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Safety profile of atorvastatin in the role of burn wound injury conversion

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ABSTRACT

Background: Atorvastatin could be beneficial in the treatment of burn patients to prevent burn wound progression from partial to full thickness. Our primary aim is to evaluate the safety of atorvastatin in burn patients.

Methods: Single center retrospective chart review of burn patients receiving atorvastatin during admission May 2016–May 2019 with historic controls was performed. Demographics, burn total body surface area, atorvastatin doses, creatinine phosphokinase, aspartate aminotransferase levels and adverse events were analyzed.

Results: 48 burn patients received atorvastatin during admission. Nine patients experienced elevated CK or AST levels during admission, but did not correlate with timing of atorvastatin administration and were comparable to levels in control patients. No adverse events associated with atorvastatin were identified.

Conclusions: Atorvastatin administered to patients with burn injuries was not associated with any adverse events or attributable lab abnormalities. We believe that atorvastatin is safe to use in patients with burns and can be safely studied to determine the drug's effect on the prevention of burn wound conversion.

Introduction

Despite advances in the field, burn injury remains a significant source of morbidity and mortality. In the United States, approximately 486,000 patients receive medical treatment as a result of burn injuries each year. Of these, over 60% require treatment in specialized burn centers, with roughly 4% of those individuals succumbing to their injuries yearly. Burn injuries amount to a total annual cost of nearly $4 billion.[1]

Burn injuries range from mild to severe and are graded as superficial, superficial partial thickness, deep partial thickness and full thickness burns. Deep partial thickness and full thickness burns require surgical treatment while superficial and superficial partial thickness burns require medical treatment only. There exists a potential for partial thickness burns to convert to full thickness in the setting of ischemia, inflammation and infection. The principles of burn conversion can be related to three different zones of tissue damage including the core zone, the threatened zone of stasis, and the outermost recoverable zone of hyperemia. The critically perfused zone of stasis is of major interest as it relates to the prevention of core zone recruitment, which represents irreversibly damaged surface area. The zone of stasis is characterized by microthrombosis, ischemia and inflammation. It has been demonstrated that this zone remains at risk for a period of 48–72 h following the burn injury.[2] Secondary burn wound conversion ultimately leads to increased rates of excision and grafting, increased length of stay, delayed healing with potential scarring and loss of function, increased pain with subsequent increased opioid exposure and most notably, increased morbidity and mortality. Additional consequences may include increases in the necessary volume resuscitation and the potential for worsened pulmonary injury. Current therapies in burn wound treatment have improved over

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time, but little is understood regarding therapeutic approaches in the prevention of secondary burn conversion.

HMG-CoA Reductase Inhibitors (statins) are a class of drugs that have been widely used for their reduction of morbidity and mortality related to cardiovascular disease and have been found to have a favorable side effect profile. They also have lesser known but widely recognized anti-inflammatory properties. These anti-fibrotic and anti-inflammatory effects have been shown in cardiac, pulmonary and renal tissue as well as the skin in animal models.[3–5] Proposed mechanisms include blocking pathways leading to TGF-Beta 1, IL-6, TNF-alpha, as well as blocking fibroblast proliferation. This is an attractive mechanism in the theoretic mitigation of the prolonged and exaggerated pro-inflammatory state known to be associated with acute burn injury.

Lessons learned from the study of various statins in reduction of pro-inflammatory states have led us to choose atorvastatin as our investigative statin of choice due to its high lipophilic properties and ability to easily permeate tissue.[6] Promising data regarding atorvastatin use to mitigate burn injuries has been demonstrated in animal studies.

A recent study supported by the Dutch Burns Foundation noted that atorvastatin administration resulted in improved graft take in a porcine burn model.[7] The study noted improved re-epithelialization of full thickness burns when utilizing atorvastatin, which was postulated to be related to reduced inflammation and improved vascularization of the wound bed. Furthermore, it was postulated that atorvastatin promotes earlier transition from the inflammatory to the proliferative phase and stimulates a faster resolution of myofibroblasts. Additional studies have also shown that statins were able to protect mice with burn injury from liver injury by suppressing the TNF-alpha signaling pathway as well as to improve survival in burn-related sepsis in the murine model.[8,9]

Atorvastatin has yet to be studied in human burn patients, and we believe that studying the safety of administration of atorvastatin to patients with burn injuries is imperative prior to beginning any such experiments due to potential side-effects of liver injury and rhabdomyolysis. This is why the aim of our study is to study the safety of atorvastatin administration in patients with burn injuries.

Table 1
Outcomes of burn patients on atorvastatin compared to controls.

	Control	Atorvastatin	P value
Number of patients	50	48	
Age	59.9	59.6	0.47
Sex M:F	7/5	3/1	0.58
Comorbidities	2.4	3.2	0.028
TBSA (%)	12.6%	14.1%	0.34
Degree of Burn:			
Superficial partial	40% (n = 20)	31% (n = 15)	
Deep partial	28% (n = 14)	48% (n = 23)	0.12
Full thickness	32% (n = 16)	21% (n = 10)	
Mechanism:			
Chemical burn	2% (n = 1)	2% (n = 1)	
Scald	22% (n = 11)	23% (n = 11)	0.13
Fire	76% (n = 38)	60% (n = 29)	
Explosion	0%	15% (n = 7)	
Presence of inhalation injury	18% (n = 9)	27% (n = 13)	0.28
Presence of trauma	0	23% (n = 11)	<0.01
Injury Severity Score	6.7	9.6	0.17
AST levels	56 (n = 13)	46 (n = 24)	0.18
CK levels	1809 (n = 3)	397 (n = 14)	0.41
Length of Stay	12.2	15.8	0.12
Ventilator days	2.3	5.5	0.051
Discharged to:			
Home	68% (n = 34)	49% (n = 20)	
Rehab	48% (n = 24)	44% (n = 18)	0.31
Long Term Care	0	7% (n = 3)	
Mortality	4% (n = 2)	14.6% (n = 7)	0.06

Material and methods

Our study design is a retrospective chart review of patients at the regional Roger W. Seibel Burn Treatment Center at the level I Trauma Erie County Medical Center in Buffalo, New York who received atorvastatin during the course of their hospital stay over the three year period from May of 2016 to May of 2019. We also chose historical controls from patients who were treated concurrently at the same institution who did not receive any statins prior to or during their care. The historic controls were age and sex-matched to our investigative cohort.

The following information was collected on both sets of patients: age, sex, co-morbidities, total body surface area (TBSA) injured, degree of burn injury, mechanism of burn injury, presence of inhalation injury, presence of trauma, injury severity score (ISS), AST levels, CK levels, length of hospital stay, days on ventilator, place of discharge and adverse outcomes including mortality. The data was then analyzed using T-test or Chi-square test where appropriate to compare our investigative cohort to our historic control cohort, as well as to compare patients who received atorvastatin prophylactically to those who were prescribed atorvastatin during their hospital stay. $P < 0.05$ was used as a marker of statistical significance.

Results and discussion

During the three year period that was analyzed, 48 burn patients were identified who received atorvastatin during their hospital stay. These patients were compared to a cohort of age and sex-matched historical controls. Demographics of both populations were compared and no statistical significance was seen between the two groups in the categories of TBSA%, degree of burn, mechanism of injury, presence of inhalation injury, injury severity score, hospital length of stay, ventilator days, and discharge disposition (see Table 1). Most importantly, there was no statistically significant difference in the AST and CK levels-which have been used in the literature as proxy indicators for rhabdomyolysis and liver dysfunction, known to occur with statin use.[6] It is important to note that the patient cohort receiving atorvastatin had an average of 3.2 comorbidities as compared to 2.4 comorbidities ($p = 0.028$). This is likely explained by the fact that atorvastatin is prescribed for a comorbidity which patients not receiving atorvastatin were less likely to have had. The difference in presence of concomitant trauma (23%, n = 11 in atorvastatin group vs 0 in historical control group, $p < 0.01$) is surprising, but may be related to the increased number of comorbidities seen in those sustaining burns in the context of concomitant traumatic injury. In addition, a common indication for initiating statin therapy was to attempt to mitigate perioperative cardiac risk in those with significant injuries requiring operative intervention.[21] Given concomitant injuries the need for operative intervention may have been somewhat higher, contributing to the increased in hospital statin use. While mortality rates did not reach statistical significance, their difference (14.6%, n = 7 in atorvastatin group vs 4%, n = 2 in historical control group, $p = 0.06$) is worth noting as well. To investigate the high mortality rate seen in the atorvastatin cohort, we compared patients who had received atorvastatin during their hospitalization as a continuation of a pre-hospital regimen (73%, n = 35) to those who had been prescribed atorvastatin *de novo* during their hospitalization (27%, n = 13) (Table 2). Atorvastatin started prior to hospitalization likely represents patients with an additional comorbidity while atorvastatin started during hospitalization represents patients with extensive burns or suspected inhalation injury and cardiac risk factors who were expected to need operative excision and were started on atorvastatin due to their high risk profile. This is

Table 2
Comparison of patients receiving atorvastatin prior to hospitalization vs patients started on atorvastatin during their hospitalization.

	Atorvastatin Prior to Hospitalization	Atorvastatin Started During Hospitalization	P value
Number of patients	35	13	
Age	61.2	55.5	0.13
Sex M:F	4/1	1.6/1	0.19
Comorbidities	3.8	1.6	<0.01
TBSA (%)	8.3%	29.8%	<0.01
Degree of Burn:			
Superficial partial	40% (n = 14)	8% (n = 1)	
Deep partial	46% (n = 16)	54% (n = 7)	0.051
Full thickness	14% (n = 5)	38% (n = 5)	
Mechanism:			
Chemical burn	3% (n = 1)	0%	
Scald	29% (n = 10)	8% (n = 1)	
Fire	57% (n = 20)	69% (n = 9)	0.35
Explosion	11% (n = 4)	23% (n = 3)	
Presence of inhalation injury	26% (n = 9)	31% (n = 4)	0.73
Presence of trauma	14% (n = 5)	46% (n = 6)	0.2
Injury Severity Score	5.4	20.8	<0.01
AST levels	33 (n = 13)	86 (n = 11)	0.42
CK levels	705 (n = 7)	301 (n = 7)	0.28
Length of Stay	11.7	26.8	<0.01
Ventilator days	2.8	12.8	<0.01
Discharged to:			
Home	59% (n = 19)	11% (n = 1)	
Rehab	34% (n = 11)	78% (n = 7)	0.037
Long Term Care	6% (n = 2)	11% (n = 1)	
Mortality	8.6% (n = 3)	49% (n = 4)	0.025

supported in our analysis, which shows that the patients who were started on atorvastatin prior to hospitalization had significantly more co-morbidities than their counterparts (3.8 vs 1.6, $p < 0.01$), while the patients who were started on atorvastatin during their hospitalization sustained significantly worse injuries with TBSA of 29.8% vs 8.3% ($p < 0.01$), injury severity score of 20.8 vs 5.4 ($p < 0.01$) and as a result experienced an increased length of stay (26.8 vs 11.7 days, $p < 0.01$), increased ventilator days (12.8 vs 2.8, $p < 0.01$), were less likely to be discharged home (11% vs 59%, $p = 0.037$) and had a much higher mortality rate (49% vs 8.6%, $p = 0.025$). Importantly, AST and CK levels were not statistically different in these two populations (86 vs 33, $p = 0.42$ and 301 vs 705, $p = 0.28$, respectively, in *de novo* vs existing prescription of atorvastatin). This signifies that atorvastatin administration did not lead to an increase of previously reported complications in the significantly more injured burn patient population.

The 7 identified mortalities in our atorvastatin group were reviewed (Table 3). One represented a young patient with a devastating explosion injury with 90% TBSA burn injury who was placed on comfort care and succumbed to his injuries, 5 patients with multiple co-morbidities with severe injuries who were also placed on comfort care and succumbed to their injuries, and one elderly patient with a 25% TBSA burn injury whose wishes were to be DNR and who also succumbed to her injuries. As previously mentioned, while this mortality rate of 14.6% was not statistically different from that of the historical control cohort, the p value does strongly trend towards statistical significance at $p = 0.06$ and thus must be examined. We believe that this increased mortality rate is well explained by the combination of pre-hospital administration of atorvastatin portending higher co-morbidity rate as compared to controls as well as the very high morbidity rate seen in the patients who were started on atorvastatin during their hospitalizations due to their high risk profile for extensive surgery with their severe injuries.

Doses of atorvastatin administered represented a wide range from 10 to 80 mg PO due to different doses prescribed by various providers prior to patient hospitalization. We compared AST and CK levels of patients receiving different dosages of atorvastatin and found no link between an increase in dosage and increase in enzyme levels (Table 4.). A total of 9 patients were noted to have either CK > 500 or AST >100 at some point during their hospital stay. Review of these cases demonstrated no correlation of the elevations with timing of drug administration and all experienced subsequent normalization. No adverse events that could be associated with atorvastatin could be identified.

Limitations of our study include being a retrospective chart review with historical controls. Our historical controls were not controlled for co-morbidities, which may have skewed the mortality rate in our experimental group to trend towards significant difference from the control group. Another limitation of our study includes missing AST and CK values on some patients due to the retrospective nature of this study. A prospective randomized study

Table 3
Description of patients receiving atorvastatin who suffered mortalities.

Age	Sex	TBSA (%)	Degree of Burn	Inhalation Injury	ISS	Comorbidities	Mechanism	Cause of Death	Comfort Care
34	M	90%	Full thickness	–	75	–	Explosion	Multiorgan Failure	Yes
59	M	7%	Full thickness	Present	5	DM, COPD on home O2, OSA, MO, HTN, HLD, CHF	Fire	Respiratory Failure	Yes
60	M	50%	Deep partial thickness	Present	29	ETOH abuse, Roux-en-Y gastric bypass	Explosion	Multiorgan Failure	Yes
67	M	25%	Full thickness	Present	15	COPD on home O2, metastatic prostate cancer	Fire, Fall	Respiratory Failure	Yes
70	M	50%	Full thickness	–	43	COPD, DM, tobacco abuse	Explosion, Crush	Multiorgan Failure	Yes
82	F	25%	Deep partial thickness	Present	15	HTN	Fire, Fall	Multiorgan Failure	DNR only
83	F	15%	Deep partial thickness	–	4	HTN, GERD, CHF, dementia, seizures, DVT	Scald	Respiratory Failure	Yes

Table 4
Observed CK and AST levels with varying levels of atorvastatin administered.

Dose	Number of Patients	Treatment Duration	TBSA %	CK range (median)	CK > 500	AST range (median)	AST> 100	Mortalities
10 mg	7	1–22 days	2–25%	178-222 (200)	0	23-42 (35)	0	1
20 mg	20	1–50 days	3–50%	90-6551 (652)	3	13-3416 (68)	3	2
40 mg	14	2–33 days	1–90%	61-17828 (251)	1	16-1866 (67)	2	4
80 mg	7	1–21 days	1–30%	705	1	11-27 (26)	0	0

of atorvastatin in burn patients is the next step and is the goal of our future directions.

We believe that our results indicate that atorvastatin is safe to continue to study in the setting of burn patient care in order to evaluate its effects on burn wound healing. In considering our next steps, we carefully reviewed the commonly referenced study in which a statin was used in an attempt to reduce inflammation and capillary leak in patients with sepsis associated ARDS.[6] This study failed to show any improvement in their chosen clinical outcome which is contrary to previous studies demonstrating benefit.[10–20] Authors of the study noted several limitations including the choice of a less lipophilic statin, inadequate dosing and improper timing of administration of the agent. The most notable limitation in interpreting the results of the study relates to the target patient population. The disease process of ARDS portends an expected and significant sepsis-related capillary leak that would have been established prior to recognized pulmonary dysfunction which triggered patient enrollment. This would limit the statin usefulness and confound its utility in other potential clinical scenarios. We aim to incorporate these lessons and study the agent atorvastatin, known for its higher lipophilic properties and therefore increased penetration to injured tissues which are already at risk of ischemia. We also aim to study atorvastatin as a preventative medication to secondary burn wound conversion with a consistent dosing schematic and early timing of administration as opposed to reactive treatment once the pathologic physiology has already taken root.

Conclusions

Atorvastatin used in the treatment of patients with burn injuries was not associated with any adverse events or attributable lab abnormalities. While a higher than expected mortality was observed in our patient cohort, we believe that this is likely a result of patients' prehospital regimen which was associated with pre-existing medical conditions as well as the addition of the drug by our providers due to an increased severity of injury in these patients.

We believe that atorvastatin is safe for further randomized prospective study to determine the drug's effect on the prevention of burn wound conversion, as well as its effects on the resuscitation volume requirements and the mitigation of inhalation injury.

Declaration of competing interest

None of our authors have any conflicts of interest to disclose.

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