Original article:

Safety & efficacy assessment of combining Quinine with Artesunate for treatment of severe falciparum malaria in comparison to monotherapy with Artesunate or Quinine

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Abstract

Introduction: Severe Falciparum malaria is responsible for 1.5 to 2.7 million deaths worldwide each year. Quinine was the main stay of treatment of severe malaria. At Present Artesunate is recommended as the treatment of choice for severe Falciparum malaria. But at times Quinine is combined with Artesunate with hope of better efficacy. Hence the present study aims to evaluate "Whether combining Quinine with Artesunate have better safety and efficacy than monotherapy with Artesunate or Quinine in patients of severe Falciparum malaria".

Method: Patients of Severe Falciparum Malaria were randomly allocated into three treatment regimens i.e. Artesunate, Quinine and (Artesunate +Quinine) combination. The mortality, drug related adverse events,Coma recovery time (CRT), fever clearance time (FCT) and parasite clearance time (PCT) were compared among three treatment groups.

Result: The mortality was highest (31%) with (Artesunate + Quinine),intermediate(25%) with Quinine and lowest (13%) with Artesunate monotherapy. The mean QTc of 0.49$\pm$0.09 seconds with (Artesunate + Quinine) was significantly prolonged than the pre drug value of 0.39$\pm$0.03($P<0.05$). QTc prolongation was significantly less in Artesunate group i.e. 3% in comparison to other two groups ($\chi2=3.12$ & $\chi2=4.28$ $p< 0.05$). Hypotension was significantly less i.e. 3.3% in patients treated with Artesunate alone, 21% in patients with Quinine and maximum i.e. 27% in patients treated with (Artesunate + Quinine) ($\chi2=3.99$ & $\chi2=4.964$ - $p< 0.05$).

Conclusion: There is no advantage of combining Quinine with Artesunate in patients of severe Falciparum malaria in view of significantly higher drug related adverse events and a trend towards higher mortality with the combination in comparison to Artesunate or Quinine Monotherapy.

Key words: (Artesunate + Quinine) combination, Artesunate monotherapy, Severe Falciparum Malaria

Introduction

Severe Falciparum malaria is responsible for 1.5 to 2.7 million deaths worldwide each year[1]. Quinine has been the main stay of treatment of severe malaria since its introduction [2]. But there is evidence of decline in efficacy of quinine [3]. Even prompt and adequate treatment with quinine was associated with mortality rate of 17% to 30% in

severe falciparum malaria with multi organ dysfunction[1]. Quinine is associated with cinchonism, hypoglycemia, hypotension and deafness etc.[1] since it's development in 1972, Artemisinin derivatives are being used in South East Asian countries including India, and found to be the most rapidly acting drug against malaria parasite for treatment of individual patient [4]. The study of Artesunate versus Quinine by SEAQUAMAT group in 2005 have shown that mortality in Artesunate recipients was 15% compared with 22% in quinine recipients,hence Artesunate should become the treatment of choice for severe Falciparum malaria in adults[2]. However Artesunate Mono therapy is also associated with a mortality rate of 15%. In vitro experiments have suggested combinations of artemisinin derivatives and mefloquine are synergistic in parasite killing [5]. In Thailand, when other treatments were failing, artesunate & mefloquine combination was successfully used as the first line drug[6]. Inspired by beneficial reports of such combination therapy, doctors in various countries i.e. Thailand, Burma & India especially in states where drug resistant Falciparum Malaria are common, were using combinations of the two most potent antimalarial [i.e. artesunate & quinine] for the treatment of severe falciparum malaria with an intention to reduce the mortality. There are sufficient basis for synergistic effect with the combination of Artesunate and quinine because 1) they have different mechanism of actions [i.e. Artesunate kills the parasite by carbon centered free radicals and quinine act by inhibition of haem polymerase [7]] 2) Artesunate has a broader parasite stage specificity affecting young rings, early trophozoites and schizonts[6] in comparison to quinine which is unable to kill the young ring stage[7]. Artesunate also has gametocytocidal effect in P. Falciparim species [7]. But at the same time there is possibility of potentiation of each others adverse effects i.e. cardiotoxic effect of quinine [3] i.e. myocardial conduction disturbances, hypotension etc. may be potentiated by the QT prolongation potential of artesunate found in high concentration in animal studies [8]. Again the very fast parasite clearance with artesunate may not be accelerated by the slower acting quinine [9].

There is limited published data regarding the in vivo or in vitro efficacy of this combination against falciparum malaria. White et al [9] in 2001 have compared between artesunate + quinine combination with artesunate alone in patients of Falciparum malaria (mainly uncomplicated) and concluded that there is no beneficial effect of Artesunate + quinine combination on parasite killing in comparison to Artesunate alone, rather the incidence of adverse events i.e. Hypoglycemia and cinchonism were significantly higher in Artesunate + quinine treatment group. But in another study Devries et al 2000 in 268 uncomplicated Vietnamese patients showed that a single dose of artesunate [20 mg/kg] orally followed with quinine 10mg/kg 8 hourly orally for 5 days resulted in significantly rapid parasite clearance than a 7 days course of oral quinine alone[7]. In a retrospective observational study in India the author has commented that combination of Quinine & Artesunate may be the best to prevent ARDS in Falciparum Malaria[10]. But there is no published reports on head to head comparison regarding safety & efficacy of use of Artesunate & Quinine combination parenterally in severe falciparum malaria in comparison to monotherapy with either Quinine or Artesunate.

Aims & Objectives:

The present work was designed to assess "whether combining Quinine to Artesunate have better efficacy and safety than monotherapy with Quinine or Artesunate in patients of severe falciparum

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malaria. The primary end point of our study was assessment of mortality rate and serious drug related adverse events. The secondary end points were comparison between coma recovery time (CRT) fever clearance time (FCT) and parasite clearance time (PCT).

Patients and Methods

Study Design: It was an open level randomized prospective interventional study, conducted between September 2002 to February 2006 in the department of Medicine in Collaboration with Department of Pharmacology, S.C.B. Medical College Hospital, Cuttack, Odisha, India. Ethical Clearance was obtained in the 4th Institutional Ethics Committee meeting of S.C.B. Medical College, Cuttack.

Patients of either sex aged 15 to 65 years with evidence of severe falciparum malaria as per WHO criteria 2000[1], and P. Falciparum positive either by blood smear or rapid diagnostic test were enrolled into this study after written consent from attending relatives. Patients fulfilling inclusion criteria were randomized (in blocks of 10 and were enrolled into 3 groups of treatment i.e. artesunate alone quinine alone or artesunate + quinine combination

Pregnant women, patients with other serious co-existing disorders i.e. chronic renal failure, heart diseases, malignancy etc., contraindication for either of the study drug or history of intake of Artesunate or Quinine more than 6 hrs earlier were excluded. But patients who have received Just the First dose of either of the study drug within last 6 hours in proper dose in IV route and with official referral slip were included in the study.

Details of Drug administration

Group 1 – received Artesunate (ART) alone : Artesunate 2.4 mg/kg IV start, 1.2 mg/kg after 6 hrs then 1.2 mg/kg/day X subsequent 6 days for a total of 7 days (when able to take orally – then 2 mg/kg/day in two divided doses for a total ration or 7 days.) *(This dose was the recommended dose during our study period which was subsequently changed to the recent dose of Artesunate (2.4 mg/kg IV start, 2.4 mg/kg after 12 hrs then 2.4 mg/kg/day X subsequent 6 days for a total of 7 days).*

Group II – received Quinine(QN) alone (quinine dihidrochloride 10 mg/kg in 10% dextrose drip given over 4 hours, three times a day till the patient is conscious, followed by 10 mg/kg orally 8 hourly up to 7 days, along with doxycycline 100 mg twice daily x 7 days. If patient did not improve after 48 hours then quinine dose was reduced by 1/3)

Group – III – received combination of Artesunate + Quinine (ART + QN) in the above mentioned dosages

Study procedure: On admission, the detailed history of the patient was obtained, a thorough physical examination was done. Diagnosis of Falciparum malaria was done by The thick and thin blood smears examination or by Rapid diagnostic test [i.e. by Optimal kit or By Binax kit]. The thick and thin blood smears were repeated at 12 hours intervals. All relevant laboratory investigation, [i.e. Hb%, plasma glucose, Serum urea/ creatinine, LFT, serum sodium/potassium etc were done and the findings were entered into the predesigned study proforma.ECG [Electrocardiogram] recordings: were taken pre drug and then within ½ to 1 hour, subsequently 6 hourly up to 48 hours, and then daily up to 7days after administration of Artesunate or Quinine or their combinations. The ECG recordings were also taken at the time of any clinically detectable irregularities, in pulse, heart rate or on ECG monitor during period of drug therapy. The last recording was taken 24-48 hrs after the completion of last dose of the drug. The ECG parameter analyzed was QTc Interval.

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The following parameters were also studied:

Patient mortality,

*Fever clearance time [FCT]:*FCT was defined as the time after which the temperature remained normal [axillary temp bellow 37.5^0c/98.6^0F] for 24 hours. *Coma recovery time [CRT] :* CRT was defined as time taken to reach a Glasgow coma score of 15/15 for at least 24 hours, after initiation of treatment whose initial come score was <11/15, *Parasite clearance time [PCT]:* Parasite clearance time was defined as the time of the first of 2 sequential negative thick films after counting 200 white cells [11].

Drug related Adverse Events (Parameters studied were)

Electrocardiographic Disturbances: [QTc, prolongation]- defined as admission ECG – within normal limits, But after drug, if QTc >0.43 sec

Hypotension: - admission systolic BP>100 mmHg & falls to <80 mmHg during treatment.

Hypoglycemia: - Admission RPG>80 mg/dl but RPG fall to <40 mg/dl during treatment.

Any other clinically detectable adverse drug reactions if found were also recorded.

Statistical analysis : Statistical analysis was performed by Microsoft excel software using ANOVA for comparing data between three treatment groups & post hoc analysis after ANOVA for comparison between two Individual data. Chi square test with Yates continuity correction using 2/2 table was applied for counting data between two different treatment regimens.

Observations & Results

Ninety patients of severe falciparum malaria [30 in each treatment group] fulfilling the inclusion criteria were enrolled into the study. During the study period one patient in ART + QN group and two patient in QN group dropped out & ultimately 87 patients [30 in ART, 29 in ART + QN and 28 in QN treatment group] completed the study. Their mean age was 34.57 ±12.56, 33.3 ± 12.03 & 32.64 ± 11.24 years respectively without statistically significant difference [F 0.20 P > 0.05] There was also no significant difference between the sex distribution in the three treatment group [p>0.05].

On admission there was no significant difference in the incidence of severe manifestation of falciparum malaria i.e. MODS (Multi Organ Dysfunction Syndrome), [GCS < 11/15], Renal failure, Jaundice, severe Anaemia & respiratory distress among the patients in the three treatment group (Table-1). The laboratory parameters i.e. mean random plasma glucose, serum bilirubin, Hb% and the mean Glasgow coma score in the three treatment groups were also nearly equal without statistically significant difference [P > 0.05] (Table-1). Only the mean serum urea and creatinine concentration were comparatively less in quinine treatment group in comparision to other two groups indicating less severe renal failure in quinine treatment group. However the number of patients with renal failure in Quinine treatment group were not significantly different than in other two treatment groups. So in our study the patients in all the treatment groups were adequately matched in terms of Age, sex and also in severity of the disease.

The following observations were made from the study by analysis of different study parameters

Mortality Assessment: The details of mortality in three treatment groups are presented in Graph-1. The Mortality was highest [31%] in ART + QN treatment group, intermediate [i.e. 25%] in QN treatment group and lowest [only 13%] in ART group. Though the mortality was least with Artesunate treatment in comparison to other two groups but the difference was not statistically significant with the present number of study population.

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The details of (FCT, CRT and PCT) (depicted in table-2).

Analysis of FCT:- On admission, 26 patients in ART, 22 in ART + QN and 22 in QN treatment group had fever [Axillary temp > 37.5^0c]. The mean FCT was earliest [i.e. 40.9 ± 10.4 hours] with ART + QN which was not significantly different than FCT with ART alone, i.e. [P > 0.05] but was significantly earlier than FCT with QN [F = 3.68 P < 0.05].The mean CRT [coma recovery Time]:- 23 patients in ART, 21 patients in ART + QN and 18 patients in QN treatment group had Unarousable coma on admission. The CRT was earliest i.e. [35.3 ± 15.6] in ART treatment group which was significantly different than CRT with Quinine alone [F = 5.06 post hoc P <0.05] but not significantly earlier than CRT with ART + QN [P>0.05]. No difference in PCT in three treatment group. [F 2.12, P>0.05].

Analysis of adverse events: Electrocardiographic [QTc] disturbances : The detail Assessment revealed the following, The mean QTc interval before administration of ART alone, ART+QN or QN alone was 0.39±0.03, 0.49±0.02 and 0.38±0.03 seconds respectively without any significant difference between them (P > 0.05). The mean QTC recorded with combination of ART+QN was 0.49±0.09 seconds, which was significantly prolonged than the pre drug value of 0.39±0.03(P < 0.05), but the mean QTC recorded after treatment with either ART or QN alone was 0.40±0.06 and 0.43±0.09 seconds respectively, without statistically significant difference from pre drug values (P > 0.05) (Table 3-B). Analysis of incidence of QTc prolongation among the three treatment regimens are depicted in table-3-A and showed that the incidence of QTc prolongation was significantly less in ART treatment group i.e.3% in comparison to 17% of patients with QN alone & highest i.e. 27% patients in (ART + QN) treatment group respectively.

Hypotension -The development of hypotension during treatment was maximum i.e. 27% in patients treated with ART + QN, 21% in patients with QN alone but was significantly less i.e. only 3.3% in patients treated with ART alone (p <0.05) Similarly vasopressure agents were required for management of Hypotension in only 3.3% patients under ART treatment group. But in comparison it is significantly higher (i.e. 21%) under ART+QN and 17% under QN alone treatment group (P<0.05) (Table -3A).

Hypoglycemia - During the treatment 6% of patients in ART + QN treatment group & 10% patients in QN group developed severe hypoglycemia [Random plasma glucose <40 mg/dl] in comparision to No hypoglycemia in patients treated with ART alone, however these differences were not statistically significant.(Table-3A)

Neurological Evaluation **:** In patients of severe falciparum malaria excluding those with unarousable coma, the detailed Neurological examination, did not reveal any Neurological adverse events in all the three treatment group rather in patients of Unarousable coma, use of artesunate was associated with earliest coma recovery time.

No other significant adverse events were detected during the treatment period with three treatment regimens.

Discussion

This randomized prospective study carried out on 87 patients of severe falciparum malaria to evaluate the comparative efficacy and safety between Artesunate + Quinine combination therapy versus monotherapy with Artesunate or Quinine, did not show any beneficial effect with the combination. Majority of our patients had multi organ dysfunction [i.e.66% in Artesunate group,65% in

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Artesunate + Quinine combination group and 61% in Quinine group]. The patients in three treatment groups were adequately matched in terms of age, sex and severity of disease [i.e. GCS, Renal failure, jaundice, severe anemia and multi organ dysfunction syndrome] without significant inter group variation [p>0.05, table – 1]. The mortality assessment and comparative adverse events monitoring were the primary end point of our study. This study showed that treatment with combination of Artesunate + Quinine was associated with highest mortality in severe falciparum malaria [i.e. 31%], in comparision to treatment with Artesunate alone which has least mortality i.e. 13% and Quinine alone having an intermediate range of mortality of 25%. Though the difference in mortality with Artesunate or Quinine alone in comparison to the Artesunate + Quinine combination did not become statistically significant [P>0.05, Graph-1] with the present number of study population but the study clearly showed a trend towards higher mortality with Artesunate + Quinine combination, and further statistical analysis showed that had the sample size been doubled then death rate with Artesunate + Quinine combination and Quinine alone would have been significantly higher in comparision to treatment with Artesunate alone. The death rates of 25% with Quinine in our study is comparatively higher than the death rate of 17% with Quinine in Artemether Quinine meta analysis study[11], this is possibly due to more number of MODS patients in our study. But the study of Artesunate versus Quinine in severe falciparum malaria SEAQUAMAT group found a death rate of 22% with Quinine which was significantly higher than artesunate which had a death rate of 15% & corroborates with our study report of death rate of 13% with Artesunate and 25% with Quinine.[2]

The Fever clearance time, coma recovery time and parasite clearance time did not differ significantly among patients treated with Artesunate alone or Artesunate + Quinine combination. However the mean fever clearance time with Artesunate + quinine combination group [i.e. 41.91hours] was significantly earlier than treatment with quinine only [i.e. 51.66 hours] and similarly coma recovery time was earliest with Artesunate alone group [i.e. 35.33hours] and was significantly earlier than treatment with quinine alone [i.e. 57.23 hrs] [P<0.05] but not than Artesunate + quinine combination(Table-2). In patients of cerebral malaria Li GQ et al have shown a CRT of as early as 12 hours [8] , but in our study the CRT with Artesunate though earliest was 36 hours, this is possibly due to less severe cases in their study (only cerebral malaria), but majority of patients in our study had MODS.

The adverse events monitoring demonstrated that the electrocardiographic disturbances (QTc prolongation), hypotension with shock and hypoglycemia were highest in patients treated with Artesunate + Quinine combination and least with Artesunate monotherapy. The mean [QTc] recorded after treatment with either Artesunate or Quinine alone was 0.40 ± 0.06 and 0.43 ± 0.09 seconds respectively, which were not significantly different from pre drug values ($P > 0.05$). But the mean QTc recorded with combination of ART+QN was 0.49 ± 0.09 seconds, which was significantly prolonged than the pre drug value of 0.39 ± 0.03($P < 0.05$)(Table3-B). Our study report are consistent with the reports of *White et al, 2001*[9]in which a significant prolongation of QTc interval occurred from a mean value of 0.42 seconds to 0.47 seconds after treatment with combination of Artesunate + Quinine, but no significant change in QTc occurs after Artesunate treatment alone (0.43 second to 0.44 seconds after drug). In our study along with

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analyzing the change in the mean QTc interval we had also comparatively assessed the number of patients developing QTc prolongation in the three treatment regimens. It was found that only 3% of patients treated with Artesunate developed prolongation of QTc interval which was significantly less in comparison to QTc prolongation in 27% of patients in Artesunate + Quinine group and 17% of patients in quinine group alone ($P<0.05$)(Table-3).

The development of hypotension and requirement of vasopressure agents were highest in ART + QN combination group followed by QN group and was significantly less in ART alone treatment group (Table-3). The higher incidence of hypotension with Quinine and Quinine + Artesunate can justifiably explained by the fact that tumor necrosis factor (TNF-α) an endogenous mediator of shock increases dramatically after quinine administration [12], so use of quinine or combination may be associated with shock, but TNF- α does not increase after Artesunate[12], indicating lack of hypotension with Artesunate.

Hypoglycemia is reported by various authors as a complication with quinine[2] & ART + QN combination[9] but in our study though hypoglycemia was found more in ART + QN combination but the incidence was not significantly more in comparision to other two groups, possibly due to use of 25% dextrose in our patients and quinine is always given in 10% Dextrose solution in our set up.

The World Health Organization recommends intravenous Artesunate (IVA) as treatment of choice for severe malaria in areas of low transmission.[14] But Various studies have reported good safety and efficacy with combination of Intravenous Artesunate and Quinine . A study from Italy in 2010 has reported a series of eight imported severe Falciparum malaria cases treated with Intravenous Artesunate (IVA) combined with intravenous Quinine (IVQ) and Concluded that this combined therapy was found to be efficacious, safe and Well tolerated.[15] In a Retrospective observational study in India the author has commented that combination of Quinine & Artesunate may be the best to prevent ARDS in Falciparum Malaria.[10] But there is lack of head to head comparative safety /efficacy assessment between use of Artesunate + Quinine combination parenterally in severe Falciparum malaria in comparison to monotherapy with either Quinine or Artesunate. The present randomized prospective study compared Artesunate + Quinine combination with Quinine or Artesunate monotherapy in severe Falciparum malaria.

Conclusion: This study showed that there is no advantage of combining Quinine with Artesunate in view of significantly higher drug related adverse events & a trend towards a higher mortality with the combination in comparison to Artesunate or Quinine Monotherapy. Rather Artesunate alone has least adverse event and least mortality in comparison to both Artesunate + Quinine combination & Quinine alone and also has earliest come recovery time. So Artesunate should be the preferred agent for severe falciparum malaria. From pharmacological point of view this is possibly another example of drug interaction, which suggests that combining two potent drugs used for same condition may not always be beneficial and at times may be detrimental.

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Table – 1
Manifestations of severe Malaria on admission in patients of three treatment regimens
(Statistical analysis by chi-square test / or / Anova)

Statistical Analysis				
Comparison between	X^2 value	F value for Anova	P Value	Significance
ART vs ART+QN ART vs QN	0.009 0.558		>0.05	NS
ART vs ART+QN ART vs QN	0.141 1.071		>0.05	NS
		1.47	>0.05	NS
ART vs ART+QN ART vs QN	0.023 1.10		>0.05	NS
		4.54	<0.05*	Sig
		6.27	<0.01**	Sig
ART vs ART+QN ART vs QN	0.871 0.01		>0.05	NS
		1.93	>0.05	NS
ART vs ART+QN ART vs QN	0.022 0.028		>0.05	NS
		0.22	>0.05	NS
ART vs ART+QN ART vs QN	0.224 0.026		>0.05	NS

MOD – Multi Organ Dysfunction NS – Not Significant Sig – Significant

The occurrence of Severe manifestations in different treatment regimens are compared by Chi square test using 2/2 table and shows no significant diferrence between three treatment Regimens & the mean value of GCS & Biochemical parameters were compared by ANOVA. Post hoc analysis was done between individual groups and no significant difference was found by ANOVA between 3 groups except serum urea & creatinine value which was higher in Artesunate treatment group..

Table-2: Fever Clearance Time (FCT), Coma Recovery Time (CRT) & Parasite clearance Time(PCT) in Three Treatment Regimens

Parameters	ART	ART+QN	QN	Anova (F Value)	P value
Mean FCT in hrs ± SD	45.92±10.45	40.91±13.93	51.82±15.66	3.68	**<0.05***
Mean CRT in hrs ± SD	36.33±15.66	40.59±18.44	57.23±24.57	5.06	**< 0.05***
Mean PCT in hrs ± SD	50.18±13.33	48.92±16.59	60.00±11.31	2.12	> 0.05

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Post hoc Analysis

Comparison Between	FCT	CRT
	P Value	P Value
ART + QN Vs QN	**< 0.05***	> 0.05
ART + QN Vs ART	> 0.05	> 0.05
ART Vs QN	> 0.05	**< 0.05***

Table – 3(A)
Adverse Drug Reactions
Incidence of QTc Prolongation / Hypotension / Hypoglycemia in three treatment regimens

	Treatment Regimens & Numbers & % of patients			Comparison between	Chi(x^2)-Value	P Value
Adverse Drug Reactions	ART (n=30)	ART + QN (n=29)	QN (n=28)			
QTc prolongation	1 (3.3%)	8 (27%)	5 (17%)	ART vs ART+QN ART vs QN QN vs ART+QN	4.248 3.12 1.92	**P < 0.05*** **P < 0.05*** P > 0.05
Hypotension	1 (3.3%)	8 (27%)	6 (21%)	ART vs ART+QN ART vs QN QN vs ART+QN	4.964 3.992 1.44	**P < 0.05*** **P < 0.05*** P > 0.05
No. of patients required Vasopressure agents (Dopamin/Nor Adrenalin etc)	1 (3.3%)	6 (21%)	5 (17%)	ART vs ART+QN ART vs QN QN vs ART+QN	4.248 2.31 1.24	**P < 0.05*** **P < 0.05*** P > 0.05
Hypoglycemia (RBG < 40mg/dl)	0	2 (6%)	3 (10%)	ART vs ART+QN ART vs QN QN vs ART+QN	0.553 0.63 0.004	P > 0.05 P > 0.05 P > 0.05

TABLE-3(B)
Pre-Drug & Post Drug QTc interval
Comparative Analysis between three Treatment Regimens

Diff. Treatment Regimen	Pre-Drug	Post Drug	P	Significant
ART	0.39±0.03	0.40±0.06	> 0.05	NS
ART+QN	**0.40±0.02**	**0.49±0.09**	**< 0.05**	**Sig.***
QN	0.38±0.03	0.43±0.09	> 0.05	NS

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