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The role of rifampicin in the treatment of chronic suppurative otitis media.

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دور عقار الريفامبسين في علاج التهابات الأذن الوسطى المزمنة

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الخلاصة:

يعتبرالتهاب الاذن الوسطى المزمن الخمجي من اهم اسباب التهاب الاذن الوسطى وتوجد انواع مختلفة من البكتريا تتسبب في هذا الالتهاب.دراسات عديدة اجريت في هذا المجال ومعظمها استخدمت عقار السبروفلوكساسين في العلاج. **هدف** هذه الدراسة هي لتقصي فائدة استخدام عقار الريفامبسين كبسول في علاج النوع الآمن من التهاب الأذن الوسطى المزمن. **تمت** الدراسة في مستشفى الكرامة العام/شعبة طب وجراحة الإذن والأنف والحنجرة /في واسط، حيث تم انتقاء 200 مريض قسموا إلى مجموعتين متساويتين لكن لم يستمر معنا بالمتابعة سوى مريض164 منهم 88 مريض في المجموعة (أ) و 76 مريض في ألمجموعه (ب). أعطي للمجموعة (ب) الدواء المعتاد من عقار سبروفلوكساسين حبوب مع قطرات السبروفلوكساسين و قطرات البيتاميثازون للأذن ،بينما أعطي لمرضى ألمجموعه (أ)نفس العلاج أعلاه مضافا له عقار الريفامبسين كبسول. تم بعدها دراسة نسبة جفاف الأذن من الإفرازات الخمجية خلال الستة أشهر الأولى بعد العلاج و نسبة رجوع الإفرازات بعد الجفاف وتوقف استخدام ألعلاج. كما تم دراسة النتائج ألمختبريه لاثر العقار مفردا ومجتمعا مع السيبروفلوكساسين على المجتمعات البكتيرية المستحصله من إفرازات الأذن .

كانت **النتائج**: بان استخدام الريفامبسين مجتمعا مع الادويه الأخرى قد ساهم بتسريع جفاف ألأذن خلال الأسبوع الأول88%و65% للمجموعة **ا** و**ب** بالتعاقب (فرق مهم ومحسوس إحصائيا)،لكنه لم يكن هناك فرق محسوس ومهم إحصائيا في مجمل حالة جفاف ألأذن من الإفرازات) ، وكذلك قلل العقار من نسبة رجوع حالة الإفرازات و ساهم في استجابة أفضل للعلاج بعد حالة الرجوع9% و75% للمجموعة **ا** و 32% و 52% للمجوعة **ب** .من خلال الدراسة وجد أيضا بان الريفامبسين كبسول دواء آمن وسهل التناول للمرضى

باختصار فان عقار الريفامبسين قد يساعد في سرعة جفاف الاذن،تقليل رجوع الافرازات الخمجية مع استجابة افضل للعلاج عند رجوع حالة الافرازات الخمجية.

Abstract:

Back ground: Chronic suppurative otitis media (CSOM) has been an important cause of middle ear disease. The bacterial flora found in chronic suppurative otitis media varies considerably**.** A number of studies used fluroquinolon derivatives especially group II of this drug, like ciprofloxacin

Objective In this study there was a trial for evaluatation of the benefit of using oral rifampicin drug in the treatment of tubo- tympanic type of chronic suppurative otitis media in combination with ciprofloxacin.

Patient & methods: In Al-Kerama general hospital/ENT department in Wassit 200 patients were selected divided in to two equal groups (A&B) but only164 patients continue in the study, 88 patients in group A & 76 patients in group B.

Group B received the usual line of treatment in the form of oral ciprofloxacin& local (ciprofloxacin drops+ betamethason drops), while group A received the same drugs in addition to oral rifampicin. The dryness rate of the ears from discharge along six months & the recurrence rate after dryness & stopping treatment were studied. Also the laboratory results of the effect of rifampicin alone & in combination with ciprofloxacin on the bacterial growth in the culture media from ear discharge were studied.

Results: Its found that the use of rifampicin in combination with other drugs used enhance faster dryness that, The percentage of ears that became dry in the 1st week were 88% & 65% for group A & group B respectively, (significant difference) . While the dryness within the 2nd week & the rest of 1st month were5.7% & 4.5% for the group A, and 15.8% & 14.4 % for group B (It was not significant).

While the recurrent rate & response to treatment after recurrence were 9% & 75% for group A against 22.3% & 52% for group B .(significant difference).rifampicin was a safe drug & well tolerated by the patients.

Conclusion: Systemic drugs like rifampicin when used might enhance rapid dryness, decrees recurrence of discharge &give us better response to treatment after recurrence**.**

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Introduction:

Chronic suppurative otitis media (CSOM) has been an important cause of middle ear disease since prehistoric times.[*(1)] The bacterial flora found in chronic suppurative otitis media vary considerably [*(2),(3)] the predominating organism are usually gram negative bacilli (most frequently is pseudomonas) & the anaerobic (bacteriodes fragillis) is the most common anaerobic micro organism cultured in chronic suppurative otitis media.

Approximately 60% of the aerobic bacteria in chronic suppurative otitis media are beta_lactimase producing organism [*(1)]

Large number of studies about treatment of chronic suppurative otitis media done, many of them used fluroquinolon derivatives especially group II of this drug, like ciprofloxacin, other studies used other drugs like gentamycin, moxalactum …etc *(4),(5)

The ciprofloxacin has excellent gram negative G^- activity but moderate to good gram positive G+ activity & in addition to that the methecillin resistant staph cocci are also resistant to ciprofloxacin while group III like gatifloxacin, moxifloxacine or sparafloxacin have improved activity against gram positive G+ especially streptococcal pneumonia & to some extant staphylococcal*(6).

It's not known whether the enhanced activity is sufficient to permit use of these agents for treatment of infections caused by ciprofloxacin resistant strains. *(6).

Resistance during therapy with fluroquinolon emerge with a frequency of about one in 10^7 _ 10^9 especially among staphylococci, pseudomonas, serratia & with the long use streptococcal pneumonia resistance merge also.*(6)

So from all the above the it seemed that ciprofloxacin is not an enough drug to treat chronic suppurative otitis media because its limited ability to cover all micro-organism cultured from chronic suppurative otitis media& the resistance that develop to this drug; & because of the limitation in getting the group III fluoroquinolones derivatives in our country now a days, so the combination of drugs was the possible idea to gain the advantage of antibiotic combination especially broadening the spectrum of the antimicrobial activity & to complete deficient property of the fluoroquinolones derivatives (6) ,.

The rifampicin was selected as the drug that will combine with the ciprofloxacin for the treatment.

Rifampicin is a semi synthetic wide spectrum bactericidal antibiotic, it acts through the inhibition of DNA dependant RNA polymerase activity in susceptible cells. Specifically it interacts with bacteria RNA polymerase but does not inhibit the mammalian enzyme.

Rifampicin kills organism that are poorly accessible to many other drugs ,such as intracellular micro-organism & those sequestrated in abscess & can be used in combination for treatment of osteomylitis , but it can not be used alone because of the bacterial resistance that can developed during the treatment.*(6)

However the choice of preparation has to be based on experience as there are no data from controlled trail on which base this decision * (7)

The principles of the treatment is to obtain a dry ear, prevent re-infection & to minimize the disability of any hearing loss.*(8)

(Absence of the discharge for six months generally indicate arrest of the chronic otitis media ,it does not preclude reactivation but a patient may be relieved of the need of the constant observation & asked to return only if discharge recurs or other aural symptoms supervene) .*(9)

Peter S. Roland said: (Why chronic suppurative otitis media is so difficult to treat, I believe that part of the reason is poor delivery of medication& drug resistance)*(10)

There is a need for further well-designed studies on the effectiveness of various management strategies for chronic suppurative otitis media) *(11)

The objective:

The aim of this study is to evaluate the effect of adding oral rifampicin to the ciprofloxacin in the treatment of the chronic suppurative otitis media.

Patients & method:

Large number of chronic discharging ears(discharge that is continue for three months & above) where received in our out patient in the ENT–department of the AL- Kerama hospital , selection of a group of them done while exclusion done for others like : patients under 18 years old (The ciprofloxacin use in children is limited as a result of possible fluoroquinolone-induced joint/cartilage toxicity observed mainly in juvenile animal studies)*(12) , atopic patients, patients had recurrent upper respiratory tract infection (URTI) with focal infection such as tonsillitis, adenoiditis, or sinusitis & patient with bilateral discharging ears (to get rid of the precipitating factors that might interfere with response of the ears to our treatment); also exclusion of patients with very small minute tympanic perforation (because a good concentration of local antibiotics to go in to middle ear cavity is needed), patients with cholesteatoma were excluded (its treatment is surgery).

This study started at 1/5/2005, 200 patients selected till 1/6/2006 & follow up continued for some patient till 15/1 /2007.The 200 patients where divided through a systematic randomization in to two equal groups, group **A** (100 patient) & group **B** (100 patients)

During this study; from group **A** 10 patients not continue in the follow up + 2 patients stop treatment because of diarrhea & from group **B** 24 patients not continue in the follow up, so all exclude from our study; so the net were:

Group A: 88 patients received (rifampicin capsule +ciprofloxacin tablet.)+ (methadin drops +ciprofloxacin drops), **Group B**: 76 patients received (ciprofloxacin tablet) + (methadin drops +ciprofloxacin drops) .The study started in two ways; one is the clinical & the other is the laboratory study.

I. the clinical work was as follow:

Patients received in the out patient of ENT department, full Ear Nose & Throat (*ENT*) history taken, full ENT examination done (inspection, otoscopic examination &examination under microscope). Ear swab for culture & sensitivity (c. & s.) were done also for the entire 200 patient. Audio logical assessment by tuning fork & pure tone audiometer (PTA), radiological assessment done by plain X-ray (Lateral Oblique view), 3 cases needed CT_ scanning because of vertigo & severs otalgia.

Treatment started as follow:

*Aural toilet

*Cleaning with dry mopping.

*Chemical cauterization of the granulation tissue by sliver nitrate.

*Insertion a ribbon gauze wick impregnated with concentrated iodine 10% & the patients were asked to keep it for 24 hour, after that the wick should be removed & the local drops applied in the displacement method to the affected ear, that is by lying down on one side & the affected ear is the upper most & instilled drops with intermittent pressure on the tragus. All patients were instructed to protect their ears from wetting by using cotton impregnated with Vaseline.

Group A (88 patients) received oral systemic antibiotic in the form of the rifampicin cap (600-900mg) divided in to 2 doses & ciprofloxacin tab (500-750 mg)divided in to 2 doses for one week in addition to the local steroid& antibiotic in the form of methadin drop (betamethasone sodium phosphate 0.1% w/v +Benzalkonium chloride 0.04% w/v) in a dose of 2-3 drops 3-4 times a day followed by ciprofloxacin 0.3%w/v (2-3 drops x 3-4 times) for 3 weeks.

Group B (76 patients) they received same above treatment except the rifampicin capsule was not given to them.

Follow up done weekly for the 1st month then monthly for the next six months., with every visit examining the ear, cleaning it & mopping canal wall& tympanic membrane with 10% povidon iodine were done .

If there has been no discharge from middle ear for six months the chronic otitis media may be consider as in active .*(9) this is considered as a base for my work & the stat of dryness for at least six months so they will have an in active ears was the goal of this study

II. The laboratory work:

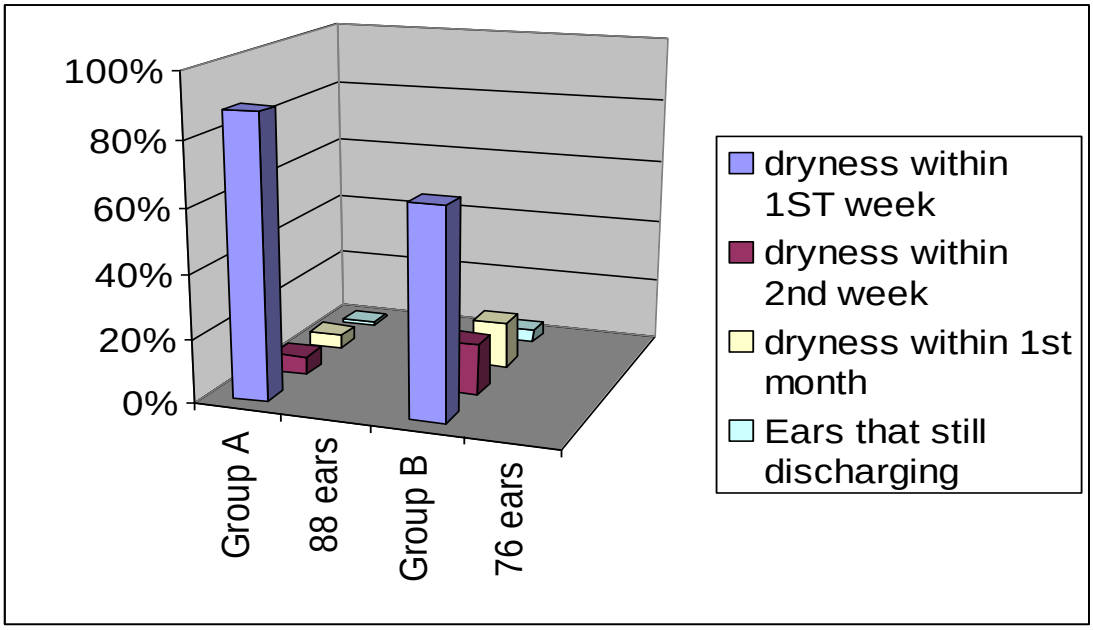
The 200 ear swabs taken were cultured on Mueller-Hinton agar, incubated at 37 ^{o}C for 24 hours, gram stain, subculture & bacteriological test were done to identify bacterial type. Standardized sensitivity test done then ciprofloxacin disc

alone were used, rifampicin disc alone & the combination effect of both of them (ciprofloxacin disc+ rifampicin disc).
The result of the inhibitory zones & its correlation were analyzed according to the instruction of the company providing that discs so it was susceptible (S1) when more than 21mm for ciprofloxacin & 16mm for rifampicin *[18].
while in cases of combination we separate the two discs by24 mm& we red the results as potentiation if inhibitory zones unit together or became larger than the inhibitory zone of one disc alone, while its considered as antagonism if there was no inhibition zone or it became smaller than one disc alone.*(13) This laboratory work done by a microbiologist in our hospital lab.

The Result:
I. The result of the clinical work:
patient in the study groups were informed to omit drop installation at morning of examination, assessment of the dryness of the ear correctly can done, the patients examined weekly for the 1st month & monthly for next six months, the ear is considered a dry if the dry mopping appear dry, so results were: dryness within 1ST week was 78 ears in group A & 50 ears in group B, ears that still discharging was only one ear in group A & its 3 ears in group B, the details are as shown in table No. (1) & the chart

	dryness within 1ST week	**dryness within 2nd week**	**dryness within rest o 1st month**	**Keeping discharge after 1 month**
Group A 88 ears	**78 ears = 88%**	**5 ears =5.7%**	**4 ears =4.5%**	**1 ear =1.1%**
Group B 76 ears	**50 ears =65%**	**12 ears =15.8%**	**11 ears =14.4%**	**3 ears =3.9%**

Table (1): Ear dryness within the 1st month of treatment



Statistical study by charts showing the figures of results for the 1st month

Follow up within the next six months appearing that only 8 patient from group A develop recurrence after 3 months & the same treatment repeated; 6 of these 8 became dry again but only 2 still discharging; on the other hand 17 patient from group B develop recurrence of discharge, 9 of them only became dry but 5 still discharging as in the table No. (2).The ears that continue discharge in spite of our treatment were ended with mastoid exploration

	Recurrent ears	**Dry ears after Recurrence**	**Ears keep discharging & Ends with mastoidectomy**
group A	**8 = 9%**	**6 = 75%**	**2 = 25%**
Group B	**17 =22.3%**	**9 = 52%**	**8 =48%**

Table (2): the recurrence & response to treatment after recurrence.

II **The laboratory results:**

The bacteriological findings (the culture results) were:

Mixed infection was the most common culture result in 82% of the 200 cultured, pseudomonas spp. alone seen in 15% of cultures & E.coli, bacteroids seen in 3%, as seen in the table No. (3).

While the result of the sensitivity show us potentiation of two antibiotics effect on bacterial growth that there was increase in the inhibition zone of the combined effect of (ciprofloxacin +rifampicin) in 40 % of the 200 sensitivity tests done,& the sensitivity to ciprofloxacin alone was susceptible (S1) in 75 %against only 55% for rifampicin to be susceptible (S1)in the entire 200 sensitivity tests done[*(14)] , table. (4).

Bacterial name	**No. of cultures showing this growth**	**The percentage**
Mixed (pseudomonas spp. ,bacteroid fragillis ,protease spp.	**164**	**82%**
Pseudomonas spp. alone	**30**	**15%**
E.coli , bacteroids fragillis	**6**	**3%**

Table. (3): the bacteriological growth findings seen by culture

Antibiotic Disc	**No. of sensitivity test susceptible (S1 (S1)**	**% of sensitivity test susceptible (S1)**
Ciprofloxacin	**150**	**75%**
rifampicin	**110**	**55%**
Ciprofloxacin +rifampicin	**increase in the size of inhibition zone seen in 80 cultures**	**40% increase in the size of the inhibition zone**

Table. (4): sensitivity test results

Discussion:

The ears that became dry in the 1st week were 78 & 50 for group A & group B respectively {\Z $_0$\=\3.5249\> Z alpha/2=2.330 when alpha = 0.02} so its highly significant difference between the dryness of the two groups within the 1st week.
While the dryness within the 2nd week was 5 for the group A, and 12 for group B {\Z $_o$ \= \ -2.11757\ < Z alpha\2 =2.330} i.e. It was not significant. Dryness for the rest of the 1st month was 4 & 11 for group A& B {\ Z o\ =\ - 2.1994452\< Z alpha \2=2.330} i.e. it also was not significance. For the ears that still discharging it was 1 & 3 for group A & B {\ Z o \ =\ - 1.1638016 < Z alpha \2 =2.330} so it was not significant.
So from this it seems to be that The addition of the oral rifampicin can enhance fast dryness of the ear, so patient can get a dry ear within the 1st week of treatment faster than that of the group B, but the over all final results of dryness for the whole 1st month was without significant difference, & the difference between ears that not responding to treatment were also of no clinical or statistical difference. So the addition of rifampicin gave us only faster dryness but no superiority over usual drugs in treating all cases.
About the recurrence rate it was high in group B 22.3% & only 9% in group A (\Z o\ = \ - 2.445395 \ > Z alpha \2 =2.330) so it was significant difference. While the response again to same treatment was better in group A 75% from recurrent cases in comparison to 52% in group B. So the benefit of using rifampicin in addition to the faster dryness of discharging ear was: decreasing recurrence rate & improving response to treatment after recurrence.
That might because rifampicin is a drug that can be used in combination for treatment of osteiomylitis[*(6)] & if chronic suppurative otitis media with its associated chronic mastoiditis is considered as an osteomylitis, so rifampicin treated that infection in a good manner.

From the in vitro laboratory study the ciprofloxacin still superior to rifampicin 75% to 55% in its potency against the micro-organism growth in the culture media, while only in 40 % of cases there was increase in the inhibitory zones when we combined both rifampicin +ciprofloxacin & this is not too much support our in vivo clinical findings & the cause behind that may be the usage of a rough method for estimation of the effect of combination of two discs of antibiotics while the perfect & precise method is the minimal inhibitory concentration method (MIC) a facility which was not available in our hospital & we hope to do it in future.
Rifampicin was well tolerated drug, no any side effect was documented apart from the loose bowel motion happened in 3 patients & the red urine from which patients warned about it before the use of the drug & even when the drug used a gain for recurrence

there was no any sign of the shock syndrome which can happen after the intermittent use of the drug, so it was a safe drug.

In this study the best way of treating chronic suppurative otitis media also searched through combining many factors with others:

(1) The combination of systemic & local antibiotics .although there was some studies found that no benefit of systemic drugs although evidence was limited *(15)

But I still think that systemic antibiotics have a good role in the treatment, & this might be supported in this study and from my experience with patients refuse using drops& use only systemic drugs & they get some benefit.

The effects of topical non-quinolone antibiotics (without steroids) or antiseptics were less clear when less is known compared to systemic treatment*(16),(17)

(2) The local steroid drops used before the local antibiotic by 10 minutes to decrease edema & local inflammation of the mucosa so local antibiotics can get in easily & to avoid in vitro interaction or in activation which might happen when two drugs mixed together & also the benefit of steroid was to decrease the local irritation which might happen from local antibiotics.(Most physicians, me included, believe that steroids are helpful despite the fact that there are no hard data to support their use). Peter S. Roland * (10)

(3) The use of Povidone-Iodine locally as a disinfectant seen to cooperate the therapy.

The use of iodine has been seen in one study. The results show that clinically, topical Povidone-Iodine PVP-I is as effective as topical ciprofloxacin, with a superior advantage of having no in vitro drug resistance, also there is an added benefit of reduced cost of therapy*(18). All the above factors mentioned worked together so relatively good results in the treatment of the chronic suppurative otitis media were obtained.

the use another factor that can give us more power in the treatment & that is the use of a second local antibiotics with the local ciprofloxacin, like neomycin as a example still a hope & there is a study of using double local antibiotics in treating otorrhea post tympanostomy *(19) & from this experience with the rifampicin, the use of it as a local antibiotic when it's available is preferable , but it has some difficulties in its stability, where till now local rifampicin is prepared for local use only as eye drops.

The stability of the eye-drops has been studied and storage condition and half-life were determined. The preparation, may be stored at minus 12 degrees C for one month and may be subsequently used when stored between 2 and 8 degrees C after the first opening for five days.*(20)

Conclusion:

Oral rifampcin potentiate the effect of ciprofloxacin in the treatment of active chronic tubotympanic otitis media.

Chronic suppurative otitis media treatment still needed more control trails.

Systemic drugs like rifampicin capsule when used might enhance rapid dryness, decrees recurrence of discharge &give us better response to treatment after recurrence.

Rifampicin was safe, effective & well tolerated drug to render with the aid of other drugs, the chronic discharging ear as inactive one.

Suggestions:

1. More studies are needed for chronic suppurative otitis media treatment to find out the best way of the perfect, safer, easier use, less coasty & simple drugs
2. The use of (local antibiotics +local steroid) +oral (rifampicin & ciprofloxacin) could be a good protocol of treating chronic suppurative otitis media
3. The manufacturation of local rifampicin drops that can use in the ear is a hope that the drugs manufacturing companies can do it.

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