

Lipid Lowering Efficacy between Morning and Evening Simvastatin Treatment: A Randomized Double-Blind Study

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Objectives: To compare lipid-lowering efficacy and high sensitive C-reactive protein (hsCRP) level between morning and evening simvastatin administration in hyperlipidemia subjects.

Material and Method: A randomized double blind controlled trial was conducted in 52 dyslipidemia subjects. A group of twenty five subjects received 10 mg simvastatin in the morning and placebo in the evening. The other group of twenty seven subjects received vice versa. Serum lipid profiles were evaluated every 4 weeks for the total course of 12 weeks. High sensitive CRP was measured at the beginning and the end of the study.

Results: Baseline LDL levels were similar in both groups ($p = 0.95$). The evening simvastatin group had significantly less low density lipoprotein level (LDL) than the morning group at 4 weeks (112 ± 26.1 mg/dl vs. 136.3 ± 32 mg/dl, $p = 0.001$) and 8 weeks after treatment (109.7 ± 28 mg/dl vs. 129.5 ± 27 mg/dl, $p = 0.006$). Difference in LDL after 12th week between two groups was not significant ($p = 0.23$). Triglyceride and HDL level were not different in both groups. Only evening simvastatin administration could significantly decrease hsCRP ($p = 0.03$).

Conclusion: Simvastatin should be taken in the evening. Although lipid profiles were not statistically different in morning and nighttime simvastatin, the inflammatory marker (hsCRP level) is significantly reduced as a result of evening simvastatin administration.

Keywords: Simvastatin, Lipid, Efficacy, Morning, Evening

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Cholesterol is synthesized predominantly at night by HMG co A reductase enzyme⁽¹⁾. This synthetic process can be inhibited by Simvastatin: a HMG co A reductase inhibitor. On account of simvastatin short half-life⁽²⁾, evening drug consumption would inhibit function of this enzyme more than morning. Subsequently, cholesterol level in evening simvastatin administration would be lower. Previous scientific studies were also supported this hypothesis. They have

shown that total cholesterol and low density lipoprotein (LDL) were produced significantly less in the evening simvastatin administration⁽³⁻⁵⁾.

However, these studies were either under dosage of simvastatin, short duration or non-double blind. Since maximal efficacy of simvastatin ranges from 6 weeks to 3 months, the results may not reflect the peak efficacy. To overcome the above shortcomings, the present study performed a randomized double blind trial to compare lipid-lowering efficacy between morning and evening simvastatin in hyperlipidemia subjects. Moreover this study also compared high, sensitive C-reactive protein (hsCRP), an inflammatory marker predicting cardiovascular disease, between two sample groups.

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Material and Method

The researchers conducted 12-week randomized double blind study with 2-week run-in period. The participants were sampled from Thammasat University Hospital and were of 18-70 years old. They all needed statin treatment as primary or secondary prevention according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)⁽⁶⁾. The participants with following characteristics were excluded: malabsorption, renal insufficiency ($Cr > 1.5$ mg/dl), chronic liver disease, hepatitis, cancer, AIDS, hypothyroidism, hypopituitarism, nephrotic syndrome, pregnant or breast feeding women, consumption of drugs or food which interfere lipid levels such as corticosteroid, cyclosporine, itraconazole, ketoconazole, diltiazem, erythromycin, clarithromycin, niacin and grape juice, retinoic acid, sex hormone and thiazide. If significant LDL difference between two groups was 10 mg/dl, type I error was 0.05, type II error was 0.1, assuming standard deviation in each group was 16 mg/dl and 15% drop-out rate; we needed at least 60 subjects.

Enrolled participants were randomized by permuted block to receive 10 mg simvastatin in the morning or evening and placebo. Definition of morning time is 6 to 10 am while evening is 7-10 pm. Total cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) have been evaluated every 4 weeks since the beginning of the study until the total course of 12 weeks. Cholesterol and Triglyceride level were measured by enzyme colorimetric method and enzymatic endpoint, respectively. HDL and LDL level were measured by homogenous method. hsCRP and liver function test were monitored at the time of randomization and at the end of the study. Diet and life style have been recorded and controlled for in the analysis. Drug compliance was checked every visit.

During trial, the randomized subjects would be excluded if they had one of the followings: drug compliance less than 80% or more than 120%, serious adverse effects from the study drug or any hospital admissions.

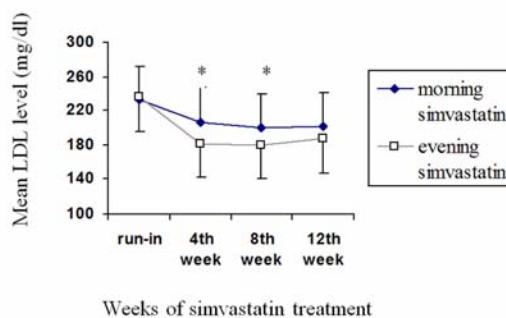
Differences of lipid profiles and hsCRP between two sample groups were analyzed by analysis of covariance (ANCOVA).

Results

The sample comprised 36 female (60%) and 24 male (40%). Three subjects failed to follow-up during the preliminary 2-week run-in period and 4 subjects

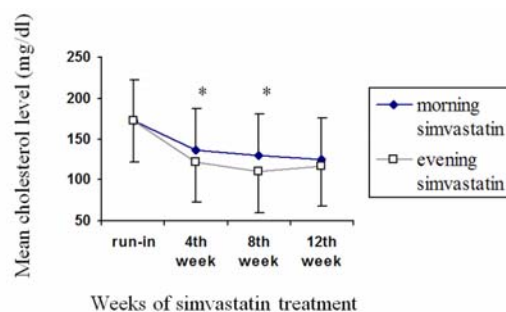
dropped out during treatment. One patient had abnormal liver function test at first visit. In total 52 subjects completed the study. Twenty-seven and 25 subjects were treated with evening and morning simvastatin, accordingly. Baseline characteristics of two groups were comparable as demonstrated in Table 1.

Compliance did not differ between the two groups (96.3 and 96% in morning and evening groups respectively). Diet and life style in both groups was similar. LDL level in evening simvastatin group was significantly less than the level of morning group at 4th (112 ± 26.1 mg/dl vs. 136.3 ± 32 mg/dl, $p = 0.001$) and 8th weeks after treatment (109.7 ± 28 mg/dl vs. 129.5 ± 27 mg/dl, $p = 0.006$). In contrast to 4th and 8th week of treatment, difference in LDL after 12th week between two groups was not significant ($p = 0.23$) (Fig. 1). Total cholesterol level was significantly lower in the evening simvastatin group in 4th and 8th week of treatment (Fig. 2). Triglyceride and HDL levels were similar in both groups (Fig. 3, 4). At the 12th week of treatment, more subjects in evening simvastatin group achieved LDL



* Statistical significant ($p < 0.05$)

Fig. 1 demonstrates mean LDL level before and after simvastatin treatment.



* Statistical significant ($p < 0.05$)

Fig. 2 demonstrates mean cholesterol level before and after simvastatin treatment

Table 1. Baseline Characteristics

Baseline characteristics	Morning simvastatin (n = 25)	Evening simvastatin (n = 27)
male	10 (40%)	9 (33.3%)
female	15 (60%)	18 (66.6%)
age	56.08 ± 8.45	53.30 ± 10.38
body mass index (kg/m ²)	25.38 ± 3.39	26.22 ± 4.04
current smoking	1 (4%)	1 (3.7%)
current alcoholic drinking more than 6 part per week	1 (4%)	2 (7.4%)
Life style		
sedentary	12 (48%)	13 (48.2%)
exercise	13 (52%)	14 (51.8%)
Underlying disease		
diabetes mellitus	4 (16%)	5 (18.5%)
hypertension	14 (56%)	13 (48.1%)
no known underlying disease	7 (28%)	9 (33.3%)
Lipid profiles (mg/dl)		
total cholesterol	242.21 ± 41.41	243.07 ± 28.43
triglyceride	155.08 ± 66.83	140.96 ± 50.1
high density lipoprotein	44.84 ± 9.87	45.55 ± 9.26
low density lipoprotein	171.58 ± 30.1	172.07 ± 29.10
high, sensitive C-reactive protein (mg/dl)	3.38 ± 4.20	3.40 ± 3.85

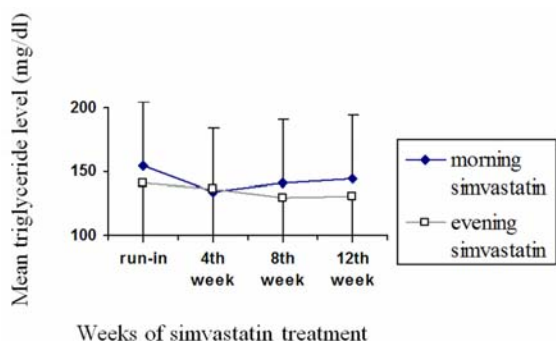


Fig. 3 demonstrates mean triglyceride level before and after simvastatin treatment

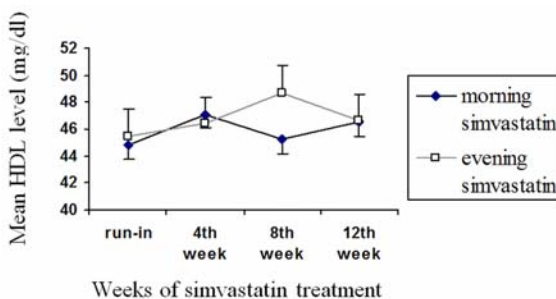


Fig. 4 demonstrates mean HDL level before and after simvastatin treatment

goal according to NCEP ATP III guideline (78% vs. 68%, $p = 0.14$). There will be one out of 6 subjects who achieves LDL goal in evening simvastatin administration.

Only evening simvastatin administration had significantly lower hsCRP comparing before and after treatment (3.5 ± 4.1 mg/dl vs. 2.4 ± 3.4 mg/dl, $p = 0.03$). There were no adverse effects such as severe myalgia, hepatitis, jaundice, angioedema or vasculitis in both treated groups.

Discussion

The present study showed insignificant difference of LDL and total cholesterol level at 12th week between morning and evening simvastatin treatment in hyperlipidemia subjects. The result was not the same as other studies, which showed significantly better LDL level in the evening simvastatin group⁽³⁻⁵⁾. This may be explained by phenotypic difference in simvastatin response due to varying half-life of this drug. The number of subjects that had LDL reaching NCEP ATP III goal was also insignificantly less in evening simvastatin consumption. According to this study, there will be one out of 6 subjects who achieves LDL goal in evening simvastatin. This study also confirmed previous findings that there was no discrepancy of triglyceride and HDL level⁽³⁻⁵⁾.

hsCRP is an inflammatory marker predicting risk of cardiovascular event. There were many studies showing that statin can reduce hsCRP independently of its effect on total cholesterol⁽⁷⁻¹¹⁾. The present study demonstrated significant reduction of hsCRP only after evening simvastatin treatment. This result was different from the previous study⁽³⁾. The mechanism of reduction of hsCRP only in evening simvastatin consumption is unknown. Whether lowering hsCRP could reduce cardiovascular disease is still unclear.

Conclusion

Simvastatin should be taken in the evening. Although lipid profiles were not statistically different in morning and nighttime simvastatin, hsCRP level is significantly reduced as a result of evening simvastatin administration.

Acknowledgements

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ประสิทธิภาพการลดไขมันในเลือดของการบริหารยาซิมวาสเตตินในตอนเช้าเทียบกับตอนกลางคืน: การศึกษาแบบสุ่ม

ทิพาพร ธาระวานิช, ศิริชัย ว่องธนาการ, นุชศิริ เลิศวุฒิสโภณ, สุกรี ธีรอังกูร, พิลาสินี ยั่งศรีพิทักษ์, ภาสกร ศรีทิพย์สุโข

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิภาพในการลดไขมันในเลือดและ high, sensitivity C-reactive protein (hsCRP) ในการบริหารยาซิมวาสเตตินในตอนเช้าเทียบกับตอนกลางคืนในผู้ป่วยที่มีระดับไขมันในเลือดสูง

วัสดุและวิธีการ: ศึกษาเปรียบเทียบอาสาสมัครแบบสุ่ม และปกปิดสองด้าน โดยรวบรวมผู้ที่มีไขมันในเลือดสูงที่จำเป็นต้องได้รับยาลดไขมันจำนวน 52 คน แบ่งเป็นสองกลุ่ม กลุ่มที่ 1 จำนวน 25 คน ได้รับยาซิมวาสเตติน 10 มก. เช้าและยาหลอกตอนกลางคืน กลุ่มที่ 2 จำนวน 27 คน ได้รับยาซิมวาสเตติน 10 มก. ตอนกลางคืน และยาหลอกตอนเช้า จากนั้นติดตามทุก 4 สัปดาห์จนครบ 12 สัปดาห์ และวัดระดับ hsCRP ก่อนการรักษาและเมื่อจบการศึกษา

ผลการศึกษา: ระดับแอลดีแอลก่อนรักษาในอาสาสมัครทั้งสองกลุ่มไม่มีความแตกต่างกัน ($p = 0.95$) ภายหลังการรักษาระดับแอลดีแอลในกลุ่มที่ได้รับยาซิมวาสเตตินก่อนนอนมีค่าน้อยกว่ากลุ่มที่ได้รับยาตอนเช้าในสัปดาห์ที่ 4 (112 ± 26.1 มก. ต่อ คล. และ 136.3 ± 32 มก. ต่อ คล., $p = 0.001$) และสัปดาห์ที่ 8 (109.7 ± 28 และ 129.5 ± 27 , $p = 0.006$) อย่างมีนัยสำคัญ ในสัปดาห์ที่ 12 กลุ่มที่ได้รับยาก่อนนอนมีระดับแอลดีแอลต่ำกว่าแต่ไม่มีนัยสำคัญทางสถิติ ($p = 0.23$) ระดับไตรกลีเซอไรด์ และเอชดีแอลไม่มีความแตกต่างกันทั้งสองกลุ่ม การรับประทานซิมวาเสเตตินตอนก่อนนอนเท่านั้น ที่สามารถลดระดับ hsCRP อย่างมีนัยสำคัญทางสถิติ เปรียบเทียบก่อนการรักษาและเมื่อจบการศึกษา ($p = 0.03$)

สรุป: ยาซิมวาสเตตินควรบริหารก่อนนอนถึงแม้ระดับไขมันจะไม่มีความแตกต่างกันอย่างมีนัยสำคัญแต่พบว่า ระดับ hsCRP ซึ่งบ่งบอกการอักเสบมีระดับลดลงอย่างมีนัยสำคัญในกลุ่มที่ได้รับยาซิมวาสเตตินก่อนนอน
