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Review Article

Systemic spiramycin therapy in periodontal disease- A review of literature

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ABSTRACT:

Antibiotics have become an integral part of the therapeutic armamentarium owing to the proven bacterial etiology of periodontal diseases. Many antibiotics can be used in conjunction with scaling and root planing, however, the emergence of bacterial resistance and side effects of the commonly used drugs warrants expansion of antibiotic spectrum and search of viable surrogates. This review aims to discuss Spiramycin a macrolide for its clinical efficacy in conjunction with non-surgical periodontal therapy in patients of advanced periodontitis. All literature available on PubMed, PubMed Central, MEDLINE, Google Scholar, and Google search engines was collected. The information extracted indicated that spiramycin is endowed with good antimicrobial activity with ability to achieve high concentrations in gingival crevicular fluid and saliva proving efficacious in terms of clinical parameters improvement in patients of advanced chronic periodontitis. It is a safe drug with potential usage in conditions where drugs like Penicillins or tetracyclines are contraindicated or show marked resistance.

Key Words: Spiramycin, periodontal therapy, antibiotics, scaling and root planing

Key Messages: Being highly concentrated in the saliva and gingival crevicular fluid, it has been proven to be effective both in terms of reducing the pathogenic bacterial masses and improvement of clinical parameters (especially pocket depth reduction and clinical attachment levels) in patients of periodontitis.

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INTRODUCTION

The bacterial causation of periodontal diseases has been clearly established in the literature. [1,2,3] The bacterial flora of periodontitis is complex and encompasses obligate anaerobes (Gram-negative bacilli and Gram-positive cocci), spirochetes, fastidious anaerobes and capnophilic bacteria. The microbial composition of the disease-producing plaque and putative host susceptibility factors for periodontitis have been elucidated during the last two decades. Therefore, the elimination of the pathogenic bacteria implicated in the etiology of periodontal diseases results in the resolution of inflammation and improvement in periodontal status.[4,5] A microbiological approach to periodontal therapy aims primarily at suppressing specific pathogenic bacteria and permitting a subsequent recolonization of a microbiota compatible with health.

Periodontal recuperation, in most patients, can be achieved by mechanical debridement (scaling and root planing), with or without surgery, in association with the establishment of meticulous oral hygiene thus reducing the bacterial load and changing the environment of microbial niches.[6] This unspecific therapy was proven effective for a long time.[7] However, despite such treatment modalities, cases of rapidly progressive periodontitis,[8] refractory periodontitis,[9] recurrent periodontitis,[10] juvenile periodontitis,[11,12] patients with poor or no maintenance,[13] acute or severe periodontal infections (periodontal abscess, acute necrotizing gingivitis/periodontitis) may protract additional benefits from adjunctive antibiotic therapy either in the form of local delivery or systemic administration. Patients with gingivitis or stable chronic periodontitis usually respond well to mechanical therapy alone and

derive little or no additional benefit from antibiotic therapy.

While the use of systemic antimicrobials for treatment of periodontitis has been controversial, enough evidence can be sought for its use in conjunction with mechanical therapy to improve the overall results of treatment. Winklehoff et al. in a systematic review stated that systemic periodontal antibiotic therapy aims to reinforce mechanical periodontal treatment and to support the host defense system in overcoming the infection by killing subgingival pathogens that remain after conventional mechanical periodontal therapy.[14] Haffajee et al. also stated that antibiotherapy provides better clinical improvement in terms of attachment loss both in chronic and aggressive periodontitis.[15]Thus, antibacterial agents have become an integral part of the therapeutic armamentarium, but systemic use of antibiotics is still contentious due to its side effects.

Persual of the literature reports a wide range of antibiotics used in conjunction with mechanical periodontal therapy. The most commonly used antibiotics include tetracyclines (doxycycline and minocycline), penicillins (amoxicillin), metronidazole, macrolides (spiramycin, erythromycin, azithromycin), clindamycin and ciprofloxacin. The most frequently used combination therapy is metronidazole and amoxicillin as it is known to combat both Aggregatibacter actinomycetemcomitans (A.a) and Porphyromonas gingivalis (Pg) attributed infections.[16] It is evident that there is no clear indication of the superiority of one antibiotic regimen over another and the choice of antibiotic should be made on an individual basis. This review aims to discuss a less explored antibiotic spiramycin and its efficacy as an adjunct to conventional periodontal therapy.

METHOD OF DATA COLLECTION

Collection of data was done using the following keywords:"Spiramycin in periodontal therapy", "spiramycin and its efficacy", "use of spiramicin as an adjunct in periodontal therapy", "antibiotics used in periodontal therapy" on pubmed, Pubmed Central, Google scholar, Google search engines, MEDLINE. Further the articles were handpicked from the references of selected articles. Total articles met the selection criteria. Search was limited to English language.

TYPE & SPECTRUM

Spiramycin is a 16 membered cyclic macrolide antibiotic isolated from Streptomyces ambofaciens and is a natural mixture of three components: spiramycin I, II, and III with a minimum of 85% of spiramycin I, and a maximum of 5% for II and 10% for III, respectively. It is rapidly transformed into a cysteinate derivative in the human plasma.

It is a medium spectrum antibiotic, belonging to the same genre as erythromycin and azithromycin ,active mainly against the Gram-positive bacteria including Streptococcus and Actinomyces species and to a lesser extent against Gram-negative, Clostridium ,anaerobes and spirochetes.

MECHANISM OF ACTION

Spiramycin inhibits translocation by binding to bacterial 50S ribosomal subunits and inhibiting protein synthesis both in vivo and in vitro.[17] It is a potent inhibitor of the binding to the ribosome of both donor and acceptor substrates, thus inducing rapid breakdown of polyribosomes.[18] The ribosomes of both Gram-positive and Gram-negative organisms are susceptible to macrolides, but these antibiotics are mainly effective against Gram-positive bacteria due to inability of spiramycin to enter the porins of Gram-negative bacteria.

CONCENTRATION IN PERIODONTAL TISSUES

In experimental animals, spiramycin is reported to be concentrated in very high amounts in the alveolar bone, gingival tissue, and salivary glands for long periods and is subsequently secreted into surrounding tissues. Approximately 1 or 2 g of spiramycin was released through saliva which is significantly higher than penicillin (1,000,000 U), dimethyl chlortetracycline (600 mg), and erythromycin (1 g).[19] Lambrou et al. found that spiramycin was secreted in the gingival crevicular fluid (GCF) at 1st to the 9th hour post administration, which enhances the activity on subgingival microbiota.[20] Yankell et al. demonstrated that spiramycin can be measured in detectable amounts in the saliva and salivary glands even when the antibiotic cannot be recovered in plasma.[21]Also, the submaxillary antibiotic levels are higher than parotid levels at all times. Leung et al. reported that after a dose of 400 mg/kg in rats detectable amounts of antibiotic was extractable from the parotid and submaxillary glands up to 14 and 21 days post administration.[22] Even the mandibular jaw and gingival tissues had detectable antibiotic levels after dosages of 100, 150, and 400 mg/kg for at least 7 days after termination of medication. Denks et al. reported that two days post spiramycin administration, GCF concentrations are ten times as high as in saliva or venous blood.[23] Rozetter et al. studied the levels of spiramycin and metronidazole in gingival fluid, saliva and blood after a single administration to 12 healthy patients and repeated administration to 4 patients with recurring severe periodontitis. [24] Analysis was performed at regular intervals during the immediate 24-h period post administration and after the first and the 15th days of repeated administration to the patients. It was concluded that gingival fluid contains much higher concentrations of spiramycin both at day 0 and day 15 exceeding that needed (higher than MIC) to inhibit the growth of periodontopathic bacteria. The standard concentrations in the body fluids has been described in [Table I]

Table-I Presents the standard concentration range of spiramycin in plasma, saliva nnd GCF

SPIRAMYCIN	CONCENTRATION RANGE
Plasma	15 to 2000 ng/ml
Saliva	15 to 5000 ng/ml,
Gingival crevicular fluid	15 to 50,000 ng/ml

whereas the various dosages of the drug used by different authors has been listed in [Table II].

Table II-presents the commonly used dose and duration of spiramycin reported in the literature

DRUG	AUTHOR	YEAR	DOSE	TYPE OF DISEASE
Spiramycin	Mills et al.[26]	1979	1 gram per day for 5 days	Advanced chronic periodontitis
Spiramycin	Rozanis et al.[27]	1979	500 mg capsules qid[@] for 5 days	Anti plaque agent
Spiramycin	Sznajder et al.[28]	1987	1 gm thrice daily 1st day and 1gm twice daily for 14 days	Chronic periodontitis
Spiramycin (Rovamycin)	Al Joburi et al .[29]	1989	1,500,000 I.U. 12 hourly for 14 days	Advanced chronic periodontitis
*Spiramycin	Bain et al.[30]	1994	1,500,000 international units, twice per day (IU[#], bid[$]) for 14 days	Advanced chronic periodontitis
Rodogyl (spiramycin +metronidazole)	Rozetter et al.[24]	1994	769,000 IU spiramycin and 128.0 mg metronidazole once daily for 15 days	Recurrent severe periodontitis
Spiramycin +metronidazole	Poulet et al.[31]	2005	1,500,000 units/250mg, three times a day for 6 days	Active periodontitis
Spiramycin(Rovamycin)	Chiappe et al.[32]	2015	3.000.000 I.U. (650.4 mg of Spiramycin) 2 tablets (loading dose), continuing with 1 tablet every 12 hours for 7 days	Severe periodontitis

*****The dosage and duration in the Heitz-Mayfield systematic review 2009.[33]
#:international unit ; $:two times a day ; @:four times a day

MIC OF SPIRAMYCIN

Sutter & Finegold demonstrated that the value of MIC for spiramycin is 11.0 µg/ml when used alone and 1.2 µg /ml when combined with metronidazole against anaerobes.[34] The susceptibility to spiramycin tested by dilution in agar against common periopathogens according to the M11A3 standard of the NCCLS was found to be 32mg/L. Also, Poulet et al. reported that the addition of a fixed dose of spiramycin to metronidazole, or of a fixed dose of metronidazole to spiramycin, doesn't result in a change in the MICs of metronidazole and spiramycin, respectively.[31]

BACTERIAL SUSCEPTIBILITY

Mouton et al. studied the susceptibilities of 65 bacterial isolates from subgingival plaque to several antibiotics, including spiramycin.[35] Their data revealed the spiramycin resistance of A.a which was later confirmed in subsequent studies by Baker et al. who tested the antibiotic susceptibilities (using an agar dilution technique) of 139 strains of anaerobic bacteria.[36] Chan et al. tested 400 strains of oral bacteria for their susceptibility to spiramycin in vitro and found that bacterial species susceptible to spiramycin were Bacteroides gingivalis (93% of 57 strains tested), B. intermedius (100% of 35 strains tested), and Bacteroides melaninogenicus (88% of 17 strains tested), all strains of Treponema denticola (three susceptible and four moderately susceptible) and all strains of the of Actinomyces were also susceptible.[37] Streptococcus mutans also showed susceptibility to the antibiotic (90% susceptible and 10% moderately susceptible of 48 strains tested) including some strains of Fusobacterium and

Veillonella. Their results indicated that about 70 % of the 400 oral bacterial isolates tested were susceptible to spiramycin, 19% were moderately susceptible, and 11% were resistant. Chiappe et al. evaluated the in vivo effect of systemic administration of Spiramycin for 7 days on Porphyromonas gingivalis (Pg), Tannerella forsythia (Tf), Treponema denticola (Td) and Aggregatibacter actinomycetemcomitans (A.a), using PCR technique rather than dark filed microscopy.[32] They demonstrated suppression of Pg, Tf, Td, but not A.a. The list of susceptible bacteria is provided [Table III]

Table III-Based on the available data the list of susceptible periopathogens

MICROORGANISMS	SUSCEPTIBILITY
Porphyromonas gingivalis	✓
Prevotella intermedia	✓
Micromonas micros	×
Aggregatibacter actinomycetemcomitans	× (resistant)
Eikenella corrodens	×
Campylobacter rectus	×
Fusobacterium	Variable
Streptococcus mutans	✓
Streptococcus sanguis	✓
Motile rods	✓
Spirochaetes	✓
Treponema denticola	✓
Tannerella forsythia	✓
Capnocytophaga	In combination with with metronidazole
Anaerobes (clostridium only)	✓ (not effective against most)
Veillonella	Variable
Lactobacillus species	×

SPIRAMYCIN AS AN ANTIPLAQUE AGENT

Keyes et al. determined that spiramycin was the most effective of nine agents used in reducing dental plaque and periodontal lesions in Syrian hamsters.[38] Rozanis et al. tested spiramycin as a chemotherapeutic plaque control agent with 63 volunteers, 29 experimental receiving 2 gram spiramycin daily for 5 days and 34 control- capsules of placebo, who abstained from mechanical oral hygiene procedures for 11 weeks.[27] At each examination visit (0, 1, 3, 7, and 11) weeks intra-oral photographs were taken, gingival and plaque indices recorded, and plaque samples collected. In the experimental group there was a statistically significant decrease in plaque as measured by wet weight, turbidity, nitrogen, and carbohydrate parameters for at least 3 weeks with significant decrease in the number of Streptococcus mutans and S.sanguis both at 1 and 3 weeks without any detectable influence on the number of Gram-negative organisms which continued to form plaque. Rossetti et al. evaluated 18 periodontal patients for bleeding, probing depth, plaque indexes before and after antibiotic therapy with spiramycin and concluded after conducting bacteriological and coaggregation tests that spiramycin is endowed with a good efficacy in periodontal diseases. [39]

SPIRAMYCIN IN CHRONIC PERIODONTITIS

Investigations as early as in 1960's reported favourable results with spiramycin in human clinical trials. Daligland conducted a three-year study on 90 periodontal patients treated for 20 days; Harvey gave a detailed account of seven of 70 cases treated; and Gendron administered spiramycin for treating 300 patients with varied oral conditions.[40, 41, 42] Winer et al. compared the effect of spiramycin v/s placebo in periodontal patients and noted improvement in patients treated with spiramycin even when local therapy was not applied.[43] The screening of the literature revealed information of only a few studies which examined the efficacy and safety of spiramycin when used adjunctively with mechanical debridement in the treatment of advanced periodontal diseases. Those which were double-blind placebo controlled randomised clinical trials designed to compare both clinical and microbiological changes after mechanical debridement with spiramycin are mentioned [Table IV].

Table IV-RCT's reporting the use of spiramycin and combination

Drug	Author	Treatment modality	Clinical parameters measured	Microbial composition change	Type of study	No.of teeth and selection criteria
Spiramycin v/s erthyromycin v/s placebo	Mills et al.[26]	SRP[@]+ spiramycin SRP+ erthyromycin SRP+ placebo	GI[#],PH[##],PPD[$],GCF[$$] Volume, Wet plaque weight	-	double-blind	Mild to severe disease
Spiramycin v/s erthyromycin v/s placebo	Mills et al.[26]	SRP+ spiramycin SRP+ erthyromycin SRP+ placebo	GI,PH,PPD,GCF Volume, Wet plaque weight	-	double-blind	Advanced periodontal disease
Spiramycin v/s placebo	Sznajder et al.[28]	Spiramycin placebo	PI[^],GI,BOP[^^],PPD,GCF flow	Coccoid cells,motile rods and spirochaetes	double-blind	3 teeth with deepest pocket
Spiramycin + metronidazole (rodogyl) v/s placebo	Chinquee et al.[44]	SRP+Rodogyl SRP+placebo	PI,GI,PPD,CAL[*]	-	double-blind parallel randomized trial	Two sites with PPD>7 mm
Spiramycin v/s tetracycline v/s placebo	Al Joburi et al .[29]	SRP+ spiramycin SRP+ Tetracycline SRP+ placebo	PI,BOP,CAL,PPD,GCF	Spirochaetes	double-blind, parallel, RCT[**]	4 PPD >7 mm
Spiramycin v/s placebo	Bain et al.[30]	SRP+Spiramycin SRP+placebo	PI,GI,BOP,PPD, CAL,GCF volume	-	randomized, placebo controlled clinical trial	
Spiramycin v/s placebo	Chiappe et al.[32]	SRP+Spiramycin SRP+placebo	PI,GI,BOP,PPD, CAL	Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola but not Aggregatibacter actinomycetemcomitans	randomized, placebo controlled clinical trial	3 sites with PPD>7 mm and <10 mm

**: Randomised clinical trial; ^: Plaque index; #: Gingival index; ^^: Bleeding on probing;
$: Pocket probing depth, *: Clinical attachment loss; $$: Gingival crevicular fluid, ##: Plaque height; and @: Scaling and root planning

Two studies used a combination regimen of spiramycin and metronidazole (rodogyl). However only one study compared the clinical parameters.

RESULTS OF THE REPORTED STUDIES

All the studies indicated that spiramycin used in conjunction with scaling and root planning (SRP), can offer an additional benefit over SRP alone, in terms of clinical attachment level (CAL) and pocket probing depth (PPD) change, especially in deep pockets. Sznajder et al. compared the effect of systemic short-term spiramycin administration on the subgingival microbiota and gingival tissues and reported that spiramycin showed a statistically significant increase in coccoid cells, and reduction of motile rods and spirochetes, as well as pocket depth decrease at 2 weeks of examination.[28] Plaque Index, Gingival Index and Crevicular Fluid only changed at 4 week examination with no changes recorded for the control group. Mills et al. in a two phased study reported that spiramycin produced a reduction in PPD (of 30%) in advanced periodontal lesions and produced the

greatest decrease in all the recorded clinical parameters amongst the 3 groups.[26] Al Joburi et al. reported that at the termination of 24 weeks, all three groups showed clinical improvement when compared to the baseline data, but there were no significant intergroup differences in any of the clinical parameters measured.[29] The proportion of spirochetes significantly decreased at second and eighth week intervals in both tetracycline and spiramycin groups (26% to 0.04% and 28% to 0.04%, respectively), compared to the placebo group (30% to 7%), but only in the spiramycin group was the proportion of spirochetes significantly lower than the placebo group at the 24-week interval (3% and 11%, respectively). Bain et al. reported statistically significant differences in probing depth at 2, 8, 12 and 24 weeks with spiramycin with, a significant improvement in attachment level noted at 12 weeks.[30] All other clinical parameters showed no difference between drug and placebo. Herrara et al. systematic review and meta-analyses showed a statistically significant additional effect of spiramycin with regard to PPD change (0.2-0.86 mm) and for CAL change (0.2-0.8 mm) for deep pockets.[45] However, Chiappe et al. did report better improvement in all clinical parameters as compared to the placebo group but the difference was statistically insignificant at all times till 3 months, although there was improvement in all parameters from baseline in both the groups. [32] After Spiramycin administration Pg, Tf and Td were suppressed showing statistically significant difference with the placebo group without any change in Aa detection in any of the groups.

The combination of spiramycin and metronidazole exhibited a greater gain in attachment level (0.67 mm) from the 2-month interval until the end of the study. A significantly greater decline in the proportion of spirochetes in the Rodogyl group at the 14-day interval which remained significant at all study intervals was noted. No difference in the proportion of motile organisms was observed with no significant differences in the proportion of resistant bacteria. There were no significant intergroup differences at baseline for any of the clinical parameters measured but a significant improvement in PII, GI and probing depth (PD) within each treatment group over the 6-month study interval.[44]

SPIRAMYCIN IN AGGRESSIVE PERIODONTITIS

Screening of the literature revealed only one study that compared the in vitro macrolide efficacy (spiramycin and erthyromycin) on principal periopathogens in 20 patients of aggressive periodontitis from which 60 subgingival plaque samples were taken. J. Slots's rapid identification method was used to isolate bacterial strains of Pg, Pi, Tf, Fusobacterium nucleatum, Peptostreptococcus micros and A.a. The results indicated that 68% of the tested anaerobic bacteria were sensitive to spiramycin but A.actinomycetemcomitans showed a high resistance limiting the use of this antibiotic in patients of aggressive periodomtitis.[46]

SPIRAMYCIN RESISTANCE

Rams et al. studied in vitro resistance of putative periodontal pathogens to therapeutic concentrations of spiramycin, amoxicillin, and metronidazole in the United States using subgingival plaque specimens from 37 adults with untreated severe periodontitis which were anaerobically cultured, and isolated periopathogens identified to a species level.[47] In vitro resistance to spiramycin at 4 mg/ml, amoxicillin at 8 mg/ml, and/or metronidazole at 16 mg/ml was noted. A total of 18 (48.7%) subjects yielded antibiotic-resistant putative periodontal pathogens with spiramycin at 4 mg/ml, as compared to 23 (62.2%) subjects with amoxicillin at 8 mg/ml, and 10 (27.0%) subjects with metronidazole at 16 mg/ml concluding that in vitro spiramycin resistance among putative periodontal pathogens of United States origin occurred in approximately one-half of severe periodontitis patients evaluated. [Table V]

Table V- In vitro resistance of spiramycin

Bacteria	% resistance
Fusobacterium nucleatum	44.4%
Prevotella intermedia/nigrescens	11.1%
Parvimonas micra	10.8%
Streptococcus constellatus	10%
Streptococcus intermedius	10%
Porphyromonas gingivalis	6.7%
Tannerella forsythia	5.3%

SIDE-EFFECTS OF SPIRAMYCIN

Being a well-tolerated drug only a few side effects have been reported in the literature. Eyraud et al. evaluated the effects of three macrolide antibiotics on rat polymorphonuclear leukocyte chemotaxis.[48] Rats were given 25 mg/kg twice a day of either erythromycin, josamycin or spiramycin by gastric intubation for 5 days. In all cases, chemotaxis was found to be impaired by 10-20% only, suggesting that these antibiotics do not exert a deleterious influence on the chemotactic response of treated patients unlike aminoglycosides and tetracyclines. Bain et al. reported

abdominal pain in 2 % of the test group patients after 2 weeks of drug administration. [30]

CONCLUSION

The appraisal of evidence from the literature indicates that Spiramycin fulfils the essential conditions required for an antibiotic to be used in conjunction with mechanical periodontal therapy. Being highly concentrated in the saliva and gingival crevicular fluid, it has been proven to be effective both in terms of reducing the pathogenic bacterial masses and improvement of clinical parameters (specially pocket depth reduction and clinical attachment levels) in patients of chronic periodontitis. It is a safe ,non-toxic, well tolerated drug with minimal side effects and can be used as a viable surrogate in cases where more commonly used antibiotics like tetracyclines (doxycycline and minocycline), penicillins (amoxicillin), metronidazole are contraindicated. With the emergence of antibiotic resistance to the more commonly used drugs further research and clinical trials using spiramycin needs to be done to enlarge the antimicrobial spectrum and exploit synergy between antibiotics to combat complex mixed subgingival infections. Although its efficacy in cases of aggressive periodontitis remains questionable, it still remains a definitive auxillary therapy in patients of severe advanced adult periodontitis. Also, it's role in the form of a local therapeutic agent needs to be elucidated.

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