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Incidence of oxandrolone induced hepatic transaminitis in patients with burn injury

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ABSTRACT

The benefits of oxandrolone in burn patients has led to its accepted use in the burn care community, however details regarding the most common adverse effect, transaminitis, remains unclear. The purpose of this study was to determine the incidence of transaminitis in patients with burn injury and identify risk factors associated with the development of transaminitis. This single-center, retrospective risk factor analysis compared burn patients on oxandrolone with and without the development of transaminitis, defined as any aspartate aminotransferase or alanine aminotransferase value >100 mg/dL. Patient demographics, past medical history, lab values, and burn characteristics were recorded. Overall 28 out of 66 (42%) patients developed transaminitis. The transaminitis group had a significantly higher proportion of other concomitant medications with a transaminitis risk (p=0.045). No significant difference in liver dysfunction or length of stay was observed between the two groups. Oxandrolone induced transaminitis is occurring in patients significantly more frequently than previously reported warranting further research to guide monitoring requirements, use of concomitant medications, and to determine if rechallenging after resolution should be considered.

1. Introduction

Oxandrolone, a synthetic derivative of testosterone, has become a standard of care treatment in patients with severe burn injury at many comprehensive burn centers. The testosterone derivative exhibits high anabolic and low androgenic effects, and has been used for its ability to counterbalance the hypermetabolism and hypercatabolism associated with severe burn injuries [1–4]. Oxandrolone promotes skeletal muscle growth in burn patients by improving the efficiency of amino acid utilization and increasing overall muscle protein synthesis [5–7]. Multiple clinical studies have proven the benefits of oxandrolone use in severely burned patients, as it can increase lean body mass, promote

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wound and skin graft healing, and decrease overall hospital length of stay [1–4]. Although the benefits of oxandrolone have been confirmed in multiple studies, one of the most common adverse effects, oxandrolone induced transaminitis, is still not yet well understood.

Although liver related adverse effects with oxandrolone therapy have previously been described, significant limitations to the current body of literature have left practitioners questioning the true incidence and severity of this adverse effect. The primary limitations include variability in the definitions of liver dysfunction and transaminitis, small sample sizes of patients evaluated, and only one study has evaluated hepatic dysfunction as a primary outcome [5]. One of the largest studies to date that assessed the benefits and safety outcomes of oxandrolone included 81 patients with burn injury, and found that more patients had an increase in liver enzymes after ≥8 weeks of therapy in the oxandrolone group (11%) compared to the placebo group (6%). It was also shown that the oxandrolone group had a significantly greater number of incidences of hepatic damage, defined as any aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >100 mg/dL [2]. Other studies have evaluated hepatic dysfunction with oxandrolone use, however the definitions vary significantly from an elevation in AST/ALT from baseline to an increase of 1.5–3 times normal [1,3–5]. The variability between studies and the use of liver dysfunction mostly as a secondary outcome, make it difficult to determine the frequency and risk of oxandrolone induced transaminitis.

Other limitations to the current literature include the institutional differences in the frequency of monitoring hepatic function during oxandrolone use and identification of risk factors that may lead to an increased incidence. Current studies and practices vary significantly in the frequency of monitoring liver enzymes, ranging from daily to twice weekly, with others only monitoring when symptoms of hepatic dysfunction are present [3–5]. Only one study currently has examined total body surface area percent (TBSA%) burn as a possible risk factor for the development of hepatic dysfunction, however there were only 14 patients in the oxandrolone group [5]. Overall the evidence to date on oxandrolone induced transaminitis is limited by few published studies, small patient sample sizes, and significant variations in transaminitis definitions and monitoring. Therefore the objective of this study is to determine the incidence of transaminitis and to identify potential risk factors associated with the development of transaminitis.

2. Methods

2.1. Study design and patient population

This was a single-center, retrospective risk factor analysis of adult patients with a thermal burn injury treated with oxandrolone therapy. The study was performed at an American Burn Association (ABA) verified adult comprehensive burn center that treats an average of 330 hospitalized burn patients a year and has over 1600 outpatient visits annually. Standard practice at this burn center includes initiation of oxandrolone after completion of fluid resuscitation at 10 mg twice daily in all patients with a TBSA thermal burn >10%, unless transaminitis is present on admission. At a minimum, weekly liver function tests are measured in all patients while on oxandrolone, and institutional transaminitis during oxandrolone treatment is defined as a single AST or ALT >100 mg/dL. If at any point during oxandrolone treatment transaminitis develops, oxandrolone is held until the patient's AST and/or ALT normalize. Rechallenging patients after resolution of transaminitis with oxandrolone is a common practice at this burn center in patients with burn injury if the treatment team determines the benefits outweigh the risks. It is important to note that our institution rarely prescribes oxandrolone for outpatient use as it is difficult to get the medication covered by insurance.

Patients admitted to the burn center between December 1, 2011 through September 30, 2016 with a TBSA thermal burn injury >10% who received oxandrolone as part of their initial treatment plan were eligible for inclusion. Non thermal burn injuries were excluded as oxandrolone is not always initiated in these patients at the institution, and the majority of patients with TBSA burn injury >10% are thermal. Patients who were <18 years of age, pregnant, incarcerated, received initial burn care with oxandrolone at an outside hospital, or did not have AST/ALT values available for evaluation were excluded. Informed consent was waived due to the retrospective nature of the study and was approved by the Institutional Review Board.

The primary aim was to determine the incidence of transaminitis and to identify risk factors associated with the development of transaminitis in patients with burn injury who are treated with oxandrolone. Normal ranges for AST/ALT were 14–40 mg/dL and 9–48 mg/dL as set by the institutional laboratory. Secondary outcomes included the percent AST/ALT elevation from baseline, hospital length of stay, mortality, and development of liver dysfunction. Liver dysfunction was identified through chart review by searching in the electronic medical record for the following terms: liver dysfunction, liver failure, hepatic dysfunction, hepatic failure. Patients who were identified as having clinical documentation of liver dysfunction were further screened for at least one of the following: AST, ALT, total bilirubin or alkaline phosphatase >3 times ULN or an INR >2 without warfarin. The electronic medical record of any patients identified as developing liver dysfunction was then fully reviewed by the physician investigators (JKB and LJ) for confirmation of diagnosis and further evaluation on possible causes of liver dysfunction.

2.2. Data collection

Data was collected retrospectively from the patients' electronic medical records and the institutional burn database. The following data was recorded for each patient: age, sex, race, height, body mass index (BMI), admission creatinine clearance, use of intravenous vasopressor during oxandrolone therapy, hospital length of stay, and pre-existing medical conditions of diabetes mellitus, obesity, liver disease, intravenous drug abuse, and chronic kidney disease. Medications that could potentially contribute to transaminitis were also collected while the patient was on oxandrolone therapy and included amiodarone, antipsychotics, azithromycin, triazole antifungals, barbiturates, caspofungin, carbamazepine, erythromycin, penicillins, phenytoin, scheduled acetaminophen, statins, sulfonamides, tricyclic antidepressants, and valproic

acid. Creatinine clearance on admission was calculated using the Cockcroft-Gault equation and comorbidities were based on provider documentation within the history and physical and progress notes. Burn characteristics collected included source and TBSA% burn for total body, partial thickness, and full thickness separately. Laboratory data included baseline and peak values for serum creatinine, alkaline phosphatase, total bilirubin, AST, and ALT. The number of days on oxandrolone therapy until peak AST/ALT was also collected. Additional data collection for patients who developed transaminitis included: number of treatment days on oxandrolone to development of transaminitis, number of days oxandrolone withheld after transaminitis, AST/ALT value if oxandrolone re-initiated, peak AST/ALT values after re-initiation, and time to development of a second episode of transaminitis if applicable.

2.3. *Statistical analysis*

Patient characteristics are presented in Tables 1–3 with continuous variables summarized by mean and standard deviation or median and interquartile range and categorical variables summarized by number and percent. Univariable logistic regression models were used to identify risk factors for hepatic transaminitis among burn patients receiving oxandrolone. Model results were evaluated at the $\alpha=0.05$ significance level. All analyses were performed using SAS software version 9.4 (Cary, NC).

A sample size of 140 burn patients was used with an initial estimation that 10% would develop hepatic transaminitis. This sample size and event rate provided at least 80% power to detect a dichotomous risk factor with an odds ratio for hepatic transaminitis of 3.59 or greater (assuming the risk factor appears in 50% of the sample) or a continuous risk factor with an odds ratio for hepatic transaminitis of 2.20 or greater for a one standard deviation increase in the risk factor, at a significance level of $\alpha=0.05$.

3. Results

A total of 96 patients were identified as receiving oxandrolone during the study period, with 66 patients meeting inclusion/exclusion criteria. Primary reasons for exclusion were lack of a repeat AST/ALT value, use of oxandrolone outside of burn injury, and TBSA burn <10% (Fig. 1). Of the 66 patients included in the study, 28 (42.4%) patients developed transaminitis while on oxandrolone therapy, while only 7 (10.6%) had transaminitis on admission, with the initiation of oxandrolone being held in these patients until initial transaminitis event resolved. For the 7 patients that had transaminitis on admission all but 1 patient were started on oxandrolone within 2 weeks of admission after their transaminitis resolved. Six out of these 7 patents also experienced a TBSA burn of >35%. The one patient initiated on oxandrolone >2 weeks after admission was started on oxandrolone 2 months after admission and had a LOS of 149 days, a TBSA of 45.1%, and a significant past medical history of liver disease. The median total duration of oxandrolone in the transaminitis group was 18 [8–26] days compared to 21 [11–46] days in the no transaminitis group. The median time to the development of transaminitis from start of oxandrolone was 11 [6–18] days, and the median time to resolution after oxandrolone therapy was held was 11 [5–14] days. Oxandrolone therapy was held or stopped within 24 h after the development of transaminitis in 15/28 (53.6%) patients. Of the remaining 13 patients that developed transaminitis, oxandrolone was stopped within 72 h in 7 patients, with 6 patients continuing past 72 h. Overall, 4 patients were rechallenged on oxandrolone therapy once

Table 1 – Patient demographics and burn characteristics for the transaminitis and no transaminitis groups.

Characteristic	Transaminitis (n=28)	No transaminitis (n=38)	p-Value
Age (years)	42.4±17.2	49.5±17.5	0.11
Female, n (%)	9 (32.1)	13 (34.2)	0.86
Ethnicity, n (%)			0.10
Caucasian	20 (71.4)	35 (92.1)	
African American	7 (25.0)	2 (5.3)	
Other	1 (3.6)	1 (2.6)	
Body mass index (kg/m^2)	29.7±4.4	29.1±7.4	0.68
Creatinine clearance (mL/min)	110±43	100±39	0.32
Medical history, n (%)			
Liver disease	2 (7.1)	0 (0)	0.18
Obesity	13 (46.4)	13 (34.2)	0.32
Intravenous drug use	7 (25.0)	5 (13.2)	0.22
Chronic kidney disease	1 (3.6)	2 (5.3)	0.75
Diabetes mellitus	4 (14.3)	7 (18.4)	0.66
Intravenous vasopressor use, n (%)	10 (35.7)	11 (28.9)	0.56
Burn characteristics			
TBSA %	36.5±17.4	30.0±14.7	0.11
Partial thickness %	18.6±13.6	17.2±13.2	0.65
Full thickness %	17.9±19.9	12.9±13.5	0.23

Data presented as mean±SD unless otherwise noted.
TBSA: total body surface area.

Table 2 – Baseline, peak, and percentage change in AST/ALT measurements during oxandrolone therapy for the transaminitis and no transaminitis groups.

	Transaminitis (n=28)	No transaminitis (n=38)
AST at oxandrolone initiation (mg/dL)	42 [30–57]	31 [20–39]
Peak AST (mg/dL)	142 [100–264]	37 [25–54]
Change start to peak AST (%)	271 [101–560]	25 [-31 to 100]
ALT at oxandrolone initiation (mg/dL)	27 [19–39]	22 [15–27]
Peak ALT (mg/dL)	176 [134–267]	35 [22–52]
Change start to peak ALT (%)	643 [375–1012]	94 [5–194]

Data presented as median [IQR].
AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 3 – Medications used while on oxandrolone therapy for the transaminitis and no transaminitis groups.

[a]Medication	Transaminitis (n=28)	No transaminitis (n=38)	p-Value
Scheduled acetaminophen	1 (3.6)	3 (7.9)	0.48
Triazole Antifungals	6 (21.4)	13 (34.2)	0.26
Amiodarone	1 (3.6)	2 (5.3)	0.75
Antipsychotics	15 (53.6)	23 (60.5)	0.57
Azithromycin	1 (3.6)	1 (2.6)	0.83
Erythromycin	3 (10.7)	4 (10.5)	0.98
Sulfonamides	7 (25.0)	5 (13.2)	0.22
Penicillins	17 (60.7)	24 (63.2)	0.84
Statins	4 (14.3)	5 (13.2)	0.90
Caspofungin	2 (7.1)	4 (10.5)	0.64
Carbamazepine	0 (0)	2 (5.3)	0.98
Tricyclic antidepressants	0 (0)	1 (2.6)	0.99
Phenytoin	0 (0)	2 (5.3)	0.98
Medication, any	26 (92.9)	30 (79.0)	0.14
Number of medications			0.045[b]
0	2 (7.1)	8 (21.1)	Reference
1	10 (35.7)	5 (13.2)	0.03[c]
2	8 (28.6)	7 (18.4)	0.11[c]
>2	8 (28.6)	18 (47.4)	0.52[c]

Data presented as n (%).
[a] Barbiturates and valproic acid were not used during oxandrolone therapy in either the transaminitis or no transaminitis group.
[b] Omnibus p-Value for number of medications.
[c] p-Value versus the 0 medication reference level.

transaminitis had resolved, with 2 patients developing a second episode of transaminitis. One of these patients received oxandrolone for over 3 months, had a TBSA >60%, and developed the initial transaminitis event after receiving 17 days of oxandrolone therapy, with the second transaminitis event occurring after 10 days of rechallenging with oxandrolone. The other patient had a TBSA >70% and had received inpatient burn care for over a year. This patient's initial episode of transaminitis developed after being on oxandrolone for 255 days with the second event occurring after 47 days of rechallenging with oxandrolone.

Patient characteristics between those who developed transaminitis and those who did not were similar with patients in their 4th decade of life, predominantly male, good renal function as demonstrated by the creatinine clearance, and a BMI of approximately 29 (Table 1). A majority of the patients presented with a TBSA burn between 21–40% (56%), with 22.7% of patients having a TBSA >41%. There were no differences in TBSA% burn injury between the two groups, or when broken into partial and full thickness burn injury (Table 1). No significant increases in serum creatinine, alkaline phosphatase, or total bilirubin were observed between the two groups. At initiation of oxandrolone, both groups had AST and ALT measurements that were within normal laboratory ranges (Table 2). The mean peak AST/ALT in the transaminitis group was 142/176 mg/dL, with patients who did not develop transaminitis remaining within normal laboratory ranges. The overall percentage change in AST/ALT from start of oxandrolone to peak was significantly higher in the transaminitis group compared to those with no transaminitis (Table 2).

Concomitant medications that carry a risk of transaminitis are presented in Table 3. Overall 92.9% of patients in the transaminitis group and 79% of the no transaminitis group received at least one other medication that could contribute to transaminitis during oxandrolone therapy, however this was not statistically significant (p=0.14). The most common medications used by both groups were triazole antifungals, antipsychotics (risperidone, olanzapine, haloperidol, or quetiapine), and penicillins (Table 3).

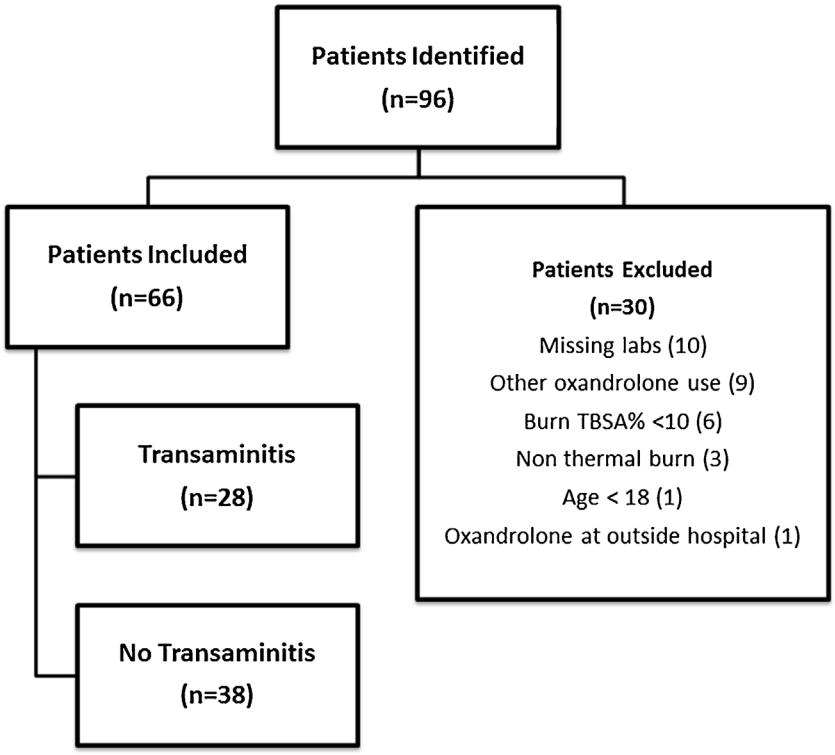

Fig. 1 – Patient population inclusion and exclusion.

When observing the total number of concomitant medications used within the groups, the transaminitis group had a significantly higher proportion of concomitant medications compared to the no transaminitis group (p=0.045). When comparing the total number of medications to the reference level of 0 medications, the transaminitis group was more likely to have 1 concomitant medication with transaminitis risk compared to the no transaminitis group (Table 3).

The transaminitis group had a hospital length of stay that was approximately 8 days longer and had a higher proportion of patients that developed liver dysfunction compared to the no transaminitis group (Figs. 2 and 3), although neither reached statistical significance. Of the 4 patients that developed liver dysfunction, all of them were reviewed by physician investigators (JKB and LJ) for confirmation of diagnosis and further evaluation on causes of liver dysfunction. Based on review JKB and LJ were unable to confirm the liver dysfunction was due solely to oxandrolone administration in all 4 cases. Other factors identified as possible causes were concomitant medications, shock liver, and use of vasopressors. Specifically, 2 of the 4 patients were in septic shock and on vasopressors at the time of liver dysfunction documentation. Mortality was

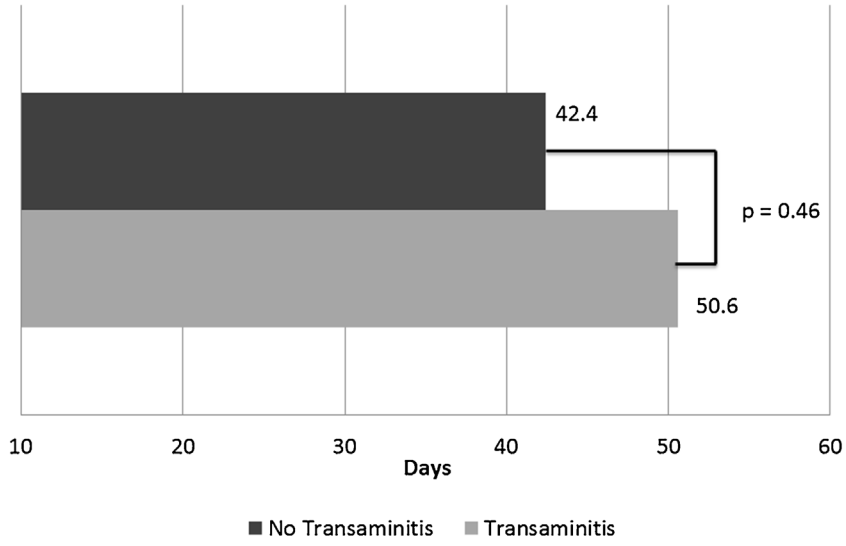

Fig. 2 – Length of hospital stay.

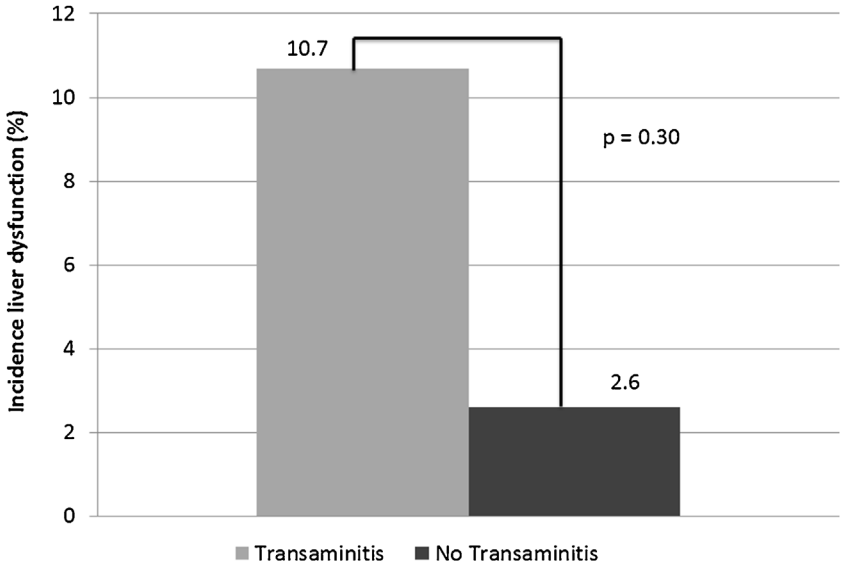

Fig. 3 – Incidence of acute liver dysfunction in the transaminitis and no transaminitis groups.

similar between the transaminitis and no transaminitis groups (17.9 vs. 18.4%, p=0.95), with no deaths among the 4 patients who developed liver dysfunction.

4. Discussion

The results of this single-center, retrospective study suggest that transaminitis is not an infrequent adverse effect of oxandrolone use in burn patients. Although no significant differences in non-modifiable patient risk factors for the development of transaminitis were identified, we believe future studies should include a larger sample size that would allow for a multivariable regression analysis to be performed to identify possible risk factors for transaminitis. We did however find that patients who developed transaminitis had a statistically significantly higher proportion of other concomitant medications with a transaminitis risk compared to the no transaminitis group. Patients with transaminitis also had an increased length of stay and developed liver dysfunction more frequently than those who did not develop transaminitis, although this did not reach statistical significance.

The reported incidence of oxandrolone induced transaminitis varies significantly between current studies, however in this study we found that the incidence of transaminitis while on oxandrolone therapy was 42%, which is significantly higher than previously published literature [1–3,5,8–11]. Wolf and colleagues found an increase in liver enzymes after ≥8 weeks of therapy in the oxandrolone group (11%) compared to the placebo group (6%). However, out of all the abnormal AST/ALT values collected from the oxandrolone group the incidence of AST or ALT >100 mg/dL was 32 out of 121 values (26%), which is significantly lower than our reported incidence of 42%. This study had a mean age of 39 and a TBSA of 35% in the oxandrolone group, which is comparable to our mean age of 46 and TBSA of 33%. However, the Wolf study did exclude patients with underlying liver disease and AST/ALT levels were reported at the discretion of the multiple study sites [2]. Therefore transaminitis may have been underreported, which in combination with a population that may have been at an inherently lower risk of transaminitis, may account for the lower rate of transaminitis in comparison to the results of this study. Demling and colleagues showed in 26 patients with TBSA burns between 10-30% and a mean age of 70, an incidence of transaminitis (defined as mild liver dysfunction with a greater than 2-fold increase in AST and ALT from patient baseline) of 20% in the oxandrolone group [3]. Using this same definition our study showed an incidence of transaminitis (mild liver dysfunction) of 45% (results previously not reported), although the patients in our study had significantly higher TBSA% burn and were much younger, which could account for our higher incidence. Using a definition of any increase from baseline in total bilirubin, direct bilirubin, alkaline phosphate, AST, or ALT, McCullough and colleagues reported an incidence of hepatic dysfunction of 67% in their oxandrolone 10 mg twice a day group. However, none of the 6 patients in this group had an AST or ALT elevation >100 mg/dL, which was our definition of transaminitis [5]. This high incidence of hepatic dysfunction reported is likely due to the very small sample size of 6 patients and the loose definition of hepatic dysfunction, which is not comparable to any other studies. By using a consistent dosing of oxandrolone 10 mg twice daily in all patients with a thermal burn injury and having a protocol put in place for monitoring of transaminitis, our study was able to show that oxandrolone induced transaminitis is occurring at a higher rate than previously reported.

Little is known about the risk factors that may contribute to the development of oxandrolone induced transaminitis or hepatic dysfunction. The study done by McCullough is the only study to date that has been published to describe potential risk factors for the development of hepatic dysfunction in patients receiving oxandrolone therapy [5]. In addition, no difference in the incidence of hepatic dysfunction was found when

comparing TBSA% burn. The small sample size of only 14 patients in the oxandrolone group, the different oxandrolone dosing regimens of 5mg and 10mg twice daily used, and an overall lower burn severity (mean TBSA 15–19%), is a significant limitation when trying to determine possible risk factors when compared to the current study of 66 patients with a mean TBSA of 33% overall. Since our sample size prevented a multivariable regression analysis from being performed, and the univariable analysis only identified concomitant medications as significantly different between groups, a larger sample size would be beneficial to more accurately describe factors increasing the risk of transaminitis in patients with burn injury receiving oxandrolone.

The current study has several notable limitations. One of the limitations that occur frequently in burn injury research is the small patient sample, which limited the evaluation of risk factors for transaminitis in the current study through multivariable regression modeling. The small sample size could also potentially lead to type 2 error. Similarly, potential confounders for secondary endpoints were not evaluated, and may explain the trends toward increased hospital length of stay and liver dysfunction among those with transaminitis noted in the current study. Additionally, other medications that have been linked to transaminitis were not avoided during oxandrolone therapy in our burn patients, and significant differences in these medications were seen between the groups. The duration and the timing proximity of concurrent medications to the development of transaminitis was also not collected in this study. Therefore, the total exposure of concurrent medications and relation to transaminitis risk is unable to be ascertained based on the study results. Although it is an institutional protocol to hold oxandrolone as soon as transaminitis develops, the protocol was not followed in all patients as only 15 out of the 28 patients had oxandrolone held within 24h. The time to transaminitis resolution in this study could be inaccurate, as the frequency of LFT monitoring after oxandrolone discontinuation was variable between patients and up to provider discretion. With the study being retrospective in nature, adherence to the holding protocol and monitoring of transaminitis resolution after oxandrolone discontinuation could not be prospectively monitored and controlled.

5. Conclusion

To our knowledge, this the first study to evaluate transaminitis associated with oxandrolone therapy as a primary outcome with the aim to evaluate possible risk factors for the development of transaminitis. This study was able to show that transaminitis is occurring in patients significantly more frequently than previously reported in the literature and can also occur again after rechallenging with oxandrolone. With the small sample size, only the number of concomitant medications was identified as a statistically significant risk factor for the development of transaminitis in univariable analysis. Further research is warranted using a larger sample size to identify patients at a high risk for developing transaminitis and to help determine the level of LFT elevation during oxandrolone use that would raise concern for harmful liver effects. Identification of risk factors for oxandrolone induced transaminitis could then help determine if more consistent hepatic monitoring is indicated, the need for possible dose adjustments of oxandrolone, and to determine if altering concomitant medications could reduce the risk of transaminitis in patients receiving oxandrolone.

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