
Effect of Statin Therapy on Early Return of Potency After Nerve Sparing Radical Retropubic Prostatectomy

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Purpose: We prospectively investigated whether postoperative statin use would contribute to earlier recovery of erectile function in men who underwent bilateral nerve sparing radical retropubic prostatectomy for clinically localized prostate cancer.

Materials and Methods: A total of 50 potent men without hypercholesterolemia undergoing bilateral nerve sparing radical retropubic prostatectomy for clinically localized prostate cancer were prospectively randomized into 2 equal groups. Group 1 patients were instructed to ingest only 50 mg sildenafil per day if needed following hospital discharge after radical retropubic prostatectomy. Group 2 patients were prescribed atorvastatin at a dose of 10 mg daily from postoperative days 1 to 90 and they were also instructed to ingest sildenafil, as in group 1. Patient status regarding potency and adverse events were assessed 6 months after surgery.

Results: The 2 groups demonstrated no significant differences regarding various baseline factors, including International Index of Erectile Function-5 scores. Group 2 had a significantly higher postoperative International Index of Erectile Function-5 score than group 1 at 6 months postoperatively ($p = 0.003$). Meanwhile, as judged by a preset definition, the incidence of potent patients 6 months after prostatectomy was 26.1% in group 1 and 55% in group 2 ($p = 0.068$). Also, 17.4% and 40% of the men reported achieving intercourse by vaginal penetration without a phosphodiesterase 5 inhibitor in groups 1 and 2, respectively ($p = 0.172$). No serious adverse events associated with medication were reported.

Conclusions: Postoperative treatment with atorvastatin in men who report normal erectile function preoperatively may contribute to earlier recovery of erectile function after nerve sparing radical retropubic prostatectomy.

Key Words: prostate, prostatic neoplasms, prostatectomy, impotence, hydroxymethylglutaryl-CoA reductase inhibitors

With the adoption by many surgeons of anatomical RRP using cavernous nerve preservation the rate of postoperative recovery of erectile function sufficient for sexual intercourse has improved dramatically. At major academic centers reported rates of erectile function recovery are between 60% and 85%.¹ On the other hand, it can also be easily understood from looking at currently reported data in the literature that a nerve sparing procedure does not always guarantee the complete recovery of potency regardless of how meticulously the procedure is performed. Today ED still lingers as a major postoperative problem.

Currently oral PDE5 inhibitors have been widely prescribed for the treatment and prevention of post-prostatectomy ED, showing varying degrees of success. Some groups reported that nightly medication with PDE5 inhibitor following RRP would be a more effective approach for recovering potency following nerve sparing RRP compared with on-demand medication.² A postulated mechanism for the potential benefits of nightly PDE5 inhibitor medication is corporeal endothelial protection. However, considering the

cost of the various PDE5 inhibitors available, nightly medication with PDE5 inhibitor for penile rehabilitation following RRP may not be a realistic option for all patients.

Statins, which are known to have a protective effect on vascular endothelium, leading to increased nitric oxide activity, may also have protective effect on corporeal endothelium.³⁻⁵ Also, the statin class of drugs is generally much less costly than PDE5 inhibitors. In that sense daily medication using a statin combined with on-demand PDE5 inhibitor may prove to be an effective and viable approach for post-prostatectomy restoration of erectile function. Thus, we prospectively investigated the effectiveness and safety of combined therapy with a daily statin plus on-demand PDE5 inhibitor for the early return of erectile function in a select group of patients who underwent bilateral nerve sparing RRP for clinically localized prostate cancer at our institution.

MATERIALS AND METHODS

A total of 50 potent men undergoing bilateral nerve sparing RRP for clinically localized prostate cancer were prospectively enrolled after institutional review board approval. All patients provided written informed consent. All men were 65 years or younger, sexually active and potent before RRP with a preoperative 5-item IIEF-5 score of greater than 21 without PDE5 inhibitors for achieving such erections. Also, patients with a history of unstable cardiovascular disease,

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uncontrolled diabetes mellitus, thyroid disorders, clinically significant renal or hepatic disease, prior pelvic surgery or radiation therapy, preoperative treatment for erectile dysfunction or penile deformity and a history or current use of any cholesterol lowering agent were excluded at enrollment. In all patients laboratory analysis, including a fasting lipid profile to assess total and LDL cholesterol, was performed before surgery to exclude those with hypercholesterolemia, defined as LDL cholesterol greater than 120 mg/dl.

Enrolled patients were randomized into 2 equal groups. Group 1 patients were instructed to ingest only 50 mg sildenafil per day if needed following hospital discharge after RRP. Group 2 patients were prescribed atorvastatin at a dose of 10 mg daily from postoperative days 1 to 90 and they were also instructed to ingest 50 mg sildenafil per day if needed following hospital discharge after RRP. A single surgeon performed all surgeries. When bilateral nerve sparing was not possible during the surgery, the patient was excluded and another was enrolled until each group had 25 patients. All patients were discharged from the hospital within 14 days after surgery without any serious complications.

Postoperatively patient erectile function status with or without PDE5 inhibitor was also assessed with the IIEF-5 questionnaire 6 months after surgery only in those who had received at least 4 doses of 50 mg sildenafil. Patients were considered potent after surgery when with or without sildenafil they had a total IIEF-5 score of 16 or greater, or a score of 4 or greater was obtained for the question, "In the last 4 weeks, when you attempted sexual intercourse, how often was it satisfactory for you?"^{6,7} Postoperative return of erections sufficient for vaginal intercourse without oral PDE5 inhibitor were also assessed. Total and LDL cholesterol were followed 6 months after surgery. Any adverse events related to medication were also assessed. Observed data were analyzed using the chi-square, Fisher exact and paired t tests, assuming equal variance. Correlations of continuous variables were analyzed via the Spearman rank procedure with $p < 0.05$ considered significant.

RESULTS

Two patients in each of the 2 groups could not be contacted 6 months after operation. One patient in group 2 indicated that he achieved adequate erections for intercourse but was not sexually active because of the lack of interest of himself and his partner. Also, another 2 patients in group 2 stated that they did not receive atorvastatin as recommended. Thus, 23 patients in group 1 and 20 in group 2 were included in the final data assessment.

For all analyzed patients mean age was 60.8 years (range 48 to 64). Mean preoperative serum PSA was 7.7 ng/ml (range 0.8 to 12). The 2 groups demonstrated no significant differences regarding various factors, such as preoperative PSA, body mass index, cholesterol and operative time (table 1).

The mean preoperative IIEF-5 score for all patients was 23.1. Patients in the 2 groups showed no significant difference in the total dose of sildenafil ingested as needed during the 6 months following RRP ($p > 0.05$). All analyzed patients received at least 5 doses of 50 mg sildenafil during the period. The mean postoperative IIEF-5 score in groups 1 and 2 was 10.6 and 13.5, respectively ($p = 0.003$, table 2). This represented a 54% decrease from preoperative levels in group

TABLE 1. Characteristics of patients in 2 subject groups

Variable	Mean \pm SD Group 1	Mean \pm SD Group 2	p Value
Age	60.6 \pm 2.3	61.3 \pm 4.3	0.427
Serum PSA (ng/dl)	7.44 \pm 4.5	7.97 \pm 2.3	0.445
Body mass index (kg/m ²)	24.3 \pm 2.3	23.6 \pm 2.7	0.284
Preop total cholesterol (mg/dl)	161.8 \pm 22.3	167.1 \pm 19.8	0.335
Preop LDL (mg/dl)	93.7 \pm 15.5	95.8 \pm 15.6	0.307
Operative time (mins)	121.5 \pm 45.5	115.8 \pm 49.5	0.579
Estimated blood loss (cc)	356.0 \pm 260.5	311.6 \pm 212.3	0.412
Pathological Gleason sum	6.1 \pm 1.2	6.2 \pm 0.7	0.385

1 and a 41% decrease in group 2 ($p = 0.001$). Group 2 demonstrated a significantly higher IIEF-5 score than group 1 6 months after RRP. As judged by a preset definition, the incidence of potent patients 6 months after RRP was 26.1% (6 of 23) in group 1 and 55% (11 of 20) in group 2. Four (17.4%) and 8 patients (40%) reported achieving intercourse by vaginal penetration without PDE5 inhibitor in groups 1 and 2, respectively.

Group 2 showed significantly larger decreases in total and LDL cholesterol than group 1, as analyzed 6 months after RRP ($p < 0.0001$). When analyzing only group 2, no significant associations were observed between postoperative changes in total and LDL cholesterol and postoperative changes in the IIEF-5 score or with postoperative recovery of potency and erections sufficient for vaginal intercourse without oral PDE5 inhibitor (data not shown).

During our study no serious adverse events were reported. In general treatments with atorvastatin and/or sildenafil were well tolerated. The most frequent adverse events observed with atorvastatin medication were constipation in 9.2% of patients and indigestion in 4.7%, which were mild. With sildenafil headache in 3% of patients, flushing in 3% and rhinitis in 3% were the most commonly reported adverse events.

DISCUSSION

Currently statins have an important part in the secondary prevention of cardiovascular diseases, of which the incidence continues to increase around the world. Even in those with normal cholesterol statin therapy is considered beneficial for decreasing the risk of atherosclerotic vascular disease.⁸⁻¹⁰ Moreover, it is known to improve endothelial function by decreasing the action of LDL cholesterol on endothelial cells and up-regulating endothelial nitric oxide synthase expression, leading to improved nitric oxide bioavailability.

Previously hypercholesterolemia treatment with atorvastatin was reported to improve ED.¹¹ Still, the question remains as to whether the improvement in erectile function was directly related to a decrease in cholesterol and/or the nonlipid related effects of atorvastatin. Statins are known to preferentially lower total and LDL cholesterol as well as increase HDL cholesterol. On the other hand, other studies showed that statins, especially atorvastatin, exert beneficial effects on vascular endothelial cells independent of lowering plasma cholesterol.

Drugs of the statin class have favorable properties related to endothelium mediated vasoactive, antithrombotic, antiproliferative and anti-inflammatory activities.¹² Statins

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