Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment

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3D analysis of a surgical technique in successfully treated stage II/III MRONJ-patients

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ABSTRACT

INTRODUCTION

The aim of this study was to analyze the surgical treatment protocol used in our hospital for successfully treating medication-related osteonecrosis of the jaw (MRONJ) patients.

METHODS

It was a retrospective study where MRONJ patients were divided into 2 groups for analysis. Group 1 comprised 15 MRONJ patients who have had unsuccessful surgical treatments outside of our hospital between the years 2009 and 2018. Group 2 comprised 15 MRONJ patients who had no history of any treatment, and who were then surgically treated at our hospital with our treatment protocol. (Cone beam) computed tomography (CB)CT scans of group 1 patients were analyzed at the time of presentation in our hospital. The surgical technique used for treatment was categorized as either sufficient or insufficient based on the evaluation of the basic principles of bone treatment such as removal of necrotic bone, removal of buccal and lingual cortex, presence of dead space and frontal aspect, on pre- and postoperative CBCT scans, respectively. The clinical outcome was also evaluated. A successful clinical outcome involved a closed mucosa, without any complaints such as pain.

RESULTS

Group 1 had low scores on the basic surgical principles for MRONJ, whereas group 2 had high scores in all features.

CONCLUSION

The surgical technique with high success rate in all stages of MRONJ is based on relatively simple surgical principles, comprising extensive saucerization and rounding off in combination with primary closure.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is one of the serious side effects of medications, such as antiresorptive drugs, which are used in the treatment of osteoporosis and bone metastasis. The first case of bisphosphonate-related osteonecrosis of the jaw (BRONJ) was reported by Marx in 2003[1]. Later, it was reported that besides bisphosphonates, the osteonecrosis of the jaw (ONJ) could also be caused by denosumab in a condition known as denosumab-related ONJ (DRONJ)[2,3]. ONJ can be very difficult to treat, and the debate on its etiology and treatment continues in the literature. The American Association of Oral and Maxillofacial Surgeons (AAOMS) stated a position paper with guidelines for the diagnosis and treatment of MRONJ[4]. MRONJ is described as exposed or probable bone in the oral cavity, present for longer than 8 weeks, without any history of radiotherapy or malignant disease in the jaws and previous or current use of anti-resorptive drugs. The treatment of MRONJ is based on the stage of the disease, which varies from stage 0 to stage 3, with increasing deterioration of symptoms and invasion of the disease throughout the entire jaw. The suggested treatment modalities vary from conservative therapy including mouth rinses, antibiotics, or removal of loosened sequestra in in the initial stages, to major and/or sometimes aggressive surgery in stage 3, involving resection with or without reconstruction. Initially most authors promoted conservative treatment for the condition, because in their opinion, any intervention would lead to worsening of symptoms, and eventually to loss of parts of the jaw[5-7]. However, more authors recently seem to promote an early surgical intervention[8-12]. These authors report an average success rate of more than 80%. The surgical modalities vary from saucerization to continuity resection of the jaw with free flap reconstruction. The basic principles of the treatment reported by several authors include thorough saucerization, smoothing of sharp edges, and closing primarily in the layers[9-11,13,14].

Our previously reported surgical protocol showed high success rates (92%) with relatively conservative surgery, such as saucerization but without segmental mandibular resection[9]. Nevertheless, there are still failures. It is important to analyze the reason of the failures and whether the surgical technique could be the cause. 3D radiological analysis of the surgical technique could give more insights into the possible causes of failure of surgical treatment of MRONJ. On a cone beam computed tomography (CBCT) scan, the extent of the MRONJ can be clearly seen in three dimensions, and it is a useful addition to panoramic radiography[15-19]. Loss of bone can be easily visualized and assessed on a CBCT scan. Therefore, the aim of our study was to evaluate the surgical technique, with a success rate of more than 90%[9]- with 3D technology. The hypothesis stated that the surgical technique used on patients treated elsewhere with unsuccessful results was different from that used in our hospital.

METHODS

In the department of oral & maxillofacial surgery of the Leiden University Medical Center (LUMC), 200 patients with MRONJ were seen and treated between January 2003 and December 2018. The criteria of the Position Paper by AAOMS[4] applied to all patients. It included the presence of exposed or necrotic bone in the oral cavity for more than 8 weeks, history of treatment with antiresorptive medication (bisphosphonates or denosumab), and no history of radiotherapy or metastatic disease to the jawbone. The clinical and radiological features together indicated the stage of MRONJ according to the criteria reported by Ruggiero et al. in 2014[4]. Patients below 18 years of age, and without a preoperative CBCT scan, were excluded. The research was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Patients

The patients were divided into two groups. For group 1, the patients were selected retrospectively. Group 1 included 15 patients with MRONJ of the mandible, who were referred from elsewhere between 2009 and 2018, and who had undergone a previous unsuccessful surgical treatment for MRONJ in other referring hospitals.

Group 2 included 15 patients with MRONJ of the mandible from the same time span as group 1, but who were not previously treated for MRONJ. These patients were treated with the standard surgical approach. The CBCT scans of group 1 patients were taken at the time of their visit to our department, and were compared with the postoperative CBCT scans of group 2 patients.

Computed tomography (CT)

For patients treated until the year 2012, a conventional CT was made, with the Aquilion One CT scanner (Aquilion One® Canon Medical Systems, Zoetermeer, the Netherlands; 120 kV; 80 mA; 500 ms; FOV 164 mm; voxel size 1 mm). The images were stored in the Picture Archiving and Communication System (PACS) of the hospital, and incorporated into the digital medical chart of the patients.

CBCT

In 2012, a CBCT scan was available, and became a part of the diagnostic protocol. Therefore, for the patients treated after 2012, the Promax 3D Planmeca CBCT scanner was used (Promax® 3D Max, Planmeca USA, Roselle, IL; 96 kV; 5.6 mA; 12 s exposure time; FOV 13x5.5 cm; voxel size 200 µm). The scan volumes were exported in Digital Imaging and Communications in Medicine (DICOM), and imported into the dental imaging software (Planmeca Romexis 5.1.1.1 Dental imaging software, Helsinki, Finland).

Surgery

In all patients, antiresorptive medication use either was stopped by the time of their presentation, or was stopped after consultation with their prescribing doctor. The surgical intervention

was performed in general anesthesia. The surgery followed the previously mentioned principles, and it was performed by two surgeons specialized in osteomyelitis. The surgical approach included removal of the diseased bone, thorough saucerization of the non-vital bone until clean bone was reached, with visually (some) bleeding bone margins, and closing in multiple, preferably periosteal, submucosal, and mucosal layers[9,20,21]. This meant minimizing the dead-space as much as possible, for tensionless closure of the overlying periosteum and mucosa. Several 'soft' criteria for the treatment included cortical rounding off until the lowest part of medullary defect, estimated absence of dead space after primary closure of the periosteal layer, sufficient total height of healthy soft tissue in primary closure above the defect.

According to the protocol, culture samples were collected during the surgery, and the diseased bone was submitted for histopathological analysis in all patients.

The surgical treatment was supported by the administration of penicillin G and metronidazole intravenously for 1 week, and amoxicillin and metronidazole orally for 3 weeks.

As per the protocol, CBCT scans of both groups were taken 2 or 3 days post-operatively during their stay in our hospital.

Analysis surgical technique

The primary aim of our study was to analyze the surgical technique in both groups. The 3D reconstructions and separate coronal, axial, and sagittal views of the (CB)CT scans from the mandible before and after surgical treatment were compared.

The surgical technique was scored based on several characteristics. The following features were scored on a 2-point scale: removal of diseased bone/sequestra, treatment of the buccal cortex, treatment of the lingual cortex, and presence of dead space/persisting alveolus in frontal aspect of the mandible. Treatment of these features was scored as either present ("1") or absent ("0"). Whether the treatment of the feature was performed sufficiently was not taken into consideration to not obscure the results when the treatment was insufficient. The treated percentages of all the scores were calculated. Scores were assigned by two surgeons together, who specialized in treatment of osteomyelitis, and were blinded for the patient group. The treatment features are shown in figures 1-4.

Another aim of the study was to evaluate and compare the surgical outcome of our surgical treatment in group 1 with the previous surgery received elsewhere, and with group 2, without any previous surgical treatment. Both groups were consequently treated with our surgical protocol.

A post-operative closed mucosa without dehiscence, after 3 weeks, was considered healed. During follow-up, the presence of fistula, dehiscence, or recurrences were evaluated. The patients were seen for at least 6 months: postoperatively after 1 week, 1 month, 3 months, and then every 6 months up to 2 years.

Figure 1: 3D reconstruction of CBCT of pre- en post-operative result showing surgical technique group 1 patient

A: Right lower jaw shows persisting extraction alveoles, some lysis and subperiosteal bone formation
B: Right lower jaw shows rounded off and smooth edges and sufficient removal of buccal and lingual cortex

Statistics

Statistical analysis was performed in SPSS software for Windows (Version 25; SPSS Inc., Chicago, IL, USA). For continuous variables, median and range were reported; for binary variable, the percentages were computed. Data was reported in median, unless reported otherwise. A p-value <0.05 was considered statistical significant.

RESULTS

In this retrospective study, 30 consecutive patients with MRONJ were included in 2 groups. 15 patients had a previous surgical treatment elsewhere (group 1) and 15 patients were treated only with the surgical technique used in the LUMC (group 2). The patient characteristics are listed in table 1.

Patients

There were 11 males and 19 females. Fourteen patients used antiresorptive medication for osteoporosis, with no statistical difference in both groups (p=0.464). Age was unevenly distributed. Group 1 had a median age of 70 (51-87) years and group 2 had a median age of 72 (60-90) years.

Sixteen patients had cancer, of which seven had breast cancer, eight had prostate cancer, and one had multiple myeloma.

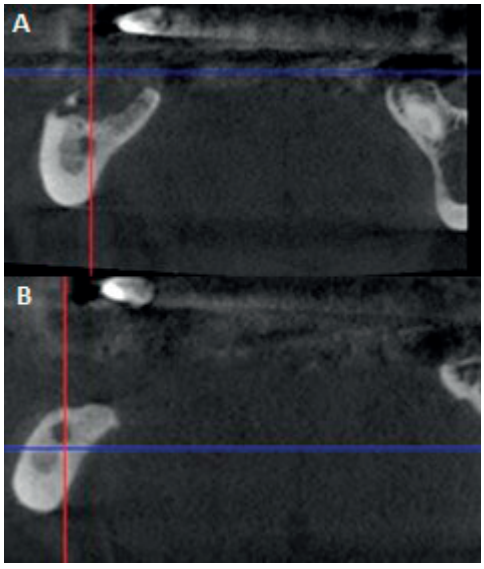
The follow-up was 3-26 months (mean 11.3±5.1). Group 1 patients mainly had stage III MRONJ; whereas, group 2 patients had stage II (p=0.008).

The median duration of medication was 77.4 months in group 1 and 19.88 months in group 2.

3D analysis of surgery

The surgical technique is illustrated in figures 1-4. The results of the study showed that in most cases of group 1, treatment of the buccal cortex was performed in 14 of 15 patients (93.7%). The

Figure 2 Pre- and postoperative treatment principle features of buccal & lingual cortex



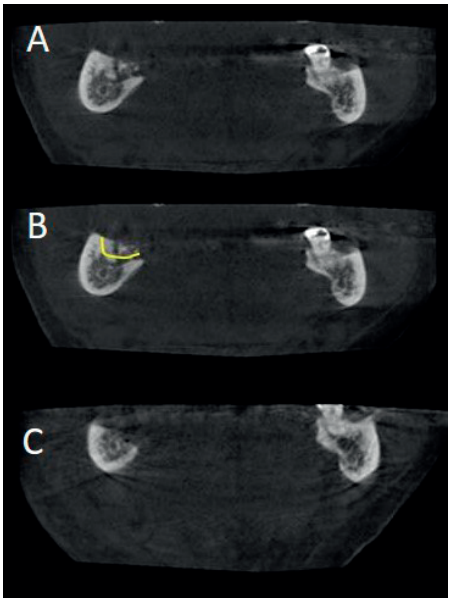
A: Pre-operative frontal view of sharp buccal edge, sequestrum and persisting lingual cortex.
B: Buccal subperiosteal bone has been minimally removed. Rounded off frontal aspect and smooth edges are reached.

Table I Clinical features

	Group I	Group II	Total	p-value
Gender				0.256[C]
Female	7	4	11	
Male	8	11	19	
Indication				0.464[C]
Osteoporosis	6	8	14	
Cancer	9	7	16	
Breast cancer	4	3		
Prostate cancer	5	3		
Multiple Myeloma			1	
Anti-resorptive medication				
Bisphosphonates			21	
Intravenous use		9		
Zolendronic acid monthly	4	3		
Zolendronic acid yearly		2		
Oral use		12		
Alendronic acid 70mg weekly	6	6		
Denosumab			9	
Xgeva 120mg monthly	5	4		
Stage[1]				0.008*[C]
II	6	13	19	
III	9	2	11	
Duration of medication (months)	77.4 (18-180)	19.88 (3-36)		
OP	90.67	24.44		
Cancer	67.5	14.0		
Follow up (months)	11.5±6.1	11.1±4.1		0.807[#]

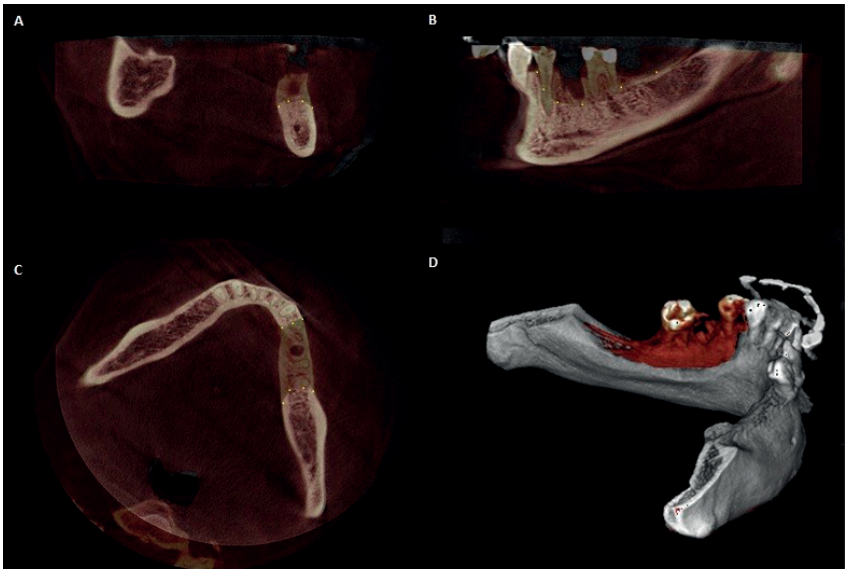
[C]=Chi-square-test
*p<0.05 was considered statistical significant
[1]=staging according to definition MRONJ AAOMS (Ruggiero et al 2014)
#=t-test

Fig 3 Pre- and postoperative treatment principles features of frontal view



A: An evident sequester on top of the alveolar process on the right mandible
B: Supposedly planned resection of the sequestrum and sclerotic bone
C: Post-operative view after saucerization and rounding off of sharp edges of both lingual and buccal cortex

Fig 4 Superimposed pre- and postoperative CBCT of LUMC treatment



CBCT scan of stage II MRONJ patient in the left lower jaw. The yellow dots represent the margins of the LUMC treatment.
A Frontal view: removal of bone with LUMC treatment of buccal and lingual cortex and clear rounded off frontal aspect.
B Sagittal view: evident lowering of the mandible and removal of the 34 and 36.
C Transversal view: removal of bone.
D 3D reconstruction of CBCT: extent of LUMC treatment is shown in red.

Table II Post-operative analysis treatment elsewhere vs LUMC treatment group I

Scan	Removal diseased bone (cumulative percentages)	Buccal cortex (cumulative percentages)	Lingual cortex (cumulative percentages)	Dead space/ Alveolus (cumulative percentages)	Transversal (cumulative percentages)
After surgery elsewhere	0=100% (0%)	0=6.7% 1=93.3% (93.3%)	0=100,0% (0%)	0=100% (0%)	0=0% (0%)
After LUMC treatment	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)

Table III Post-operative analysis of LUMC treatment group II

Scan	Removal diseased bone (cumulative percentages)	Buccal cortex (cumulative percentages)	Lingual cortex (cumulative percentages)	Dead space/ Alveolus (cumulative percentages)	Transversal (cumulative percentages)
After LUMC treatment	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)	1=100% (100%)

other features, such as removal of diseased bone, treatment of lingual cortex, and the presence of dead space, were scarcely scored in most of the cases, as shown in table 2.

The results of the patients of group 2 showed maximum scores of treatment of the buccal cortex in all fifteen cases (100%), as indicated in table 3. Removal of diseased bone, treatment of buccal cortex, and the presence of dead space had nearly maximum scores.

Surgical outcome of LUMC treatment

Group 1 showed healing and a closed mucosa in 14 of 15 patients (93.3%). However, two patients from this group developed a pathologic fracture after treatment in the LUMC. One patient had full recovery after a soft diet, and the other continued to have an extraoral fistula with denuded bone extraorally, but with a closed mucosa intraorally, and died a few months later due to metastatic disease.

Complete healing was found in all patients of group 2 (100%) with a closed mucosa and no further complaints. The follow-up of this group was also uneventful.

DISCUSSION

In this study (CB)CT scans from patients with MRONJ and a previous surgical treatment were compared to scans from patients who were treated at our department, according to our previously reported surgical technique[9,21].The hypothesis was that there is a difference in surgical

technique in unsuccessful results of patients treated elsewhere. A 3D analysis was performed, and the bone was evaluated for several surgical principles of the treatment. In addition, the clinical outcome of the used surgical technique was analyzed.

The results of this study showed that in other institutes except for the buccal cortex, the other surgical features, such as treatment of removal of diseased bone, the lingual cortex, and the frontal aspect, were scarcely treated in patients who had undergone surgery previously outside of our department. This may have resulted in sharp bony edges, dead space and insufficient primary closure thus giving inferior results. The findings confirm our hypothesis that a difference in surgical technique plays an important role in its success rate.

The primary goal of the surgical treatment of MRONJ is to remove as much as necessary but as little as possible[14]. During the surgical procedure for treatment of MRONJ, the diseased bone is removed, which is followed by saucerization with rounding off of the edges of the bone to provide an easy tension-free primary closure. Furthermore, the rounding off helps prevent the development of secondary mucosal lesions.

The first step during the surgery is the determination and removal of the diseased bone. Clearly discolored and necrotic bone is removed. Secondly, as much sclerotic bone is removed as possible, and rounded off in order to obtain primary closure, and as little dead space as possible without challenging the remaining strength of the jaw.

According to the literature, the use of autofluorescence as an aid to find the healthy bone margins has been suggested[22-25]. In this technique, tetracycline is administered to the patient, which is incorporated in the healthy, viable bone. This can be made visible with ultraviolet (UV) light during surgery, indicating the viable bone margins by lighting them up. This is an old technique and can sometimes be difficult to interpret[26].

The reactive sclerosis, which is caused by MRONJ, but also the sclerosis caused by the antiresorptive medication, may cause difficulties in interpreting the viability of the bone.

The present study showed that treatment of the buccal cortex seemed to be done mostly in group 1. After removal of the diseased bone, removal of the buccal cortex is the next step in the procedure for most surgeons. It is probably the easiest step of the procedure. Removal of bone up to the lowest medullar level of the defect is necessary. The lingual cortex can sometimes be difficult to reach due to the small opening of the mouth and the angulation of the bur. Removal of the lingual cortex also facilitates coverage of the mandible with the floor of the mouth. Similarly, this also counts for removal of the buccal cortex, facilitating coverage of the mandible with the vestibulum. Closure of the wound in layers, with the periosteum as first layer, is easier and tension-free if the lingual cortex has been lowered and rounded off. The wound can then be closed up in 2 layers if possible[10-14]. With a non-lowered lingual cortex, primary closure is difficult, because automatically dead space is introduced.

It seems that surgical a center with less experience in ONJ or osteomyelitis, may lead to insufficient surgical treatment. The insufficient treatment of the scored features automatically leads to suboptimal circumstances for closure primarily, and thus healing, as seen in the results

of the group 1 patients. Sometimes the surgery can be difficult and certain (lingual) angles can be clinically hard to reach with the bur. The presence of present edges, but smoothened, may not necessarily be of clinical relevance. Nonnenmuhlen et al. (2019) also confirmed this with their study on different mucosal flaps for closure of the wounds[27]. Therefore, these patients showed uneventful healing, showing that some treatment of the lingual cortex in combination with optimal treatment of the other features could still lead to complete healing. This supports the hypothesis that healing is dependent on the combination of the surgical principles.

Since in this group of patients the expected physiological bone resorption will not take place due to altered bone metabolism caused by the antiresorptive drugs, regardless of whether it concerns the surgical treatment of MRONJ or a dental extraction, it is advisable to remove bone to the level of the expected normal physiological bone resorption after 6 months. If this is not taken into account, extraction alveoli, or sharp edges will remain, and cause recurrent problems, starting with mucosal dehiscence. This counts especially for the alveolar process and extraction alveoli. Special attention is needed for the amount of removed bone. As mentioned earlier, surgeons should aim to remove as much as necessary, but as little as possible, to not compromise the surgical or functional result.

Some authors promote resection of the affected area and reconstruction with a microvascular fibula flap in stage III MRONJ[28-32]. Considering our success rate, resection of the mandible seems a very drastic surgical approach with a relative high comorbidity. It can certainly be of use in ultimum refugium cases, but also as an alternative in case the above mentioned surgical technique fails. Due to the recent reported success rates using comparable surgical techniques and a less invasive character of the surgery, the approaches of these authors should be the first choice of treatment in stage II and III MRONJ[9-14]. Many patients are medically compromised making major surgery not preferable or even not possible[33].

The results also promote early intervention, instead of a wait and see policy. In an early stage, sufficient treatment is less difficult than in an advanced stage III (with or without pathologic fracture). The stage did not seem to influence the outcome with our surgical approach. Even though underlying diseases could also worsen the surgical outcome, this was not the case with a success of more than 90% in group 1. Basic principles of treatment remained the same: removal of diseased bone, saucerization, and primary closure. Viable and smooth bone margins are necessary for tension-free primary closure. One of the two pathologic fractures was cured with conservative treatment and a soft diet, proving the reason why the basic principles should always be followed. The clinical outcome of the surgical treatment in both groups was 93.3% and 100%, respectively. This suggests that prior treatment does not influence the current treatment result, but could lead to a possible higher incidence of pathological fractures due to the loss of vertical height. Our results are in line with other authors[10-14]. In literature there are no other studies addressing specifically the surgical technique of the bone. This is the first study to perform a radiological analysis in order to obtain more insight on the possible factors for failure of the surgical treatment.

One of the limitations of this study was the relative small sample size, especially for group 1. Further studies are being performed in a larger cohort of patients in our hospital, with and without previous surgical treatment.

Another limitation was the statistically significant difference in the stages between the two groups. There were more stage III patients in group I. That could also be a reason for primary failure of the surgery elsewhere. Patients with severe oncologic conditions may have a decreased healing and thus worse outcomes. Despite the staging, underlying diseases, and duration of therapy, the first group was successfully healed with our surgical technique.

In addition, the circumstances of previous surgeries, such as an underlying disease, could have led to an initial surgical treatment under local instead of general anesthesia. Therefore, extensive surgery could not be performed, which could have affected the outcome. However, being able to heal these patients shows that when the basic principles of surgery are followed, complete cure can be achieved.

This study seems to support the hypothesis that the surgical technique of MRONJ is based on the treatment of diseased bone, buccal, and lingual cortex, and if treated sufficiently, altogether provides an easy primary closure without dead space leading to complete healing of the bone. Further research is necessary regarding the ongoing debate on the best treatment for MRONJ.

CONCLUSION

The surgical technique with high success rate of more than 93.3% in all stages of MRONJ is based on a few simple surgical principles comprising of extensive saucerization and rounding off in combination with primary closure. Therefore, this relative conservative surgical approach should be the first choice in the treatment of MRONJ. Further research toward the surgical technique to prevent deterioration, recurrence or failure of MRONJ is recommended.

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