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Clinical Outcome of Azithromycin dehydrate used in treatment of acute apical periodontitis and severe chronic marginal gingivitis compared to other antibiotics

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Abstract

Ninety six patient aged between 12 – 50 years attending the college of dentistry , Al- mustansyria university and the investigators clinics , they were divided into two equal groups; 48 Patients suffering acute apical periodntitis (painful) were subjected to different antibiotics after drainage and their prognosis towards non-painful chronic apical perioddontitis was observed and were as follows : 29.3% with Azithromycin, 20.8 % with ampicilline and 29.3% with ampicilline plus metronidazole with a total of 79.4 % .

The second group, were 48 students aged 12- 20 years suffering from severe marginal gingivitis (GI-3) and were subjected to different antibiotics after prophylaxis and some of them were kept on prophylaxis alone and their progress to mild marginal gingivitis (G.I.1) was observed and were as follows :20.8 % with azithromycin , 16.7 % with ampicilline, 22.9 % with ampicilline plus metronidazole and 20.8 % with prophylaxis and oral hygiene practice alone with a total of 81.2 % showing no significant difference between prophylaxis alone and those with prophylaxis and antibiotics .

Keywords: GI = gingival index.

Introduction

Apical periodontitis and marginal periodontitis treatment needs became very important in epidemiological surveys in most industrialized countries particulary those with nationalized health care systems like the

United Kingdom because of the increasing costs of their treatment provision[(1)].

In a comprehensive summary of prevalence data for apical periodontitis based on Scandinavian and European studies in treatment needs (i.e. , infected pulp canal space requiring complex intervention) compared to data of marginal periodontitis (score 4 , CPITN. , i.e. the need for complex intervention) , it was found that apical periodontitis is far more prevalent in western socities than advanced forms of periodontal disease which indicate resource allocation for it's conservative

treatment, risks of acute flare – up or the need for extraction [2].

A) Apical Periodontitis

Apical periodontitis , is a term to describe inflammatory conditions of the periodontal tissues are around the apex of the root that are caused by irritants in the pulp canal system .

It remains a prominent cause of pain and loss of oral function in all countries with high prevalence of dental caries, dental trauma and operative dentistry and their treatment is costly of time , financial resource and dental tissue[1].

Endodontic infection usually derived from the normal and flora gaining entry to the pulp through a carious lesion, pulp exposure by trauma or operative dentistry or through incomplete enamel / dentin cracks .

Species which invade and colonize the dying pulp are predominantly aerobic, gram positive, but with time these give way to an increasingly anaerobic gram negative flora, typically comprising of 2 to 8 species in any canal. This mixed collection of microbial species have shown to interact nutritionally supporting each other with the growth and evolution of a mature microbial climax community[2]. However some evidence exist that single Species infection are just as capable of producing periapical inflammation as mixed infection. Specific species have been associated with the development of symptoms and it's likely that virulence factors such as proteolytic enzymes, immunogenic capsular material, or ability to compromise host defence mechanism may be responsible. The gram negative anaerobic prevotella , prophyromonas and fuso bacterium species have special association in this regard[1].

In painful pulpoperiapical pathosis the inflammatory response of periapical connective tissue to pulpal irritants leading to exudative (acute) forces thus increasing intra periapical pressure resulting in pain for example in acute apical periodontitis an incipient initial exudative and mildly symptomatic inflammation of the periapical connective tissues with fluid exudates, while in acute periapical abcess there is (advanced) exudative and severly symptomatic inflammatory response of periapical connective tissue with oedema , leukocyte infiltration and suppuration.

Clinically, pain will range from slight tenderness of early stage of acute apical periodontitis to intense and continuous throbbing of acute periapical abcess. This pain become localized and tooth become tender to vertical percussion. Swelling is not present at early stages but a firm pressure against the mucosa over the root incite a positive painful response . As abcess extends towards the surface swelling increase and may be preceded by oedema and cellulites and resorption of overlying cortical bone and localization of suppurative mass beneath the mucosa producing a palpable fluctuant swelling [4].

One of the forms of acute apical periodontitis is the recrudescent (phoenix) abcess which is an acute periapical exacerbation arising from a previously existing chronic (granulomatous lesion) as it become contaminated or infected by elements from the root canal (zone of necrosis), this result from pressures exerted during operative procedures on the related tooth creating a negative pressure in the apical periodontium thus necrotic pulp debris may be sucked into the highly mobilized periapex.

Many studies attempting to quantity pulp death and development of apical periodontitis in response to operative dental procedures.

For example there is increasing evidence that crown preparation is associated with increasing levels of endodontic breakdown as observation periods increase , for approximately 2 - 4 % of pulp may loose vitality within the first 5 years of crown cementation and this figure rises to almost 20 % at 20 to 25 year recall[5].

Also the risk of acute flare up in chronic apical periodontitis has been estimated as 5 % per year , in other words , 50 % over a 10 year period [6].

The subacute periapical abcess (painful phase) , come from a chronic periapical abcess cycle , since in (non-painful phase) pain and swelling regress because there is drainage through the stoma of the sinus tract, but when this is blocked with a coagulum and / or proliferation of mucosal epithelium drainage ceases , periapical pressure increase and tooth become mildly tender to percussion . when this inflammation spread to soft tissues adjacent to this sinus tract stoma , it will balloon outward. A parulis (gumboil) develop on the mucosa and gingiva may develop a circumscribed red swelling.

In non-painful pulpoperiapical pathoses, there is inflammatory defence responses of periapical connective tissue to a pulpal irritant. Here a proliferative (chronic or granulomatous) component playing a dominant role and pain is absent because of diminished intra periapical pressure.

So in chronic periapical abcess (suppurative apical periodontitis) there is low grade inflammatory reaction of periapical connective tissue to pulpal irritants and is characterized by the formation of parulis and active pus formation drainage through stoma of sinus tract. The formation of periapical granuloma is characteristic of this type of pulp pathoses whose at it's periphery toxicity of root canal irritants become so diluted and diminished that the irritant act as a stimulus to fibroblast and osteoclasts in the area and a wall of collagen fibers is laid down by fibroblast in attempt to encapsulate the entire inflammatory complex separating the granulomatous tissue from bone. In a study by Langeland et al (1977)[7] on 35 biopsy specimens revealed bacterial cells in the periapical granulomatous tissue in only one case, thus indicating that these granulomas have either destroyed or contained the irritating pulpal bacteria.

In condensing osteitis, there is a productive response of periapical bone to a low – grade long standing pulpal irritation leading to increase in density of periapical bone, not because of greater concentration of minerals (hyper calcification), but because of osteoblastic hyperactivity.

The bony trabeculae increase in thickness to such a degree that the narrow spaces are eliminated or reduced to small tags of fibrous tissue i.e. there is more bone tissue in a given space. This is found in young persons around the apicies of mandibular teeth with large carious lesions . This return to normal after root canal therapy[4].

B) Marginal Periodontitis

Periodontitis, is inflammation of peridontium that extends beyond the gingiva and produces destruction of the connective tissue attachment of the teeth[8].

Gingivitis, is the inflammation of gingival tissue adjacent to tooth surfaces[9]. It can be developed as a result of local irritation of substances derived from microbial accumulation near the cervical region of teeth.

Dental plaque, is soft, non mineralized deposits which form on teeth that are not adequately cleaned [10], which can be recognized clinically when it reaches a certain thickness as a whitish or a yellowish layer primarily

along the gingival margin[11, 12], when dental plaque is deposited on the clinical crown it is called supragingival and when it extend in the gingival sulcus or in a periodontal pocket, it is called subgingival plaque.

Calculus, is an adherent calcified mass deposits on natural tooth surfaces. This fixture of calculus to the tooth surfaces promotes plaque accumulation and retension of irritant bacterial deposits which it play a major role in the progression of periodontal disease[11, 13, 14].

The accumulation of dental plaque on teeth supragingivally will be colonized by a complex microflora which is predominantly gram positive cocci (streptococcus sanguis) accompanied by increasing proliferation of gram negative cocci and rods (mainly actinomyces and bacteroides) starting after 2 days of plaque formation and becoming the predominant plaque flora after 4-9 days[9, 15].

Later this supra gingivally located microflora start to proliferate subgingivally and is characterized by relatively more gram negative anaerobic micro-organisms and motile bacteria (Bacteroids Melaninongenicus and spirochates causing gradual spread of the gingival inflammation into deeper connective tissue and loss of periodontal attachment and alveolar bone loss , followed by gingival pocket formation and periodontitis .

Bacteriological studies of dental plaque during the development of gingivitis suggest that there are more than 200 different species in mature plaque . Gingivitis is believed to result from quantitative changes in plaque rather from the overgrowth of specific micro-organism[16].

The most prevalent type of gingival disease among children and adolescent is chronic marginal gingivitis which is characterized by changes in color of gingiva , consistency and texture but with no radiographic evidence of bone loss [17], but different epidemiological studies showed that gingivitis reach its peak at (11-13) years of age and its prevalence declines constantly through (17-18) years[17,18].

Although periodontal disease is often associated with physical maturity, onset may be early in susceptible individuals at or shortly after puberty[19].

C) Antibiotics used in Treatment

In apical periodontitis , the drainage of an acute periapical abcess is either through the canal by widening the apical constriction and antibiotic coverage in the febrile patients , but if the patient is afebrile, no antibiotic is needed or by process of trephination (cutting a hole in the bone) and artifistulation (i.e. incision just below the most dependent point of the swelling with no.11 Scalpel) then antibiotics are prescribed with hot mouth rinses[20].

As most microorganism found in root canals are gram positive , penicilline is the drug of choice but because of development of resistant strains and possible allergy, alternative drugs and particularly erythromycin are widely used[21].

Gram negative microorganisms may cause endodontic infections makes indiscriminate use of penicilline or erythromycin for every case of infection may not always yield acceptable results . So, sensitivity tests are indicated to determine the most effective antibiotic . Also plating out a culture for sensitivity may prevent serious consequences if the infection develope rapidly .

Ampicilline

Is acid-stable (active orally) and effective against gram negative bacilli in addition to those susceptible to benzyl penicilline . It has a broad

spectrum of activity as that of tetracycline with the additional advantage of being bactericidal.

Like benzyl penicilline , ampicilline is destroyed by penicillinase enzyme so it is somewhat less active against organisms sensitive to benzyl penicilline .so it has a wider spectrum than potassium Penicilline V .

Its adult dosage is 500 mgm orally every 4 to 6 hours[22].

Erythromycin

Slightly broader antibacterial spectrum than penicillin and does not produce resistant organisms[20]. It is bactericidal in adequate concentrations and act on growing organisms by interfering with protein synthesis. It is an excellent antibiotic to be used in endodontics until sensitivity results are received . It is useful when penicillin is contra indicated and is usually given by mouth but it's activity is reduced by gastric acid and that is the reason for giving it as enteric-coated tablets or as a form of stearate or estolate. Sometimes erythromycin ethylsuccinate is placed instead of stearate in erythromycin mixtures .Erythromycin estolate is the most reliably absorbed preparation and if taken in short course (up to one week) , it is effective in dental infections and the risk of its hepatotoxicity is slight[22] i.e it is potentially hepatotoxic, while erythromycin stearate is not hepatotoxic[23] Erythromycin was recommended by the American Heart Association (1977) as a safe prophylaxis for patients with prosthetic heart valves to prevent endocarditis. The adult dosage is 250 mgm or more every 4 to 6 hours[20].

In a study by Jokinen M.A. (1970)[21] testing the sensitivity of 133 bacteremia strains to 11 chemotherapeutic agents erythromycin proved that out of 128 strains tested there were no strains resistant to it, indicating it high potency among other antibiotics.

Azithromycin

It's available as Azithromycin dehydrate, hydrogen citrate, monohydrate, Zithromax Tri-PAK, Zithromax Z-PAK.

The usual oral dosage for periodontal disease is 500 mgm, once daily for 4 – 7 days.

As a prophylaxis for subacute bacterial endocarditis, for children 15 mgm/kg and for adults > 16 years 500 mgm 30 – 60 minutes before the operative procedure and then continues for 2 – 3 days[24].

Azithromycin is a broad-spectrum macrolide antibiotic which possesses antimicrobial activity against gram-positive and a few gram negative microorganisms. Its widely used in dentistry for treatment of oral infection such as pericoronitis, gingivitis, and chronic conditions associated with secondary infections, especially for patients who are allergic .to penicillin's.

Azithromycin is one of the drugs recommended by the American heart association for prevention of bacterial endocarditis in susceptible patients. Azithromycin and its salts and esters are generally well tolerated and serious adverse effects are rare. Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are fairly common after both oral and parenteral use, probably because of the stimulant activity of Azithromycin on the gut. Gastrointestinal effects are dose- related and appear to be more common in young than in older subjects. Suprainfection with resistant organisms may occur and pseudomembranous colitis has been reported. . All forms of Azithromycin should be used with care in patients with existing liver disease or hepatic impairment, and the estolate is best

avoided in such patients. Repeated courses of the estolate or use for longer than 10 days increase the risk of hepatotoxicity Azithromycin may aggravate muscle weakness in patients with myasthenia gravis. Azithromycin and other macrolides have the potential to interact with a large number of drugs through their action on hepatic cytochrome P-450 isoenzymes, particularly CYP1A2 and CYP3A4. Such interactions can result in severe adverse effects, including ventricular arrythmias with terfenadine and pimozide.

Metronidazole

A Synthetic antimicrobial highly effective against trichomoniasis (a common vaginal infection) .and is active against bacteria and protozoa which are obligate anaerobes and it is not active against aerobic bacteria or fungi , it is also active against spirochetes such as those causing syphilis but less effective than penicilline .

It is mainly excreted in urine and also appear in saliva , but its toxicity is minor such as nausea or experiencing a metallic taste. But it cause interaction with alcohol causing flushing, sweating , palpitation and nausea .

It is active against organisms causing ulcerative gingivitis and its use does not cause disturbances of normal oral microflora , so that is why recurrences are less common to occur than if treated with penicillin .

In treatment of ulcerative gingivitis with metronidazole, plaque , calculus and debris must be removed because they harbour anaerobes that depend on other bacteria to maintain low local oxygen tension .

It is also effective in treatment of pericoronitis and other dental infections[22]. It's suitable course of treatment is 200 mgm tablets three times daily for 3 days .

In marginal gingivitis several antibiotics have been shown to suppress plaque formation and gingivitis to various degrees whether used topically or systemically. These include broad spectrum antibiotics such as tetracycline and kanamycin, those with narrow spectrum like penicillin, erythromycine and spiramycin, those specifically antagonistic against gram positive organisms like vancomycin and niddamycin (CC10232) and those with purely gram negative spectrum like polymyxin. But the danger of using indiscriminately antibiotics they might cause resistant strain or hypersensitivity & superinfection[25, 26]. None of the presently available antibiotics can be recommended for control of supragingival plaque .

Material and Method

Nintey six patients aged between 12-50 years attending the college of dentistry Al-Mustansiriyah University and private clinics of the researchers from August 2006 to September 2007 & were suffering from:-

A) Acute apical periodontitis .
B) Chronic marginal gingivitis (In severe form) .

There were 60 males & 36 females patient & were divided into 2 groups, 48 patients each. These groups represented the original oral conditions and azithromycin drug was trialed on them.

Group 1: 48 patients suffering acute apical periodontitis were divided into 3 subgroups each consists of 16 patients after pus drainage either from the root canal or by opening the overlying fluctuant mucosa (artifistulation) and inserting a corregated drain

Subgroup (a): These 16 patients were given 500 mgm of

azithromycin 2 capsules (1000 mgm) on first day and then one capsule for next two days.

Subgroup (b): These 16 patients were given 500mgm Ampicilline capsules 4 times daily.

Subgroup (c): These 16 patients were given 500mgm ampicilline capsules and 200 mgm metronidazole tablets 3 times daily .

All these patients were given mefanamic acid (Ponstan) 500mgm tablets for 3 days as anti-inflammatory and pain – killer. Then all these patients were examined after 3 days to see the outcome of each treatment This outcome was based on Ingles classification of pulpo periapical pathoses[22] which included :

I) Painful pulpo-periapical pathosis:

1) Acute apical periodontitis
2) Advanced stages of acute apical periodontitis such as:
    a) Acute periapical abcess.
    b) Phoenix (Recrudescent) abcess .
3) Sub-acute apical periodontitis (painful phase)

II) Non-painful pulpo-periapical pathosis:

1) Pulpo-periapical osteosclerosis (Condensing osteitis) .
2) Incipient chronic apical periodontitis .
3) Advanced chronic apical periodontitis , such as :
    a) periapical granuloma .
    b) Apical cyst .

4) Sub-acute apical periodontitis (non- painful phase) .

Group 2: 48 patients suffering marginal periodontitis were selected between age 12-20 years and all suffering from severe gingivitis (Score 3 – GI – Index). These patients were divided into four sub-groups each consists of 12 patients & after having complete prophylaxis (scaling & polishing) to their teeth & instructing them on effective tooth brushing twice daily (early morning & before sleep at night), they were divided as follows :

Subgroup (d): 12 patients were given 500 mgm azithromycin 2 capsules (i.e. 1000 mgm) at first day and then one capsule for next two days.

Subgroup (e): 12 patients were given 500 mgm ampicilline capsules 4 times daily.

Subgroup (f): 12 patients were given 500mgm ampicilline capsules & 200mgm metronidazole tablets 3 times daily .

Subgroup (g): 12 patients were left on prophylaxis and oral hygiene practice alone without giving them any treatment .

All these patients were examined after one week to see the outcome of each treatment . This outcome was based on gingival Index criteria[28] by examining the gingiva surrounding each tooth (as 4 gingival scoring units) using a mirror and sharp (00) Michigan periodontal probes on these areas:

1) The disto –bucal or labial papilla .
2) The buccal labial margin .
3) The mesio-bucal or labial papilla .
4) The lingual gingivial margin .

Then each site examined was scored as follows :-

0 = normal gingiva .

1= mild inflammation ,slight change in color , slight inflammation , no bleeding in palpation .

2= Moderate inflammation , redness, edema , glazing , bleeding in palpation .

3 = Severe inflammation , marked redness, edema , ulceration , tendency to spontaneous bleeding .

Then calculation for a single tooth = (Sum of all scores of 4 surfaces / 4)

For entire dentition = (Total of GI Scores / number of teeth examined)

The calculation will be accordingly.[28]

Condition		Score
Mild gingivitis	=	0.1 to 1
Moderate gingivitis	=	1.1 to 2.0
Sever gingivitis	=	2.1 to 3

Patients less than 12 years were excluded because of mixed dentition, also patients who are sensitive to any of the drugs used in this study, pregnant women, patients with cardiac or chronic bowel diseases, immuno compromised patients, and those who received any antibiotic within 24 hours before the start of treatment of this study were all excluded .

Results

From the result on table (1) out of 48 patients suffering of acute painful apical periodontitis, 42 (i.e. 87.6%) were relieved from pain as a result of having chronic or Subacute non-painful apical periodontitis. But only 6 patients continued suffering from subacute painful apical periodontitis (12.4%).

From table(2), it seems that all patients have improved their gingival index score & about 81.2% of them have improved their GI to score (1) & none of them achieved score (0) after one week of treatment & non of them stayed the same i.e. with GI score (3).

Discussion

Although there were 60 male & 36 female, the gender difference did not have a significant role on the results, since both groups were patients suffering from two different oral diseases, where they can affect both genders equally as in the first group who were dental emergency cases attending as a result of pain caused by acute apical periodontitis & the second group were patients selected by investigators because they have severe gingivitis (GI Score 3).

Table (1), showed that Azithromycin subgroup & Ampicilline with Mertonidazole subgroup gave similar prognostic effects on improving the patient acute apical periodontitis (painful) to chronic apical periodontitis which is non-painful & they have shown advantage of about 9% over those who use Ampicilline alone.

This may be due to that the root canal microbial flora whether the tooth is related to acute periapical abscess which developed after pulp exposure with its death & infection or the abscess is of the recrudescent (phoenix) type, which are gram -ve anaerobic type[1, 3] & since Erythromycin is bactericidal when used in adequate concentration & it has broader spectrum than Ampicilline[20, 21].

The other reason for Erythromycin effectiveness compared to Ampicilline when used alone, it seems that it reduce Penicillin gram +ve bacteria in a short time[29] & most of the reduction appear in the presence of alpha hemolytic streptococci in saliva which is reduced by 90% & when a Penicillin trochy is used three times daily for 5 days period[30].

This reduction lasts for 3 to 4 days accompanied by invasion of gram -ve bacilli which disappear when the use of antibiotic is discontinued.

Table (1) results have proved that patients who developed subacute non-painful apical periodontitis comprised 8.2% of the patients. Therefore the number of patients relieved from pain

was 42 or 87.6% while those who continued to have Subacute painful apical periodontitis were 6 (12.4%) patients & this was not to be related to the antibiotic used but it was due to incomplete drainage of pus or to blockage of stoma of the sinus tract or the formation of a coagulum or proliferation of mucosal epithelium ceasing the drainage of the fistula[4].

Table (2) have proved that prophylaxis (scaling & polishing) & oral hygiene instruction of effective tooth brushing was significantly equally effective as using antibiotics in addition to prophylaxis in reducing the severity of gingival inflammation, for the use of Azithromycin, Ampicilline+Mertronidazole & even using Ampicilline alone did not have significant reduction of GI score compared with prophylaxis & oral hygiene instruction alone, thus this have proved that gingivitis result from quantitative changes in plaque rather from the overgrowth of specific microorganism[16].

Also, this table showed that the use of Azithromycin is nearly effective as Ampicilline+Metronidazole in improving GI score for the reason that both Erythromycin & Metronidazole act against gram -ve anaerobic bacteria which is more predominant in the gingiva with high score as GI(3) & they also proved that they are superior to Ampicilline when used alone[21]. Since all the subgroups in table(2) were instructed to practice oral hygiene & that was the decisive factor in the prognosis of gingivitis from severe GI score(3) to mild GI score(1). But this differ from one individual to another in their performance which will be reflected on the results. So individuals with healthy gingiva & no history of periodontal disease can prevent gingivitis by effective tooth brushing every 48 hours[31] while those with established inflammation ,colonization of cleaned tooth surface occur sooner[32] & plaque grows more rapidly[33] & mature faster[34].

Therefore selecting a suitable frequency of tooth cleaning is the important factor[35].

On the other hand it was found in a study in Scandinavian countries that the duration of brushing was found to have greater influence on plaque removal than its frequency or pattern[36].

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Table (1): Clinical out-come of acute periodontitis after treatment with different Antibiotic Regimen.

Percentage of Pulpopathoses out comes				Treatment Method
Subacute Non-painful Apical periodontitis	Chronic Apical Periodontitis	Subacute painfu1 Apical periodentitis	Acute Painful Apical Periodontitis	
-	14 (92.3%)	2 (4.1%)	-	Subgroup(A) Azithromycin
2 (4.1%)	10 (20.8%)	4 (8.3%)	-	Subgroup(B) Ampicilline
2 (4.1%)	14 (29.3%)	-	-	Subgroup(C) Ampicilline + Mertronidazoe
4 (8.2%)	38 (79.4%)	6 (12.4%)	-	Total

Table (2): Clinical prognosis in the gingival index among patients suffering marginal gingivitis (GI Score 3) after treatment with & without different antibiotic regimen.

Percentage of Scores of Gingival Index				Type of Treatment
GI Score (3)	GI Score (2)	GI Score (1)	GI Score (0)	
-	2 (4.2%)	10 (20.8%)	-	Subgroup(D) Azithromycin
-	4 (8.3%)	8 (16.7%)	-	Subgroup(E) Ampicilline
-	1 (2.1%)	11 (22.9%)	-	Subgroup(F) Ampicilline + Mertronidazole
-	2 (4.2%)	10 (20.8%)	-	Subgroup(G) Prophylaxis+ Oral Hygiene Alone
-	9 (18.8%)	39 (81.2%)	-	Total