Treatment of periimplantitis - electrolytic cleaning versus mechanical and electrolytic cleaning - a randomized controlled clinical trial – 18 months results

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Abstract:
Background:
this RCT assesses the 18 months clinical outcomes after regenerative therapy of periimplantitis lesions using either an electrolytic method (EC) to remove biofilms or a combination of powder spray and electrolytic method (PEC).

Materials and Methods:
Twenty-four patients (24 implants) suffering from periimplantitis were randomly treated by EC or PEC followed by augmentation and submerged healing. Probing pocket depth (PPD), Bleeding on Probing (BoP), suppuration and standardized radiographs were assessed before surgery (T0), 6 months after augmentation (T1), 6 (T2) and 12 (T3) months after replacement of the restoration.

Results:
Mean of PPD changed from 5.8 ± 1.6 mm (T0) to 3.1 ± 1.4 mm (T3). While BoP and suppuration at T0 was 100 % BoP decreased at T2 to 36.8 % and at T3 to 35.3 %. Suppuration could be found 10.6% at T2 and 11.8% at T3. Radiologic bone level measured from the implant shoulder to the first visible bone to implant contact was 4.9 ± 1.9 mm at mesial and 4.4 ± 2.2 mm at distal sites (T0) and 1.7 ± 1.7 mm and 1.5 ± 17 mm at T3.

Conclusions:
Significant radiographic bone fill and improvement of clinical parameters were demonstrated 18 months after therapy.

Keywords: peri-implantitis, electrolytic cleaning, air abrasive, augmentation, long term
Introduction

While dental implants changed the treatment strategies of missing teeth significantly, however implant therapy is not without complications. Progressive bone loss around implants accompanied by inflammation has been described as “periimplantitis”. Various definitions of periimplantitis are causing conflicting results in prevalent data. Therefore the workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions initiated by numerous multinational dental societies consented a new classification. Profuse bleeding and/or suppuration after careful probing and increased PPD and progressive bone loss after initial remodeling are the parameters for a positive diagnosis of periimplantitis in case of patients under clinical control. If radiographic history of bone loss is not available radiographic evidence of bone level ≥ 3mm and/or probing depths ≥ 6mm in conjunction with profuse bleeding on probing can be classified as periimplantitis [1]. The primary etiology of periimplantitis remains to be the bacterial biofilm [2], with many possible contributing factors, such as iatrogenic issues (e.g. implant malposition), foreign body reactions, debris particles, etc. Hence the clinician is faced with bone defects, inflamed soft and hard tissues and bacterial biofilms contaminating implant surfaces. Therefore the aim of a successful treatment of periimplantitis is the complete re-osseointegration of the implant surface or at least an elimination of the inflammation and stabilization of the clinical situation. Implant health can only be maintained if bone levels are stable over time and the soft tissue complex is not infected. The latter is difficult to manage over time if re-osseointegration is not achieved due to possible re-infection of implant surface [3] which may not be accessible to proper oral hygiene. Anyhow the bacterial biofilm and endotoxins need to be removed and the implant surface has to be put into a condition which allows a re-integration into the tissues [4,5]. This can be a significant challenge for the clinician to manage due to the defect morphology and the macro- and micro-morphology of the implant.

Several mechanical methods for implant surface detoxification – most of them ablative - have been described in the literature, either performed as the only detoxification technique or in combination with other mechanical/chemical detoxification approaches. Bone fill has been proven radiologically but animal studies showed that most of the bone was not attached to the implant but separated by a more or less thick layer of connective tissue. Reosseointegration between 39% and 46% of treated implant surfaces was reported in animal studies [6]. Reviews of literature following up long term result of different treatment modalities demonstrated no proof of superiority of any method. Furthermore none of them showed the ability to maintain infected implants over time with predictable results and low complication rates [7,8].

Initially introduced for removing stain from enamel surfaces, powder spray systems (PSS) have been used in the treatment of periodontitis and periimplantitis [9,10]. PSS accelerate abrasive powders (sodium bicarbonate, sodium hydrocarbonate, Erythritol or amino acid glycine) by compressed air and water. In vitro and in vivo studies demonstrated its ability to reduce biofilms [10,11]. Bone fill was demonstrated in animal studies but reosseointegration was limited to 39-46% and no additional benefit was detected when air abrasive therapy was compared to other treatment modalities [6]. An in vitro study assessing the vitality and detectability of surviving bacteria after cleaning mature biofilms with a PSS showed disappointing results, nevertheless confirmed its ability for a limited cleaning efficacy [12]. Schlee et al. achieved complete reosseointegration after electrolytic cleaning in a preclinical study [13]. In a clinical controlled study Schlee et al. investigated the clinical outcome of electrolytic versus electrolytic plus PSS cleaning in a randomized. The aim of this study were first to assess the efficacy of the electrolytic method (EC) in cleaning the contaminated implant surface and secondary to evaluate if PSS provides any additional benefit. Bone
gain visually and radiologically attached to the implant surface was assessed 6 months after treatment and submerged healing. Bone fill could be proven in both groups without reaching significant differences. In 50% of the cases a complete bone fill was observed [14]. The long term clinical results of this cohort are very relevant for evaluation of the technique. It is unproven yet if these results can be maintained over time. Therefore the patients were reexamined clinically and radiologically 6 and 12 months after submerged healing period of 6 months. In contrast to regular augmentation procedures the bony reconstruction of periimplantitis related defects is compromised by inflammatory conditions in surrounding tissues [2]. Hence the efficacy of the approach to treat periimplantitis is primarily related to successful elimination of infection and inflammation [15].

The aim of this study was to follow up the cases 18 months after treatment and 12 months after replacing the restoration to assess clinical stability of the results.

Materials and Methods

Legal

The study was conducted according to the Helsinki declaration and complies with the Consort checklist. The study was registered (BfArM DA/CA99, DIMDI 00010977) and approved by the “Ethik-Kommission der Bayerischen Landesärztekammer (BASEC-No. DE/EKBY10) with the registration code 17075.

Sample size calculation

Based on previous in vitro tests using a paired t-rest with a power of 90% and a level of significance of 5% a sample size of 12 per group was calculated. The sample size calculation was done using G*Power 3.1 (Heinrich Heine University of Duesseldorf).

Devices and mode of action

The mode of action of this electrolytic approach (EC) was described before [14]. In brief the infected parts of implants have been loaded with a direct maximum current of 600 mA negatively. A sodium formiate solution, acting as an electrolyte, is pumped by a device (GS1000, GalvoSurge Dental AG, Widnau, Switzerland) through a platinized ring acting as an anode and sprayed on the exposed and infected implant surface. Electrolysis produces hydrogen cations (H+) which penetrate the biofilm. By deoxidation hydrogen bubbles emerge on the implant surface and lift the biofilm off the implant surface. This process leaves a clean implant surface with no visible, stainable and breedable bacteria [12].

Patient and sample selection, randomization

Twenty-four patients with periimplantitis (definition according Berglund et al.) [1] where enrolled to the study and allocated to test group (EC) or control group (PEC). Sealed envelopes were used for randomization. If more than one implant was affected, one implant was chosen by dice.

Inclusion criteria

Patients older than 18 years, capable to understand and sign an informed consent, smoking less than 10 cigarettes per day, no uncontrolled periodontitis, BoP <20%, Plaque Index < 20%, no allergy against used
drugs or materials, not pregnant or nursing were suitable to be enrolled to the study. Any infected implant without regard to bone defect morphology, three-dimensional implant position, inter-implant distance were included to the study in contrast to most of the literature.

Outcomes and endpoints

BoP, PPD, suppuration and radiologic bone levels At T0, T1, T2 and T3.

Procedures and measurements

Periodontal treatment was performed if necessary before patients were enrolled to the study. Suprastructures were removed 14 days before surgery (T0) and efforts to reduce inflammation were done (PSS cleaning (PerioFlow, Nozzle, Erythritol, EMS, Nyon, Switzerland), rinsing with chlorhexidine (Chlorhexamed Forte 0.2%, GlaxoSmithKline Consumer Healthcare GmbH & Co. KG, Munich, Germany).

At baseline (T0) clinical photos were taken, standard radiographs in right angle manner, suppuration, PPD and BoP were assessed at 6 defined points (mesio-bucal, mid-buccal, disto-bucal, disto-lingual, mid-lingual and mesio-lingual) using a periodontal probe with a 1 mm scale (PCPUNC 15, HuFridy, Chicago, IL, USA). The surgical approach was described before [14]. Summarized a flap was raised after crestal incision, mobilized, granulomatous tissue was removed and calculus was debrided if applicable. In EC group the implants were cleaned for 120 s electrolytically as described before [14]. In PEC group powder spray (Airflow Plus powder, Airflow, EMS, Nyon, Switzerland) was applied to the infected implant surface according manufacturer’s manual followed by the treatment described for EC group. Thereafter the implants were augmented with autogenous bone harvested from ramus area (Micross Safescraper, Zantomed, Duisburg, Germany) and Bio-Oss (Geistlich, Wohlhusen, Switzerland) in a 50:50 ratio. Sites were over-augmented up to 2 mm to ensure an adequate bone volume after shrinkage and healing. A collagen membrane (Bio-Gide, Geistlich, Wohlhusen, Switzerland) was used and if necessary tented up with Umbrella screws (Umbrella-Screw, Ustomed, Tuttlingen, Germany). The flap was sutured passively with 6-0 propylene monofilaments (Medipac, Kilis, Greece). Sutures were removed 2 weeks later. During the period of healing the patients were supervised and exposures or infections were documented. Second stage surgery was performed after 6 months (T1) and P-B was assessed. In exposed implants P-B was assessed by bonesounding under local anesthesia. Furthermore infections, BoP, and recessions were documented. For all implants restorative parts were replaced, photos were taken and a standardized x-ray in right angle position was performed. Sutures were removed after 14 days if applicable [14].

PPD, BoP, suppuration, secretion, recessions, photos and radiographs were recorded 6 months (T2) and 12 months (T3) later (12 and 18 months after baseline). Changes in those variables as well as radiologic bone levels were compared and statistically evaluated. For radiographic evaluation a software (DBS Win, DentsplySirona, Bensheim, Germany) was used. To minimize examiner bias they were not informed about the aim of the study and calibrated until their results correlated adequately as measured by Cohen’s Kappa (κ ≥ 0.6). In addition, the assessment data where tested for correlation (Spearman) and for paired differences (Wilcoxon) and agreement between two methods of clinical measurement were assessed (Bland-Altman).

Bone level implants were judged to be completely osseointegrated if bone level reaches the platform. For tissue level implants, it is counted as 1mm below the platform due to initial biological bone remodeling. For implants with a polished neck, completely osseointegrated was regarded as if bone level reaches to
the junction of rough-polished [19, 20]. All the surgical procedures and clinical assessments such as PPD, recessions and BoP were performed by the first-named author.

Statistics

The statistical analysis was done by an independent statistician. Quantitative values are presented as mean and standard deviation, minimum and maximum, as well as quartiles. They are tested for normal distribution using the Shapiro-Wilk test which is appropriate in case of small samples. Wilcoxon test was used to compare two related samples. McNemar's test was used to test paired nominal data. Repeated measures ANOVA was used to compare bone levels at different time points. Testing the accordance of the two assessors of radiologic bone levels, Spearman's Rank correlation analysis, Wilcoxon matched pairs test and Bland-Altman analysis, were performed. The tests were two sided with a significance level of 5%. An alpha adjustment for multiple testing was not applied, and the results were interpreted accordingly. Statistical calculations were carried out with SPSS Statistics 26 (SPSS Inc. an IBM Company, Chicago, IL).

Results

Gender and age were distributed homogenously (12f/12m, age 57.13 y). Fourteen days after removal of restorative parts and cleaning with PSS all the sites were infected, BoP was positive, suppuration drained from pockets and all sites probed deeper than 5 mm at baseline. PPD was 6.64 mm in EC and 7.02 mm in PEC group in median. Four patients (3 EC, 1 PEC smoked < 10 cigarettes per day. 19 implants were exposed at suture removal, 15 after 6 months. No implant was lost during healing phase (Table 1).

|                | N/mean years/mm | percentage |
|----------------|-----------------|------------|
| gender         |                 |            |
| female         | 12              | 50.00%     |
| male           | 12              | 50.00%     |
| age            |                 |            |
| female         | 59.2 y          |            |
| male           | 51.44 y         |            |
| jaw            |                 |            |
| maxilla EL     | 4               | 16.67%     |
| maxilla PEL    | 8               | 33.33%     |
| mandible EL    | 8               | 33.33%     |
| mandible PEL   | 4               | 16.67%     |
| maxilla total  | 12              | 50.00%     |
| mandible total | 12              | 50.00%     |
| smokers        |                 |            |
| EL             | 3               | 12.50%     |
| PEL            | 1               | 4.17%      |

|                | (T00/T0)        | percentage |
|----------------|-----------------|------------|
| BoP            | 24/24           | 100.00%    |
| PUS            | (T00/T0) 24/24  | 100.00%    |
| PPD            | EL              | 6.64 mm    |
|                | PEL             | 7.02 mm    |

Table 1. Overall patient data at T0
One implant had to be removed nine months after T2. 4 implants had to be removed before T2 and one more implant before T3. All implants which had to be explanted were re-infected, and bone regeneration was incomplete. Further characteristics could be identified: exposures (7), periodontal history (5), previous augmentation (5), bad axis (3), placed too deep (1), placed too high (1) (Table 2)

Table 2. Explanted implants

At T1 one patient did not show up for the appointment. Because 6 implants had to be removed at T2, only 23 and at T3 18 implants could be assessed.

Figure 1 displays the consort flow chart of the study.

The correlation between the assessments of the two investigators of the radiographs was almost perfect (R=0.999, p<0.001 (Spearman), p=0.781 (Wilcoxon)). Figure 2 shows the Bland-Altman-Plot.
Figure 2. Bland-Altman-Plott

Figure 3 expresses the change of radiographic bone level at T0, T1, T2 and T3. Globally the gain of bone at T1, T2, and T3 compared to T0 was statistically significant (p<0.001, ANOVA). Also comparing pairs (Post-Hoc-Bonferroni-Tests) significance was achieved in all pairs (p<0.001).

Figure 3. bone level changes at the assessed time points

Absolute numbers are expressed in Table 3.
Table 3. bone level changes from T0-T3

| bone level changes | N  | mean     | Std.-deviation | minimum | maximum | 25. | 50. (Median) | 75. |
|--------------------|----|----------|----------------|---------|---------|-----|-------------|-----|
| mesial T0          | 24 | 4.8521   | 1.90722        | 0.95    | 8.00    | 3.125| 5.2000      | 6.4125 |
| mesial T1          | 23 | -1.6326  | 1.10058        | -4.90   | 0.00    | -2.0000| -1.5000     | -1.0000 |
| mesial T2          | 23 | 0.6917   | 1.92753        | -2.30   | 3.80    | -0.8750| 0.6000      | 2.7625 |
| mesial T3          | 18 | 1.6611   | 1.73651        | -1.50   | 4.95    | 0.1875| 1.3250      | 3.3000 |
| distal T0          | 24 | 4.3777   | 2.15775        | 0.65    | 8.65    | 2.8125| 4.5000      | 5.5500 |
| distal T1          | 23 | -1.6239  | 1.12380        | -5.70   | 0.00    | -1.9000| -1.6000     | -1.0000 |
| distal T2          | 23 | 1.1333   | 1.79799        | -2.20   | 4.10    | -0.6500| 1.3000      | 2.8750 |
| distal T3          | 18 | 1.4694   | 1.86051        | -1.55   | 5.95    | 0.1500| 1.3250      | 2.6750 |

PPD was assessed at six points (m, mb, db, dl, l, ml). A significant reduction in probing depth was assessed at all probing points when T3 (mean 3.1±1.4 mm) was compared to T0 (mean 5.8 ± 1.6 mm) (Wilcoxon-Test for pair differences, p<0,001) (Figure 4).

While BoP and suppuration at T0 was 100 % BoP was assessed at T2 with 36.8 % (7 sites) and T3 BoP 35.3 % (6 sites). The Values for pus were 10.6% (2 sites) at T2 and 11.8% (2 sites) at T3. Two sites were diagnosed as having a mild periimplantitis at T2. Statistically no significant change was assessable for BoP.
(McNemar’s test, p=0.275) and in the diagnosis periimplantitis (Bowker’s symmetry test, p=0.392) between T2 and T3.

Discussion

A pre-requisite for a successful treatment of peri-implantitis is the elimination of its provoking factor. This includes the complete debridement of the peri-implant defect, thoroughly decontamination of the implant surface, and removal of potential contributing factors as well as the protected wound environment during treatment healing (flap closure). Hence the initial phase (T00) aimed to reduce inflammation. As PSS cleaning demonstrated some but limited benefit in literature we treated the implants after removing restorative parts by a powder spray system. Nevertheless positive BOP and pus was assessed at all of the implants at surgery date. In our data PSS failed to eliminate infection and inflammation after this 14 day period. Nevertheless the investigator’s clinical feeling expressed a certain reduction of inflammation. More data should be collected to investigate if a repeated pretreatment with PSS would reduce inflammation and by this may be beneficial for later surgery. Initially this study has been designed as RCT to assess differences in healing and efficacy after EC and PEC [14]. It pointed out no statistical difference between both groups meaning additional cleaning with PSS demonstrated no additional benefit. At T2 (12 months after surgery) 2 EC and 5 PEC implants had to be removed. In contrast to the majority of other studies we did not exclude severe cases and other compromising factors. Bony reconstruction of periimplantitis related defects is compromised by inflammatory conditions in surrounding tissues [2] compared to augmentation procedures in conjunction with implant placement. This might be a causing factor for the high exposure rate published before and the rate of late implant loss in the study. It is not surprising that exposed implants achieved less bone gain and all implants which had to be removed suffered exposure during healing. In further studies attention has to be turned to identify factors reducing exposure rate after flap surgery. The high rate of patients with periodontal history is conspicuous. Whether the bacterial biofilm is the only causing factor or if bone loss caused by surgical, mechanical or patient related reasons and bacterial colonization occurs on the exposed surfaces secondarily [16] is still a matter of discussion. This debate on etiology is not only an academic question but influences success rate of possible therapy due to possible different specimen susceptibility and uncorrectable surgical or mechanical obstacles. Anyway biofilm needs to be removed to prevent progression of disease or to treat peri-implantitis successfully. Furthermore the defect morphology has major impact on the amount of regenerated bone in median and on the amount of complete reossseointegration [14]. Further studies will have to investigate the risk factors for treatment with EC. These studies should aim to develop a clear treatment decision tree whether an implant should be removed or treated.

As additional PSS cleaning did not enhance the outcome in the 6 months result aiming on the amount of bone fill we did not investigate the group differences in this follow up study. As we achieved the same amount of bone respectively the same amount of still exposed implant surface 6 month after treatment (T1) no difference in the presented data was to be expected.

In this CE Mark approval study all patients meeting the inclusion criteria where enrolled to the study despite uncorrectable factors such as bad implant depth and axis, too think diameter or severe defects difficult to augment. For this study venous blood had to be drawn at several time points to prove that no cleaning solution or reaction products could be detected in the blood of the patient treated. For this a waiting time of 30 minutes with no action had to be followed which among other things extended surgery...
This might explain the relatively high failure rate in the follow-up. The rate of implants which had to be removed in the next 102/161 cases/implants which were treated after this study in our clinic was seven out of 161 implants. If treatment outcome would be the aim of a study, case selection should have applied to optimize the cohort. This was not done as described and might be a risk for the interpretation of this data.

The evaluation of bone levels based on radiologic findings is difficult. Casetta et al. compared clinical and radiologic measurements of bone levels and concluded a statistically significant overestimation of the level of peri-implant marginal bone compared with surgical measurements [17]. Serino et al. confirmed the results and stated an overestimation of 1-2 mm [18]. As all the radiologic measurements were done by the same investigators for both groups and in all time points the risk of bias during the assessment of differences in bone level should be neglectable. A prerequisite of successful augmentation is providing immobile space and stabilization of the blood clot by bone or bone substitutes. For this Umbrella-Screws or 2 mm high healing posts have been used to tent up the augmented area if the defects were not self-contained. All of the cases where “over”-augmented up to 2 mm. This explains the “negative” bone loss at T1. As the bone remodels during healing the bone height was reduced at T2 and T3 compared to T1. The results outline a significant gain of radiologically assessable mineralized bone structure in contact to the implant surface. Of course this is not a proof for re-osseointegration. Nevertheless an animal study [13] and a histomorphometry of the explanted implants of this study proved the occurrence of successful re-osseointegration (article is submitted). Figure 4 expresses the clinical course of one of the failed cases. After electrolytic cleaning and augmentation the flap exposed during wound healing. A part of the bone graft got lost and an incomplete bone fill was achieved. Over time the implant surface which was not covered by bone was recolonized by bacteria. After 11 months the implants had to be removed because of infection, suppuration and swelling. The patients agreed in histologic evaluation of the implant and the surrounding bone. The sites were not augmented during initial implant placement. This proves that the area were bone substitute (“bone mineral”) could be found must be new bone achieved after treatment. The crestal part of the histology demonstrated clearly new bone attached to the implant. According to the author’s knowledge re-osseointegration of an implant treated for periimplantitis has never been published before. This happened despite of an ongoing infection crestal to the investigated area.
Figure 4 clinical course of a failed case: a. implants 15 and 16 with a severe combined intra- and supra-osseous bone defect (RP Class 3), b. augmentation after electrolytic cleaning with a combination of mineralized bovine bone mineral and autogenous bone using the Umbrella technique, c. tensionless suturing after crestal mobilization of the flap, d. radiograph demonstrated the augmented volume, e. clinical situation 6 month after flap surgery, Exposure of the flap caused some loss of augmented volume, f. radiograph 11 month after surgery. The implant had to be removed because of suppuration, g. histology with a field of interest in the augmented area pointing out regenerated bone and reosseointegration to the implant surface, *particle of bone mineral, + pus

For determination of long term results a change of the clinical parameters PPD, BoP and suppuration are relevant. In the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions implants were judged healthy if PPD was < 6 mm [1]. Carcuac et al. [19] achieved an improvement in PPD and BoP comparing different cleaning modalities combined with apical flap surgery from T0, 6 month and 1 year (PPD 7.82 ± 1.52 mm, 5.11 ± 1.71mm and 5.24 ± 1.97 mm, BoP 100%, 52% and 41,9%). Suppuration changed from 68.7 % to 14.4. % and 17.4 %.

In our study the surviving implants showed a mean PPD in all sites of 3.1 ± 1.5 mm after 1 year (T2). While suppuration and BoP at T0 was 100 % both parameters were reduced at T2 and T3 with no statistical difference between the latter (McNemar’s test, p=0,275) (BoP/T2: 36.8 % (7 sites), suppuration/T2: 10.6% (2 sites) and BoP/T3 35.3 % (6 sites) and suppuration/T3 11.8% (2 sites). No statistic significant change was asssesable for BoP (McNemar’s test, p=0,275) and in the diagnosis periimplantitis (Bowker’s symmetry test, p=0,392) between T2 and T3. Only two sites (11.8%) were diagnosed as a mild periimplantitis and two (11.8%) as a mucositis. Our surgical protocol aimed for bony regeneration and required a coronal advanced flap. Carcuac’s et al. approach aimed at pocket reduction by an apical repositioned flap.
usually causing a reduced pocket depth and thus reduced inflammation. Our outcome compared to the cited clinical study is better although even apical reposition of the flap was avoided by us. This positive results might encourage the community to investigate larger case series or even in translational medicine to transfer the results to orthopedic and trauma surgery were medical devices made of metal also suffer in biofilm induced infections.

Conclusions

Electrolytic cleaning of contaminated implants re-achieves an implant surface which allows a re-integration of the implant in the surrounding tissues. A significant radiologic gain of bone and reduction of PPD, BoP and suppuration was proved and stable over an 18 months period.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Helsinki declaration and complies with the Consort checklist. The study was registered (BfArM DA/CA99, DIMDI 00010977) and approved by the “Ethik-Kommission der Bayerischen Landesärztekammer” (BASEC-No. DE/EKBY10) with the registration code 17075.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data available on request due to restrictions eg privacy or ethical.

Conflict of interest: The authors Schlee, Zipprich and Brodbeck declare to own shares in this company. The other authors declare to have no conflict of interest.

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