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The Efficacy of Short-Term, High-Dose Atorvastatin in Prevention of Contrast-Induced Nephropathy in Patients with Impaired Renal Function

Susanne E. Hotchkin

Pacific University

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Abstract

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Methods: An exhaustive search of available medical literature from MEDLINE-Ovid, MEDLINE-PubMed, and Google Scholar was performed using the search terms “contrast-induced nephropathy,” “acute kidney injury,” “statins,” “atorvastatin,” “HMG-CoA reductase inhibitors.” Studies were excluded if they were not written in the English language, did not have human subjects, included patients without renal impairment, were not randomized control trials, or were published more than eight years ago.

Results: Quintavalle et al\(^9\) performed a randomized control trial evaluating a single 80mg dose of atorvastatin 24 hours before percutaneous coronary intervention (PCI) or coronary angiography (CAG) vs placebo. Results demonstrated incidence of CIN in 9 of 202 patients (4.5%) in the atorvastatin group and in 37 of 208 patients (17.8%) in the control group. Shehata and Hamza\(^10\) also performed a double-blind randomized control trial evaluating the use of 80mg daily of atorvastatin vs placebo for 48 hours prior to PCI. The incidence of CIN was 5 of 65 patients (7.7%) in the atorvastatin group compared to 13 of 65 patients (20%) in the control group.

Conclusion: As demonstrated by both studies, a high loading dose of atorvastatin is significantly efficacious in reducing the incidence of contrast-induced nephropathy in patients with mild to moderate chronic kidney disease undergoing PCI or CAG.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Jennifer VanAtta PA-C

Keywords
Contrast-induced nephropathy, acute kidney injury, contrast-induced acute kidney injury, CIN, CIAKI, statins, atorvastatin, prevention, contrast, chronic kidney disease

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Medicine and Health Sciences

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The Efficacy of Short-Term, High-Dose Atorvastatin in Prevention of Contrast-Induced Nephropathy in Patients with Impaired Renal Function

Susanne Hotchkin

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2016

Faculty Advisor: Jennifer VanAtta PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

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**Keywords:** Contrast-induced nephropathy, acute kidney injury, contrast-induced acute kidney injury, CIN, CIAKI, statins, atorvastatin, prevention, contrast, chronic kidney disease.
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To my parents and Scott Bruneau: Thank you for your continued love and support, and for always encouraging me to challenge myself. You instilled the confidence in me to accomplish what I thought I could only dream of.

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Table I: Quality Assessment of Reviewed Articles

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Figure I: Contrast-Induced Nephropathy Risk Score

List of Abbreviations

CIN contrast-induced nephropathy
AKI acute kidney injury
CIAKI contrast-induced acute kidney injury
CAG coronary angiography
PCI percutaneous coronary intervention
sCr serum creatinine
sCyC serum cystatin C
BUN blood urea nitrogen
The Efficacy of Short-Term, High-Dose Atorvastatin in Prevention of Contrast Induced Nephropathy in Patients with Impaired Renal Function

BACKGROUND

Contrast-induced nephropathy (CIN) is a form of acute kidney injury (AKI) that occurs in some patients who undergo radiologic studies that utilize iodinated contrast media. While the overall average occurrence of CIN is approximately 2%,\textsuperscript{1} comorbidities and risk factors greatly affect each patient’s likelihood of developing CIN. For example, among patients who are healthy and have no risk factors, the incidence of CIN is less than 1%.\textsuperscript{2,3} In comparison, the incidence of contrast-induced nephropathy can be as high as 50% in patients with multiple risk factors\textsuperscript{4}.

The pathophysiology of contrast-induced acute kidney injury (CIAKI) is not completely understood though multiple theories exist. First, it is thought that the contrast agent causes alterations in endogenous vasodilators, such as nitric oxide and endothelin, resulting in medullary hypoxia due to renal vasoconstriction. Another theory claims the contrast agent increases the viscosity resulting in decreased medullary blood flow as the small diameter vessels in the vasa recta cannot accommodate this thick fluid. In addition, the hyperosmotic effect of the contrast inhibits water reabsorption resulting in swelling of the renal tubules which causes increased intrarenal pressure. Due to this increase in pressure, both renal blood flow and glomerular filtration are decreased. Third, it is hypothesized that contrast agents may have direct cytotoxic effects on the renal tubules as a result of the release of free radicals.

The most commonly used diagnostic criteria for contrast-induced nephropathy (CIN) is the observance of a serum creatinine increase of 25% or more or a greater than 0.49mg/dl from baseline within 24 to 48 hours of contrast administration. In addition to these laboratory changes, clinical observations could include fatigue, poor appetite, dependent edema, orbital
edema, dry or itchy skin, and changes in urine color or characteristics. Other laboratory abnormalities could include hyperkalemia, hyperphosphatemia, and metabolic acidosis.

Multiple variables affect a patient’s probability of developing contrast-induced nephropathy. In addition to accounting for each patient’s risk factors, the dosing and type of contrast being used must be taken into consideration. The most accurate prediction of a patient’s probability of developing CIN is made based on a series of risk factors. Mehran et al⁴ developed a risk stratification score that assigns points (1-5) for eight risk factors based on correlation of the comorbidity to the development of CIN. The eight risk factors are: hypotension, intra-aortic balloon pump use, congestive heart failure, serum creatinine greater than 1.5 or decreased glomerular filtration rate (stratification of points based on level), age greater than 75, anemia, diabetes mellitus, and contrast volume. Based upon the risk score, patients in the study were placed into four risk categories: low, moderate, high, and very high. The risk score is very accurate at predicting occurrence rate in each population as demonstrated by the high correlation between the predicted occurrence rate and the actual occurrence rate in the studied population (figure 1). Of these risk factors, decreased baseline renal function has the greatest influence on the patient’s probability of developing a contrast-induced acute kidney injury.

Though contrast-induced nephropathy most commonly resolves within five to ten days and less than one percent of affected patients will require acute hemodialysis, the renal injury can have lasting effects—especially for patients who had decreased renal function before the acute insult⁵,⁶,⁷. Patients who develop CIN have demonstrated longer average length of hospital stay, increased 5-year mortality rates, as well as increased incidence of myocardial infarction than those patients who do not develop CIN⁸.
Due to the lack of effective treatment options for contrast-induced nephropathy, efforts are being made to find better prevention methods to decrease the incidence of CIN. Multiple therapies have been used in an attempt to prevent acute kidney injury in patients undergoing contrast imaging. These include, but are not limited to: prehydration with saline both orally and intravenously, sodium bicarbonate, theophylline, n-acetylcysteine, and most recently statin therapy. Though prevention recommendations have been established, no universal standard of practice currently exists for the prevention of CIN in patients with renal compromise.

HMG-CoA reductase inhibitors, more commonly referred to as “statins”, are medications that reduce synthesis of cholesterol in the liver. While these medications are most commonly used to treat dyslipidemias and hyperlipidemia in an attempt to reduce occurrence of acute coronary syndrome as well as other arterial insufficiency, recent research has found additional benefits to statin therapy. Statin therapy has demonstrated conflicting results in preventing contrast-induced nephropathy in patients with and without renal impairment. The purpose of this systematic review is to evaluate the efficacy of high-dose, short-term atorvastatin use in prevention of contrast-induced nephropathy in patients with chronic kidney disease undergoing coronary angiography or percutaneous coronary intervention.

METHODS

An exhaustive search of available medical literature from MEDLINE-Ovid, MEDLINE-PubMed, and Google Scholar was performed using the search terms “contrast-induced nephropathy,” “acute kidney injury,” “statins,” “atorvastatin,” and “HMG-CoA reductase inhibitors”. Studies were excluded if they were not written in the English language, did not have human subjects, included patients without renal impairment, included patients undergoing
contrast studies other than percutaneous coronary intervention or coronary angiography, were not randomized control trials, or were published more than 8 years ago.

**RESULTS**

Exhaustive search efforts, as described above, produced 38 articles. However, many articles evaluated the use of a high loading dose of atorvastatin in prevention of contrast-induced nephropathy in patients without renal impairment or in patients undergoing contrast studies other than CAG or PCI. Once the search criteria were narrowed down to eliminate studies that included patients without renal impairment, only two studies\(^9,10\) met all inclusion criteria. The first study\(^9\) was found using MEDLINE-Ovid, while the second\(^10\) was found using MEDLINE-PubMed. An exhaustive search of Google Scholar resulting in both previously mentioned studies with no further qualifying studies. See Table I.

**Quintavalle et al (2012)**

This study\(^9\) was double-blinded with computer-generated assignment and compared two groups: one group received a single dose of 80mg of atorvastatin within 24 hours before injection of contrast, while the other group did not receive atorvastatin. In addition to either atorvastatin or no atorvastatin, both groups received 1200 mg \(N\)-acetylcysteine by mouth twice daily on both the day before and the day of the performance of the contrast study, and both groups were hydrated with sodium bicarbonate solution in accordance with current recommendations for prevention of contrast-induced acute kidney injury. All patients included in the study had baseline glomerular filtration rate of less than 60 ml/min/1.73m\(^2\). Serum creatinine (sCr), serum cystatin C (sCyC), blood urea nitrogen (BUN), sodium and potassium were all measured the day before the contrast procedure and at 24 hours, 48 hours, and 1 week after contrast administration.\(^9\)
In this particular study, contrast-induced acute kidney injury (CIAKI) was defined as an increase greater than 10% of serum cystatin C concentration within 24 hours of contrast exposure. Secondary outcomes of serum creatinine increases of ≥0.5mg/dL or 25% from baseline were also evaluated. An increase in sCr ≥0.5mg/dL from baseline at 48 hours after contrast administration was observed in 7 of 202 patients (3.5%) in the atorvastatin group and in 16 of 208 patients (7.7%) in the control group (P=0.085). Also, an increase in sCr ≥25% from baseline at 48 hours after the contrast procedure was observed in 6 of 202 patients (3%) in the atorvastatin group and 14 of 208 patients (7%) in the control group (P=0.10). The incidence of CIAKI as defined by >10% increase in sCyC occurred in 9 of 202 patients (4.5%) in the atorvastatin group and in 37 of 208 patients (17.8%) in the control group (P=0.005). Relative risk reduction (RRR) varied between 0.545 to 0.747 and number needed to treat (NNT) values varied between 7.52 to 26.6 patients depending on the diagnostic criteria for CIN used. See Table II.

Shehata and Hamza (2015)

This double-blinded randomized control trial compared two groups: one group who received 80mg of atorvastatin daily for 48 hours prior to contrast media injection and one group that was given placebo. Both groups were also given isotonic saline for hydration in addition to 1200mg N-acetylcysteine 24 hours before and after percutaneous coronary intervention. Serum creatinine, estimated GFR, serum potassium and sodium were evaluated immediately prior to performance of PCI (baseline), 72 hours after, and 10 days after. Contrast-induced nephropathy was defined as an increase of ≥ 0.5 mg/dL or ≥25% in serum creatinine from baseline. CIN occurred in 5 of 65 patients (7.7%) in the atorvastatin group compared to 13 of 65 patients (20%)
in the control group (P<0.05). Relative risk reduction (RRR) with the use of atorvastatin was 0.615 and the number needed to treat was 8.13 patients. See Table II.

**DISCUSSION**

As demonstrated in these two studies, a high loading dose of atorvastatin significantly decreases the incidence of contrast-induced nephropathy in patients with mild to moderate chronic kidney disease undergoing coronary angiography or percutaneous coronary intervention. Though both studies had relatively low incidence of CIN (ranging from 3-7%, 5-18%, and 7-20% depending on the diagnostic criteria used and the study), the designs of both studies increase the validity of the results. Both studies reduced the risk for bias by using computer-generated randomization to carry out randomized control trials. The control groups and experimental groups were almost identical in both studies in accordance with baseline renal function, age, cardiovascular risk factors, medications, and body mass index. In addition, both studies reported identical contrast agents used in control and experimental groups with very similar contrast volumes. Other variables, including prehydration dosage and agents as well as N-acetylcysteine use were standardized between groups. Objective outcome data were measured which significantly decreases any risk for bias or compromised results.

The data analysis of the results of each study demonstrated significant relative risk reduction (0.545-0.747 depending on the diagnostic criteria used and the study) and markedly low numbers needed to treat (7.52-26.6 depending on the diagnostic criteria used and the study) with use of atorvastatin for the prevention of CIN (See Table II). It is important to note that the study performed by Quintavalle et al also evaluated in vitro outcomes to determine the extent of renal damage in each study group (atorvastatin vs no atorvastatin). This study found that in addition to reducing the occurrence of CIAKI, a high loading dose of atorvastatin prevented
contrast media-induced renal cell apoptosis by reducing stress kinases activation. This cellular-level examination adds further evidence of the efficacy of a high loading dose of atorvastatin in prevention of contrast-induced nephropathy.

Although variables were standardized within each study, a difference in contrast-induced nephropathy diagnostic criteria as well as prehydration technique did exist between studies. While Quintavalle et al\(^9\) used an increase of ≥10% increase in serum cystatin C within 24 hours of contrast injection as the criteria for diagnosing CIN, Shehata and Hamza\(^10\) used an increase of ≥0.5mg/dL or ≥25% increase from baseline serum creatinine within 72 hours of contrast administration as the diagnostic criteria for CIN. However, Quintavalle et al\(^9\) also measured secondary outcomes of increases in sCr consistent with the diagnostic criteria used in the study by Shehata and Hamza.\(^10\) This allows for parallel comparison between results further increasing the validity. Quintavalle et al\(^9\) used a sodium bicarbonate solution for prehydration, while Shehata and Hamza\(^10\) used a normal saline solution. Both hydration techniques have been proven beneficial in comparison to a lack of hydration techniques prior to contrast imaging; however, it has not yet been established if one is superior to the other. Regardless of the variance between methods used in each study, the protocol was standardized between the control group and atorvastatin therapy group in each study which further strengthens the results.

The benefit of using a high loading dose of atorvastatin prior to percutaneous coronary intervention or coronary angiography in patients with mild to moderate renal impairment is clearly demonstrated in these two studies.\(^9,10\) However, multiple questions still exist. For example, the optimal time frame for treatment with atorvastatin is not distinct. While one study\(^10\) used two doses of 80mg of atorvastatin prior to contrast injection, the other study\(^9\) used a
single dose. While both studies demonstrated the efficacy of atorvastatin therapy, the question of the optimal dosing regimen remains. In addition, each study used a combination of measures to prevent CIN, including hydration therapy and N-acetylcysteine administration. Further research should focus on the optimal combination of therapies for the maximal preventive effect. An especially important area of research would be the investigation of the efficacy of atorvastatin therapy without concomitant hydration in prevention of CIAKI. This research would prove very beneficial in helping providers make clinical decisions regarding fluid-intolerant patients, such as those with uncontrolled or significant congestive heart failure, who require contrast imaging. If atorvastatin alone is efficacious in preventing contrast-induced acute kidney injury, clinicians could avoid fluid-overloading patients who might not tolerate the additional intravascular volume well.

As HMG-CoA reductase inhibitors have become more widely and chronically used, a significant amount of research has been performed evaluating the benefits of statin therapy in addition to the risks. Adverse reactions to statin therapy have occurred, though serious adverse effects are rare at 0.01%. More common adverse effects include gastrointestinal upset, myalgia, and muscle cramps. With the cost of one 80mg atorvastatin pill being approximately $2.24, the potential benefit clearly outweighs the factors of risk and cost.

Both studies included in this systematic review evaluated the efficacy of atorvastatin in prevention of CIN in statin-naive patients. Considering the large population of patients who take statins chronically, it would be important to evaluate the efficacy of a high loading dose of atorvastatin (or the established statin) in prevention of CIN. This would be especially valuable information considering the recent changes to cholesterol control guidelines outlined by ATP IV
resulting in an increased number of patients receiving long-term statin therapy. Though many questions remain, the most important aspects of atorvastatin therapy in prevention of CIAKI that should be investigated are: the efficacy of a high loading dose of atorvastatin without concomitant hydration in prevention of CIN, and the efficacy of a high loading dose of atorvastatin in prevention of CIN in patients who are chronically on statins.

CONCLUSION

Though more research is needed to define the optimal regimen, it is apparent that a significant reduction in the development of CIN results from use of high-dose, short-term atorvastatin in patients with mild to moderate chronic kidney disease undergoing coronary angiography or percutaneous coronary intervention. This evidence could prove especially vital to patients, such as those with congestive heart failure, who cannot tolerate the hydration protocol that is currently recommended. Short-term atorvastatin therapy could provide an alternative measure for prevention of contrast-induced nephropathy in this particular population, as well as an additional preventative therapy for the general population. With the risk of serious adverse effect with statin therapy being approximately 0.01%, the benefit of using atorvastatin for prevention of CIAKI highly outweighs the risk. With this evidence presented and the insignificant risk of adverse effect, those patients with mild to moderate chronic kidney disease should receive a high loading dose of atorvastatin prior to iodinated contrast media use.
References


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<td>Quintavalle et al a</td>
<td>RCT</td>
<td>Not serious a</td>
<td>Not Serious</td>
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<td>Not Serious</td>
<td>Unlikely</td>
<td>Large Magnitude of Effect c</td>
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<tr>
<td>Shehata and Hamza b</td>
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<td>Serious d</td>
<td>Unlikely</td>
<td>Large Magnitude of Effect c</td>
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a The lack of placebo substitution in the control group risks compromise of blinding, but objective outcome measure makes variation in results due to lack of complete blinding very unlikely.

b The subgroup of patients with stage IV or V CKD (GFR≤30 mL/min/1.73m²) did not demonstrate the same benefit as those with mild to moderate CKD. This subgroup demonstrated a wide confidence interval with odds ratio 0.10-4.93 and a p value of 0.75.

c The RR for this study is 0.253, with a NNT of 7.52 using sCyC increase (≥10%) as criteria for CIAKI diagnosis. The RR for this study is 0.455, with a NNT of 23.8 using sCr increase (≥0.5 mg/dL) as criteria for CIN diagnosis.

d The sample size for this study was only 130 patients with 65 in each group: control and experimental.

e The RR for this study is 0.385, with a NNT of 8.13.
<table>
<thead>
<tr>
<th>Study</th>
<th>CIN Diagnostic Criteria</th>
<th>Relative Risk (RR)</th>
<th>Relative Risk Reduction (RRR)</th>
<th>Absolute Risk Reduction (AR)</th>
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<tr>
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<td>Increase in sCr ≥0.5mg/dL or ≥25% from baseline within 48hrs of contrast administration</td>
<td>0.385</td>
<td>0.615</td>
<td>0.123</td>
<td>8.13</td>
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Figure I: Contrast-Induced Nephropathy Risk Score

The contrast-induced nephropathy risk score derived from the development dataset (prediction based on risk score) predicted this complication in the validation set (actual measured incidence).