type root canal filling sealer and hot-melt gutta-percha (SuperEndo B&L, Korea) were adopted for root canal filling. The yellow-highlighted content above has been supplemented to the first part of the **TREATMENT** part in the revised MS.

7. I recommend authors to expand the clinical case presentation adding more information about all methods, techniques, that were used. Also all products and should be added with manufacturers and country.

Response: We thank the reviewer for this helpful suggestion. Some specific methods and techniques are added into the **TREATMENT** part of the revised MS and highlighted in yellow. The information of the manufacturer of the materials used in the treatment process were also supplemented in the revised MS.

8. In the Discussion section, possible limitations should also need to be added and future research suggestions should be formulated.

Response: We appreciate the reviewer's comments. According to your suggestion, the limitations and future research suggestions have been supplemented to the last part of **Discussion** and highlighted in yellow in the revised MS.

To Reviewer 5

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

However, for it to be better the authors need to go through this manuscript again and check minor typographical errors, language structure, and spelling issues.

1.Title: Comment: The reviewer suggests rephrasing the title to: Rescue of "Hopeless" Avulsed Teeth using Autologous Platelet-Rich-Fibrin following Delayed Reimplantation: Two Cases Report

Response: We thank the Reviewer for the kind suggestion. We have revised the title of the work to"Rescue of "Hopeless" Avulsed Teeth using Autologous Platelet-Rich-Fibrin following Delayed

Reimplantation: Two Cases Report" in the revised MS.

2. Abstract. Does the abstract summarize and reflect the work described in the manuscript?

Response: We appreciate the reviewer's comments. The Abstract has been re-organized to make it more relevant to the main text. The modifications have been highlighted in yellow in the revised MS.

3. Comment: CASE SUMMARIES: The introductory sentence of case 1 is more comprehensive if phrased: "In case 1, a 14-year-old boy fell and knocked out his left upper front tooth 18 hours prior to his arrival to the department" The Introductory sentence of case 2 should read: In case 2, a 17-year-old boy fell 2 hours prior to his presentation to the hospital, and had his upper front tooth completely knocked out of the alveolar socket.

Response: We sincerely appreciate the helpful suggestion for the Reviewer. We have revised the relative part of CASE SUMMARY according to you suggestion.

4. Last line of the summary should read: In addition to the avulsed teeth, the other injured teeth were treated using corresponding conventional treatment methods.

Response: We sincerely appreciate the helpful suggestion for the Reviewer. We have revised the last sentence of CASE SUMMARY according to you suggestion.

5. Core tip. Comment: Check spelling of platelet-rich fibrin.

Response: We are sorry for the spelling errors, which have been modified in the revised MS.

6. Introduction. Comments: Reference number 3 could not be found in available publications

Response: We appreciate the reviewer's comments. We have repeatedly confirmed that the reference is officially published and available on Pubmed as following.

7. The paragraph after reference 5 had run-on sentences, it can better be re-written as: Unfortunately, in most cases, an avulsed tooth is kept out of the alveolar socket for a significantly long time or is stored under improper conditions.

Response: We sincerely appreciate the helpful suggestion for the Reviewer. We have revised the relative sentence according to you suggestion.

8. Eventually, these contribute to periodontal ligament cell necrosis and result into ankylosis and replacement resorption of the tooth root after reimplantation. Findings of a study are reported in the paragraph that follows reference 15, was this study published? If so, it should be included in the references. Also, check typos, spelling errors and structures of sentences 11 References. Comment: Some references need review eg number 3.

Response: We thank the reviewer for the careful reading. The study reported in the paragraph that follows original reference 15 is just by our research team, and the work has been published before. We are sorry to neglect to quote the reference. In the revised MS, the reference has been quoted as Ref. 20. Accordingly, the typos, spelling errors and sentences structures of Ref. 11 have been checked and corrected. The screenshot of the index page of Ref.3 has been appended in the Response of Q6.

To sum up, we have made every effort to incorporate every suggestions into the manuscript. We wish to express our sincere gratitude to both the editors and the reviewers for your

patience, efforts and support, which we believe has led to a more reasonable and understandable cases report. We also hope that the revised manuscript will meet with your approval.

Thank you again for your consideration.

Sincerely,

Min Zhang