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Efficacy and safety of iodized lecithin tablets versus spironolactone in alleviating central serous retinopathy among Chinese patients with uncontrolled diabetes

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Abstract: To compare the effectiveness and safety of spironolactone versus lecithin-bound iodine in patients with central serous retinopathy (CSR). Chinese diabetes patients aged>18 years with CSR with persistent increased level of subretinal fluid (SRF) were enrolled. Subjects were randomized to receive either oral lecithin-bound iodine (390µg/kg/day) or oral spironolactone (50mg/day) for 6 months. A total of 200 patients were randomized and completed the study. Compared to spironolactone group, patients treated with lecithin-bound iodine had greater proportion of eye with complete resolution (87% vs 81%, p>0.005). Higher improvement in height of SRF was observed in lecithin-bound iodine-treated patients as compared with Spironolactone-treated patients (91.2[87.5] vs 142.5 [121.1]; p>0.005). However, no statistically significant difference was observed on none of comparisons. Compared to Spironolactone, the patients treated with lecithin-bound iodine had greater improvement in lesion size, central macular thickness and best-corrected visual acuity. However, no statistically significant difference was observed in any of parameter assessed. (p>0.005). The results of the present study suggested that the lecithin-bound iodine was found more effective (nnumerically) than spironolactone in Chinese diabetes patients with CSR.

Keywords: Spironolactone, lecithin-bound iodine, central serous retinopathy, subretinal fluid.

INTRODUCTION

The global prevalence of central serous retinopathy (CSR) is rapidly increasing at alarming rate, with estimated incidence at 5.8 per 100000 individuals, predominantly occurred in men as compared to women (Liew G *et al*., 2013, Semeraro F *et al*., 2019; Liu B *et al*., 2016; Chatziralli *et al*., 2017; Loo *et al*., 2002). Although the exact cause of CRS is not clear and current treatment are focusing on subretinal fluid (SRF), choroidal vascular hyperpermeability, choroidal thickening, SRF height, lesion size and visual acuity. The patient with acute CSR had good diseases prognosis, with higher chance of relapse among 60% of the patients (Ma J *et al*., 2014; Lu HQ *et al*., 2016; Salehi *et al*., 2015; Lim *et al*., 2014). Nevertheless, the recurrent CSR can even lead to permanent visual loss, therefore, efficacious and safe treatment modalities is critical.

There are several therapeutic treatment options available for management of CSR, included but not limited to acetazolamide, anti-vascular endothelial growth factor (VEGF) therapy, rifampicin, photo therapy and anti-glucocorticoid (Lu HQ *et al*., 2016; Salehi *et al*., 2015; Lim *et al*., 2014; van Dijk *et al*., 2018). It was reported that the use of lecithin-bound iodine in patients with CSR was found effective in accelerating the recovery of visual acuity and promote the absorption of macular edema among patients undergoing laser photocoagulation (Huang *et al*., 2022). However, there was no studies investigating long-term safety and efficacy of lecithin-bound iodine in CSR. Also, there is no head to head study comparing the efficacy and safety of spironolactone versus lecithin-bound iodine in patients with CSR (Gilbert CM *et al*., 1984; Pichi F *et al*., 2017; Falavarjani KG *et al*., 2017; Bousquet E *et al*., 2019). Pre-clinical evidences recommended the use of mineralocorticoid receptor antagonists in treatment of CSR and showed that there was favourable outcome among patient with CSR after using spironolactone/eplerenone. It was reported that spironolactone/eplerenone act on choroidal vessels. However, long-term safety and efficacy of mineralocorticoid receptor antagonists has not been evaluated in clinical practices. Moreover, several studies showed that mineralocorticoid receptor antagonists do not have any role or effect among patients with CSR. In contrast, survey conducted in 2016 suggested that mineralocorticoid receptor antagonists have been suggested as promising treatment options for non-resolving CSR (Gilbert CM *et al*., 1984; Pichi F *et al*., 2017; Falavarjani KG *et al*., 2017; Bousquet E *et al*., 2019; Zola M *et al*., 2019).

Thus, the present study was designed to compare the effectiveness and safety of spironolactone versus lecithin-bound iodine in patients with CSR.

MATERIALS AND METHODS

Patients and ethics

Chinese diabetes patients aged>18 years with CSR were enrolled. The patients were eligible if they had persistent

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increased level of SRF for>3 months. The patients were excluded if had history of optic nerve diseases and/or receiving any other therapy for CSR and/or thepatient with hypotension, hyperkalemia, kidney disease and pregnancy. Each patient were informed about the off-label use of oral spironolactone at the time of informed consent process. Written informed consent was obtained from each enrolled patient. The study received approval from the institutional ethics committee of The First Affiliated Hospital of Shanghai Jiaotong University, Hongkou vide approval no. IRB-2022/34-CT/234. The procedures used in the study were in line with the ethical principles laid down in the Helsinki Declaration and its later amendments (Falavarjani *et al.,* 2017). Also, the patients with history of severe renal impairment, liver disease, lung disease, severe heart and thyroid disease were excluded. Moreover, the patients with any other pathology likely to affect the study outcomes and patients who received concomitant and contra-indicated medications, as well as patients undergoing any other form of surgery, were excluded.

Treatments and procedures

Subjects who met the eligibility criteria were randomized to receive either oral lecithin-bound iodine (390µg/kg/day) or oral spironolactone (50mg/day). Each enrolled patient was carefully monitored and followed up for 6 months.

Assessment of efficacy and safety profiles

Baseline characteristics of each patient was assessed. The primary outcome of interest was number of patients (%) of eyes with complete resolution of SRF during study period (at 6 months). The secondary outcome of interest were changes in height of SRF from baseline, changes in central macular thickness from baseline, changes in lesion size from baseline and changes in best-corrected visual acuity from baseline. Also, the safety profile of both the study drugs were evaluated.

STATISTICAL ANALYSIS

Since this was a pilot study and hence no formal sample size calculation was performed, however, a total of 200 patients (100 in each group) were planned to include to draw the conclusion of this study. Appropriate statistical tests was used to analyse data (quantitative data) based on type and distribution (normal and non-normal). In case of non-normal data, Man Whitney test was used to compare the data of two groups. In case of normal data distribution, unpaired t test was used to compare the data of two groups. In case of categorical data, data were analyzed using fisher exact or chi-square test based on the size of data. Statistical analysis was performed using Graph Pad (version 9.4.1) software. Statistical significant difference was assumed at $p<0.05$.

RESULTS

A total of 200 patients (100 patients in each group) were randomized and all patients completed the study. Demography and baseline characteristics of patients in both treatments groups were comparable (table 1).

A summary of primary outcomes is presented in table 2. Patients treated with lecithin-bound iodine had greater proportion of eye with complete resolution as compared to the patients with spironolactone. The difference was not statistically significant. This demonstrate that the lecithin-bound iodine had numerically better efficacy in terms of complete resolution as compared to spironolactone.

A summary of secondary efficacy endpoint (SRF height, µm) is shown in table 3. Patients treated with lecithin-bound iodine had greater improvement in height of SRF as compared to Spironolactone. The difference was not statistically significant at each time point.

A summary of secondary efficacy endpoint (CMT height, µm) is shown in table 4. Patients treated with lecithin-bound iodine had greater improvement in CMT as compared to Spironolactone. The difference was not statistically significant at each time point.

A summary of secondary efficacy endpoint (lesion size, µm) is shown in table 5. Patients treated with lecithin-bound iodine had greater improvement in lesion size as compared to Spironolactone. The difference was not statistically significant at each time point.

A summary of secondary efficacy endpoint (best-corrected visual acuity, µm) is shown in table 6. Patients treated with lecithin-bound iodine had greater improvement in best-corrected visual acuity as compared to Spironolactone. The difference was not statistically significant at each time point.

DISCUSSION

In China, there is no head to head study comparing efficacy and safety of spironolactone versus lecithin-bound iodine in diabetes patients with CSR. This is the first clinical study carried out to evaluate the efficacy and safety profiles of spironolactone versus lecithin-bound iodine in diabetes patients with CSR. The findings are consistent with those reported in previous studies in which spironolactone (50mg/day) showed significant visual improvement and it was considered as an alternative treatment option in CSR patients who were unable to use photo therapy treatment (Gilbert CM *et al*., 1984; Pichi F *et al*., 2017; Falavarjani KG *et al*., 2017; Bousquet E *et al*., 2019). Also, a prospective interventional study reported that spironolactone (25mg per day) after 6 week of treatment showed that the SRF resolved in 18.75% of studied eyes. However, Bousquet

Table 1: Baseline characteristics of patients

Characteristic	Llecithin-bound iodine (n=100)	Spironolactone (n=100)	P value
Median age (years)	57	59	>0.05
Female sex (%)	45	52	>0.05
Disease durations (months), mean(SD)	5.1±2.1	4.8±1.8	>0.05
SRF, µm, mean (SD)	221±87.1	234±89.3	>0.05
CMT, µm, mean (SD)	387.2± 201	398.1± 298	>0.05
Lesion size, µm, mean (SD)	2879.3±1234	2987±2381	>0.05
Best-corrected visual acuity (log MAR)	0.54±0.3	0.65±0.5	>0.05

Table 2: Summary of comparison of eye with complete resolution of SRF in both groups

Characteristic	Llecithin-bound iodine (n=100)	Spironolactone (n=100)	*P*
Resolution of SRF (complete)	87 (87 %)	81 (81%)	>0.05
1 month	23	21	
3 month	24	20	
6 moths	40	40	
No complete resolution of SRF	13 (13%)	19 (13%)	>0.05

Values of *p* based on categorical variables were calculated using Chi-square test.

Table 3: Summary of secondary efficacy endpoint (SRF height, µm) in the two groups

Characteristic	Llecithin-bound iodine (n=100)	Spironolactone (n=100)	*P*
1 month	97.0 ± 101.3	175.4 ± 125.8	>0.05
3 month	102.3 ± 98.3	134.2 ± 102.6	>0.05
6 moths	91.2 ± 87.5	142.5 ± 121.1	>0.05

Table 4: Summary of secondary efficacy endpoint (CMT, µm) in the two groups

Characteristic	Llecithin-bound iodine (n=100)	Spironolactone (n=100)	*P*
1 month	224.1 ± 115.4	346.2 ± 234.2	>0.05
3 month	273.4 ± 113.1	258.1 ± 128.1	>0.05
6 moths	246.3 ± 95.3	318.2 ± 89.2	>0.05

Table 5: Summary of secondary efficacy endpoint (lesion size, µm) in the two groups

Characteristic	Llecithin-bound iodine (n=100)	Spironolactone (n=100)	*P*
1 month	1791.1± 1360.1	3021.2 ± 1387.3	>0.05
3 month	2016.4 ± 1018.7	2278.3 ± 1621.4	>0.05
6 moths	1886.1 ± 1231.4	2230.3 ± 1473.1	>0.05

Table 6: Summary of secondary efficacy endpoint (best-corrected visual acuity, µm) in the two groups

Characteristic	Llecithin-bound iodine (n=100)	Spironolactone (n=100)	*P*
1 month	0.33 ± 0.42	0.22 ± 0.31	>0.05
3 month	0.33 ± 0.41	0.21 ± 0.32	>0.05
6 moths	0.33 ± 0.39	0.22 ± 0.33	>0.05

Values of *p* based on categorical variables were calculated using Mann Whitney test.

et al, showed that spironolactone reported complete SRF resolution in 26.56% of treated eyes at 6 months (Gilbert CM *et al*., 1984; Pichi F *et al*., 2017; Falavarjani KG *et al*., 2017; Bousquet E *et al*., 2019; Zola M *et al*., 2019).

In our study, patients treated with lecithin-bound iodine had greater proportion of eye with complete resolution as compared to the patients with spironolactone, however, the difference was not statistically significant. The results

related to spironolactone was consistent with the previous reports (Han *et al*., 2022; Yang *et al*., 2017; Wardani *et al*., 2022; Yavuz *et al*., 2021). This demonstrate that the lecithin-bound iodine showed numerically better efficacy in terms of SRF height as compared to spironolactone. . Moreover, the patients treated with lecithin-bound iodine had greater improvement in CMT as compared to Spironolactone, however, the difference was not statistically significant. The results related to spironolactone was consistent with the previous reports (Yavuz *et al*., 2021; Sanhueza *et al*., 2020; Felipe *et al*., 2022; Cakir B *et al*., 2019; Sinawat *et al*., 2020; Sun X *et al*., 2018). This demonstrate that the lecithin-bound iodine showed numerically better efficacy in terms of CMT improvement as compared to spironolactone. In the present study, the patients treated with lecithin-bound iodine had greater improvement in lesion size as compared to Spironolactone, however, the difference was statistically not significant. The results related to spironolactone was consistent with the previous reports (Yang *et al*., 2017; Wardani *et al*., 2022; Yavuz *et al*., 2021; Yavuz *et al*., 2021; Sanhueza *et al*., 2020; Felipe *et al*., 2022; Cakir B *et al*., 2019; Sinawat *et al*., 2020). This demonstrate that the lecithin-bound iodine showed numerically better efficacy in terms of lesion size improvement as compared to spironolactone. Patients treated with lecithin-bound iodine had greater improvement in best-corrected visual acuity as compared to Spironolactone, however, the difference was not statistically significant. The results related to spironolactone was consistent with the previous reports (Yang *et al*., 2017; Wardani *et al*., 2022; Yavuz *et al*., 2021; Yavuz *et al*., 2021; Sanhueza *et al*., 2020; Felipe *et al*., 2022; Cakir B *et al*., 2019; Sinawat *et al*., 2020). This demonstrate that the lecithin-bound iodine showed numerically better efficacy as compared to spironolactone. It was reported that spironolactone/ eplerenone act on choroidal vessels. It was also reported the use of lecithin-bound iodine in patients with CSR was effective in accelerating the recovery of visual acuity and promote the absorption of macular edema among patients undergoing laser photocoagulation (Huang *et al*., 2022).

Overall, both study drugs were statistically similar with respect to primary and secondary efficacy endpoints. However, lecithin-bound iodine is numerically more effective than spironolactone in Chinese diabetes patients with CSR. The possible reason for the non-statistical ssignificant differences in clinical outcomes between the both groups might be due to the low sample size. Hence, the present study encourages to conduct larger randomized multicentric study to confirm the finding of the present study.

The results of this study may not be generalized to the Chinese population due to the low sample size used. Thus, a study with large sample size is required to validate the results reported here.

CONCLUSION

This study has demonstrated that lecithin-bound iodine was slightly more effective than spironolactone in Chinese diabetes patients with CSR.

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