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DENTAL TRAUMATOLOGY

Letter to the Editor

Is anti-resorptive regenerative therapy working in case of replantation of avulsed teeth?

The authors of the letter to the editor comment on our publication in which a 'changed treatment strategy for tooth avulsions' and a 'radical approach' is presented. The choice of the words imply ONE strategy, instead this strategy comprises three different and independent approaches that also can be used separately. As all these approaches have distinct advantages in our opinion we use all these approaches together.

The first approach is to enhance the chance of immediate physiologic rescue and therefore the chance of functional healing and permanent retention by the distribution of tooth rescue boxes. This immediate physiologic rescue is of overwhelming importance, and, as demonstrated in a new analysis given later in this text, the distribution of rescue boxes increased the rate of functional healing to unknown levels. The usefulness of the immediate physiologic rescue was not questioned in the letter to the editor.

The second approach is the extraoral endodontic treatment, definitely a radical new view. By this treatment the incidence of infection related complications could be 'radically' reduced. This is acknowledged by the authors of the letter to the editor. The concerns about possible negative effects of the titanium post can be dispersed, as was clearly written in our publication and is repeated later in this text.

The third approach is to enhance the healing of teeth by a temporary storage in tissue culture media (to use a possible 'reconditioning effect') and the use of anti-resorptive regenerative therapy (ART; to enhance periodontal healing by application of some medicaments). The authors of the letter to the editor question whether our conclusions are reliable because of methodological problems in our study. They obviously assume that we drew definite conclusions concerning the use of ART. In contrast we were very careful in the interpretation of our results, using the subjunctive throughout. Nevertheless we have another view than the authors of the letter to the editor: as there are no negative influences of this treatment but several hints of a better outcome, we use and continue to use this treatment to take every chance for our patients.

Design of study

Our study is, at the best, a case control study – as are ALL other clinical long-term studies on tooth avulsion to date. This is because of a low case number of tooth avulsions and a high variation of the conditions in which the teeth arrive at the clinic or dentist. With these prerequisites also a 'randomization' is not applicable. Nevertheless we see the problem, and indeed we are planning an international and multicentre study together with other centres.

The lack of a control group also has an ethic aspect: Once you are convinced that a certain method is clearly advantageous compared with another method you cannot use the mean method any more in treating patients and especially children. At least we cannot. Therefore, in these cases, comparative studies are limited to animal or *in vitro* investigations or to a comparison with the data of other groups with other opinions and treatment methods. However NO study to date presented data in a way that such a comparison could be possible (see 1 and later in the letter). That is the reason that we tried to present our data completely in the tables, and everyone is invited to compare with his own data but should regard the restrictions for comparisons as mentioned in our publication and later in the letter.

Criteria for healing

Of the 28 teeth four were observed for <12 months. Three of them showed complications or had even been removed, and of course these have to be included. So there is SINGLE case left with functional healing and 6.6 months observation. Removing this single case from the study does merely influence the basic outcome. It is withdrawn from the calculations that occur later in this letter.

General healing outcome

Survival of avulsed and replanted teeth is dependent on the healing type. Complications (infection related resorption, replacement resorption) will – in the end – result in tooth loss. Teeth exhibiting functional healing (favourable healing) can be maintained, possibly life-long. Thus functional healing is the

goal. We could confirm in our study (2) the common sense that only by an immediate physiologic rescue this functional healing can be achieved on a regular basis. Thus the outcome, including survival, is dependent on luck (availability of tooth rescue box nearby or immediate replantation at the site of an accident by lay persons) rather than on a treatment method; luck for the patient and luck for the one doing a study. This should be kept in mind when studies shall be compared with respect to healing rates and survival. The meaning of the tooth rescue box is to increase the chance of physiologic rescue, and according to a new analysis presented later in this letter and according to some unpublished material (publication is submitted) this chance seems to have been increased clearly so that the concept of distributing tooth rescue boxes seems to be successful.

We wonder why the authors of the letter to the editor come to the conclusion that we consider 'optimal' a healing rate of nine of 28 teeth, or, eight of 27 teeth, respectively (=32%, or 30%, not '25%'). This is far from our opinion. The optimum is 100% healing, and that is our aim, clearly knowing that we will never reach that. Nevertheless with this point the authors of the letter found the real disaster of our study: we forgot to do another analysis. We already corrected this and presented the data in an oral presentation recently (3, also available as printout through the AAE), and we are glad to get the opportunity to repeat it in a written form. As demonstrated in our study the periodontal healing is primarily depending on an immediate physiologic rescue, that means storage in a tooth rescue box. This box was not available until 1995/1996. From the years 1996/1997 the rescue box was distributed at schools in Germany. Before 1997 all avulsed teeth arrived in our clinics in disastrous conditions, and no functional healing occurred after replantation. Since 1997 more and more rescue boxes were available, and more and more teeth were rescued in the boxes. The healing rate since 1997 is exactly 50%, or 47% without the 6-month case (Table 1). Thus it is clearly higher than the healing rate in any other study. When Fisher's exact test is applied, the differences to other studies mostly are on a significant level (Table 2).

Table 1. Healing before and after the introduction and distribution of tooth rescue boxes at schools and other accident prone locations (number of teeth), tooth with functional healing and observation of 6.6 months not included

	Total	Functional healing	Complication
≤1996	10	0	10
≥1997	17	8	9

The comparison of the survival rates of our study to those of the study of Andreasen et al. (4) is not possible for various reasons. The patient groups of the compared studies are not homogenous concerning age of patients and case selection and the treatment options and protocols in case of complication differ clearly between the two centres. We already discussed the background thoroughly in part III of our publication in general (1), and here we refer this to that distinct study.

First, Andreasen included grown-up patients while we only included patients still growing. These groups are completely different and may not be mixed: The progression of resorption is much faster in younger individuals (5, 6), resulting in earlier tooth loss. Additionally, in growing patients ankylosed teeth get into an infraposition, often dictating an early removal because of functional or aesthetic reasons. In contrast in adults there are no such consecutive complications and therefore no needs for removing ankylosed teeth, and the teeth may be retained for decades (5).

Second, the removal (and therefore the survival) depends on a decision towards that removal. This decision depends on the treatment protocols of the individual clinic, and the protocols depend on the treatment options available at that clinic: the factor consecutive transplantation was the dominant factor determining the survival (1). We use the transplantation of primary canines whenever possible (root of primary canine not yet resorbed too much) and as soon as possible (easier removal of ankylosed tooth, progressive physiologic resorption of primary canines when waiting) in case of an ankylosis of a permanent incisor. This regularly and naturally results in very short survival times of the ankylosed teeth. Since we developed this treatment and described it in 2001 for the first time (7), this option was most probably not

Table 2. Healing rates after replantation of avulsed teeth

	No. of teeth	Favourable healing (%)	Fisher's exact test *P* value (2-sided)
Pohl et al. (2005) (2) ≥1997	17	8 (47)	0.01
Pohl et al. (2005) (2) ≤1996	10	0 (0)	
Andreasen & Hjörting-Hansen (1966) (20)	110	22 (25)	0.03
Andreasen et al. (1995) (4)	400	94 (24)	0.04
Boyd et al. (26)	50	18 (36)	0.57

available for the patients that were evaluated in the study of Andreasen in the year 1995. Thus the questions arise which criteria or indications are used for removal of teeth exhibiting complications after replantation, and when the removal is performed. These information were not given in ANY study up to now and this should be changed immediately, because this is a basic prerequisite for comparing survival rates, especially in growing patients.

And third, there was a 'negative preselection' of the immature teeth in our study in the meaning that we only did the extraoral endodontic treatment (which was an inclusion criterion for the study) when pulp necrosis was highly predictable. This means that the teeth had been stored unphysiologically, and this means that also the periodontal ligament (PDL) had been severely damaged. In contrast Andreasen included all teeth, also those that had been replanted immediately (=a kind of physiologic rescue with good healing prognosis and therefore a high survival expectation). Again, these reasons strongly forbid a comparison between the two studies.

Effect of conditioning

Beyond this subtitle the authors of the letter mention two aspects, the interim storage and the use of ART. We divide our answer in two parts:

Storage in cell culture medium:

We included the topic 'reconditioning' in the introduction and the discussion of part II of our publication (2). The authors of the letter present just a selection of publications which shall demonstrate that the extraoral interim storage before replantation is 'speculative' and of 'little benefit'. However, when all of the literature is considered the picture changes.

The extraoral interim storage in saline (for periods limited to about 30 min) or in tissue culture media (for even longer periods) showed better healing results in two clinical and three animal studies (8–12) or equal results in an animal study (13) compared with immediate plantation. Two of the animal studies (8, 13) had a widely similar design, but completely different results: after storage for 30 min in dry conditions the teeth were stored for additional 30 min in saline. In the first study the sites without resorption comprised 75% of the root, while in the latter, with the same periods, the rate was just 26%. This difference between the studies has never been analysed, not even mentioned up to now, neither in the original literature nor in later reviews (14). The only difference in the study design that could explain the healing differences was that in the first study the teeth stored in saline were shaken every 5 min, while this was not carried out in the second study. Obviously the shaking prevents the establishment of a diffusion barrier and provides a better supply with nutrients and a better washing out of deleterious metabolites and microorganisms. This assumption is supported by own observations (15, 16). Therefore we strongly recommend intensive rinsing of the root and a repeated shaking of the stored teeth within the medium when this approach is followed.

The cited study of Andreasen (17) is of no value in this context. In that study the 'storage media' were saline or saliva, and the duration of the storage in these media was not given. From the figure in that study (Fig. 11) it can be concluded that the storage was up to 250 min (!). Saline and saliva are known to be detrimental to cells, causing cell death. After 30 and 60 min of storage in saline *in vitro*, only 60% or 30%, respectively, of PDL fibroblasts showed vitality, and after 150 min not a single cell had survived (18). Thus it is clear that storage for so long times can of course not have any positive effect when the medium itself damages the cells completely. It is of high interest in this context, and was not yet addressed, that even these definitely deleterious media improve healing when the storage is not too long. This clearly demonstrates that the damaging potential of the toxic metabolites or microorganisms that are left in the PDL is much higher than the damaging potential of saline. What a potential when tissue culture media are used for storage and as cleansing solutions!

The authors of the letter demonstrate that even storage in a tissue culture medium (for several days) did not result in improved healing when the teeth had been stored dry for 60 min (11). Yes, no surprise. Sixty minutes dry storage is a period after which no – or perhaps a few – vital cells can be expected on the root surface. Therefore, in our presentation, exactly these 60 min was the borderline for judging a tooth 'hopeless' (2). And as we clearly indicated, this severe damage in the PDL cannot be resolved by any treatment to date. Therefore we concluded that the immediate physiologic rescue is of that extraordinary importance. The authors of the letter do not cite the other part of that study: the immediate storage of extracted teeth in the tissue culture medium for several days significantly increased the healing results compared with an immediate replantation (11). This could be named 'reconditioning'.

Of course, an interim extraoral storage increases the extraoral time, and in some older studies this longer time was related to a higher incidence of healing complications. In these studies the isolated teeth were not kept in tissue culture media, but in dry conditions or in unphysiologic wet media like saline (4, 5, 19, 20). In their discussion, the authors of the letter do not take into account that meanwhile

tissue culture media are easily available (by means of tooth rescue boxes even specialized for isolated teeth) and that in our concept the interim storage is within such a tissue culture medium. Tissue culture media maintain vitality and viability of PDL cells, even of the specialized population of the very important cementoblasts, for hours and days and weeks. This has been well documented by our and several other working groups, *in vitro*, *ex vivo*, *in vivo* in animals and in humans (among many other studies: 2, 15, 16, 21, 22, 23). As presented in our publication the storage of isolated teeth was possible for up to 53 h in such a medium without compromising the healing. And as demonstrated already about 30 years ago by one of the authors of the letter, this is also true for storage for 5–14 days (11). So we really do not care at all for additional 30 or 40 min in such a medium.

In conclusion · there are several independent studies consistently indicating better healing after storage in certain media compared with immediate plantation as long as the already inflicted damage by a previous inadequate storage (i.e. dry) is limited. There is not ANY study demonstrating a negative effect of an interim storage. With definitely no risk of harming and only a vague chance of improvement, we would always take this chance. And according to the literature as discussed above we consider that the chance is much more than vague.

Anti-resorptive regenerative therapy

This reflection is also the basis for the use of ART. The authors of the letter claim that there were statistical problems (sorry and thank you for the hints), and that ART did not prove to be successful in neither group (hopeless, compromised, not compromised) on a significant basis. Yes, we agree, and that is exactly what we wrote in our publication: we are lacking of a sufficient data basis, we could not demonstrate any effect (positive or negative) in the not compromised group or in the hopeless group. Despite the fact that in our statistics (with a possibly wrong chi-square test and a not criticized regression analysis) the *P*-values were at or below the borderline of significance we concluded very careful that 'There are hints that ART might promote healing in teeth with an extraoral non-physiologic storage of limited duration.' Again, with definitely no risk of harming and the potential of improvement we use this treatment option for this specific group of teeth.

Effect of non-physiologic media

The authors of the letter claim that the two teeth which had been stored dry for 90 min before storage in milk should be excluded from the analysis of the non-physiologic media. Exactly this has been implemented in our publication. We referred only to the four teeth with short dry storage, and three of these showed complications. The authors of the letter state that storage in milk produces the same (bad) results as the other teeth in this group that were stored (timely limited) in other unphysiologic conditions. Yes, that is exactly the reason why we judged milk as an unphysiologic medium and included these teeth in the group 'compromised'. We define a medium 'physiologic' when the available cells are kept vital and viable. During storage in milk, saline and saliva the number of vital cells decreases with time, cell death is progressive and inevitable (see literature in 2). These media are therefore judged to be unphysiologic.

Effect of the titanium post

We thank the authors of the letter that they acknowledge the positive effect of the immediate endodontic treatment by extraoral insertion of posts which diminishes the rate of infection related resorption. The question 'whether ankylosis could actually start by osseous integration of the titanium post' is discussed in an own paragraph with an own subtitle in our publication (24). An osseointegration will not occur – and according to our data (24, 25) did not occur – because of the immediate 'loading' of the tooth – post combination that is splinted in a non-rigid way. No implant would osseointegrate under these conditions. To repeat and to clarify: The primary intention of the insertion of the post is to achieve an immediate and complete (in all three dimensions) root canal filling, thus preventing infection related complications by preventing microorganisms from entering the root canal. The resection of the root tip is to remove the apical ramifications in which microorganisms might enter. The post can be shortened before cementation, if desired, so that there is no projection. This will leave a 'root resected tooth' with a somewhat higher mobility. By the apical projection – and that is only the secondary intention – the fulcrum of the tooth – post combination is moved to a more apical region, and thus the tooth – post combination reaches the mobility of a sound tooth (Fig. 6 in 24).

Conclusion

With the new analysis presented in this letter the overall healing rate has increased to about 50% after introduction and distribution of the tooth rescue box. This is clearly higher than rates reported up to now by any other study. We regret that we did not

include this analysis in the original publication, for this might have prevented the necessity of writing letters to the editor. Nevertheless we feel that this initiated discussion is very important in order to optimize the treatment of avulsed teeth.

The high healing rate and the detailed data of our study demonstrate that the different parts of the treatment protocol did not negatively influence the outcome. The extraoral endodontic treatment diminished the infection related complications to minimal levels and has therefore proven to be successful. A conventional endodontic approach produces much higher complication rates and has several other disadvantages (24). The part still in question is the usefulness of ART and of an interim storage of the isolated teeth in order to use a 'reconditioning effect'. We confess that there is still no safe evidence because of the lack of comparative and prospective clinical studies. However, there is enough evidence in our opinion that these treatment options do not compromise the results. And as there are enough hints that healing might be promoted, we use and recommend these options unless it is clearly proven that they are unnecessary. The really disastrous results after replantation of avulsed teeth and the dramatic consequences following healing complications allow – no: demand – every effort that promises even minor improvements.

We agree with the authors of the letter to the editor that systematic research is thoroughly needed. However, as mentioned earlier, because of the low case number and ethical qualms we don't believe that this is possible for a single center. Consequently, we are just building up an international cooperation, including centres with different treatment approaches. Also, it was one major goal of our publication to define criteria for homogenizing groups, for case selection and for stratification. May it be helpful for future studies.

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