Original Article

Severity and outcomes of acute alcoholic pancreatitis in cannabis users

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Background: Cannabis is the most commonly and widely used illicit drug in the world and is also the most commonly used drug of abuse in alcohol drinkers. Experimental studies have shown conflicting results of the effects of cannabis on the severity of acute pancreatitis (AP). The purpose of this study is to ascertain the clinical effects of simultaneous alcohol and cannabis use on severity at presentation and outcomes of acute alcoholic pancreatitis (AAP).

Methods: A retrospective review was conducted on the patients discharged with principle or secondary diagnosis of AP using ICD-9 & ICD-10 codes during the time period from January 2006 to December 2015 at a large community-based hospital in Central Georgia. Patients with alcoholic pancreatitis with cannabis (CB^+) and without cannabis (CB^-) use were identified and were matched with sex and age.

Results: Our study findings showed that a greater percentage of CB^+ patients did not have a systemic inflammatory response syndrome (SIRS) score (P=0.043), had a lower BISAP score (P=0.031), and had a significantly lower BUN level (P=0.033), but there was no difference in the Balthazar Index and revised Atlanta classification severity between the two groups. CB^+ patients tended to need less ICU care than CB^- patients (P=0.059).

Conclusions: Based on our findings, we found that CB^+ patients had less severe presentation of AAP indicating that cannabis could modulate the inflammatory effect of alcohol on the pancreas. Further large scale prospective studies are needed to confirm our results.

Keywords: Cannabis; marijuana; acute pancreatitis (AP); severity; outcomes; alcohol

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Introduction

Clinical effects of cannabis on gastrointestinal (GI) disorders are unclear although it is used in chemotherapy related nausea and vomiting, and is Food and Drug Administration (FDA) approved for this indication (1). According to the United Nations Office of Drugs and Crime (UNODC), cannabis is the most commonly and widely used illicit drug globally with an estimated annual prevalence of 2.7–4.9% of the adult population in 2012 (2). It also remains the most commonly used drug of abuse in the United States (US) with steady increase in its consumption in the younger population. Cannabis is now legally allowed for medicinal and/or recreational purposes in many states in the US (3). Alcohol stands as the second most common cause of acute pancreatitis (AP) in the US after gallstones. Cannabis is also the most commonly used drug of abuse in the alcohol drinkers (4). Consumption of cannabis in alcohol abusers ranges from 20–50% (5). In the National Alcohol Survey in 2000, about 7% of respondents reported drinking alcohol and using cannabis at the same time (5). It has been found that simultaneous use of cannabis and alcohol is associated

with increased frequency of use of both drugs and also with the increased quantity of alcohol itself (6). Alcohol increases the absorption of delta-9-tetrahydrocannabinol (THC), resulting in enhancement of the positive subjective mood effects of cannabis smoking, which has possibly contributed to the popularity of this alcohol-cannabis drug combination (7). In a report from the National Surveys on Drug Use and Health (NSDUH) in US civilians aged ≥12 years, the lifetime risk of developing pancreatitis increased with use of cannabis and was directly related its duration of use (8).

Recently, several cases of cannabis-induced pancreatitis have been reported in the literature (9-12). However, no clinical trials or clinical studies are published on the effect of cannabis on AP. In experimental models, studies on the effect of cannabis on cerulein induced pancreatitis in mice have produced conflicting and confusing results. This study evaluates the effects of simultaneous alcohol and cannabis use on disease severity and clinical outcomes in patients with acute alcoholic pancreatitis (AAP).

Methods

Study population

We retrospectively reviewed the electronic medical records of all consecutive adult patients who were discharged from The Medical Center, Navicent Health, Macon, Georgia; United States with a principal or secondary diagnosis of AP from January 2006 to December 2015. The Medical Center, Navicent Health is a tertiary care teaching hospital affiliated with Mercer University and is the second largest hospital in the state of Georgia. This study was reviewed and approved by joint Institutional Review Boards (IRB) of The Medical Center, Navicent Health and Mercer University (protocol no. H1411315). Patients were identified by the International Classification of Disease, ninth revision, Clinical Modification (ICD-9 CM) code 577.0 and ICD-10 CM code of K85. AP patients who were adult (>18 years old), non-pregnant, had urine drug screen testing on that admission and stayed more than one day in the hospital were included in the analysis. Patients who were transferred from other acute care hospitals were excluded. If a patient had multiple admissions during the study period then only the very first admission of that patient during the study period was included in the study and it was referred to as the index admission. The diagnosis of AP was again confirmed with revised Atlanta Criteria (13). Causes of pancreatitis were sought and only patients with AAP were included in the study. Patients were determined to have AAP if no other obvious cause of pancreatitis other than alcohol was found and/or if alcohol was charted as the cause of pancreatitis. The demographic, clinical, laboratorial, and radiological data for all eligible patients were collected. Patients with a positive urine drug screen test for THC on that hospitalization were identified. Patients with presence of pancreatic fibrosis or calcification suggesting chronic pancreatitis were excluded from analysis.

The clinical severity and outcome parameters

Clinical severity at admission was assessed by the following parameters: blood urea nitrogen (BUN) (14,15), bedside index for severity in acute pancreatitis (BISAP) score (16), systemic inflammatory response syndrome (SIRS) (17) and Balthazar computed tomography (CT) scan grade (18). The BISAP score consists of: BUN >25 mg/dL, impairment in mental status, presence of the SIRS, age >60 years, and presence of pleural effusion. SIRS is defined by the presence of two or more of the following: pulse >90 beats/min, respirations >20 per min, or $PaCO_2$ <32 mmHg, temperature >100.4 or <96.8 °F and white blood cell count >12,000 or <4,000 cells per mm^3. Balthazar grading depends on the appearance of the pancreas on CT scan; it is graded from A to E with Grade A representing normal CT, Grade B representing focal or diffuse enlargement of the pancreas, Grade C representing pancreatic gland abnormalities and peripancreatic inflammation, Grade D representing fluid collection in a single location and Grade E representing the worst grade with two or more collections and/or gas bubbles in or adjacent to the pancreas.

Outcomes were defined by median length of stay (in days), need for Intensive Care Unit (ICU) management, and need for surgical intervention in relation to pancreatitis and mortality. Comorbidities were defined as the pre-existing disease or conditions in addition to AP, and Charlson's comorbidity index (19) was used to assess the effect of comorbidities on severity and outcome.

Statistical analysis

AAP patients were divided into two study population groups: CB^+ and CB^- as evident by presence of THC in urine at the time of admission. We matched the CB^- patients to CB^+ patients with age and sex to a 2:1 ratio.

Categorical variables were analyzed with the Chi-square

Table 1 Characteristics of alcoholic acute pancreatitis patients using cannabis (CB^+) and not using cannabis (CB^-)

Characteristic	Overall (N=114)	CB^+ (N=38)	CB^- (N=76)
Age, mean (± SD)	49.82 (±8.16)	49.66 (±8.26)	49.89 (±8.16)
Sex, N (%)			
Male	87 (76.32)	29 (76.32)	58 (76.32)
Female	27 (23.68)	9 (23.68)	18 (23.68)
Race, N (%)			
White	38 (33.33)	10 (26.32)	28 (36.84)
Black	74 (64.91)	27 (71.05)	47 (61.84)
Other	2 (1.75)	1 (2.63)	1 (1.32)
BMI, mean (± SD)^	26.64 (±7.20)	24.24 (±6.08)	27.86 (±7.45)
Smoking, N (%)			
Yes	85 (75.56)	37 (97.37)	48 (63.16)
No	29 (25.44)	1 (2.63)	28 (36.84)
Diabetes, N (%)			
Yes	26 (22.81)	8 (21.05)	18 (23.68)
No	88 (77.19)	30 (78.95)	58 (76.32)

SD, standard deviation, BMI, body mass index. ^, 1 missing BMI.

test or Fisher's exact test, and continuous variables were analyzed with the independent *t*-test or Wilcoxon-rank sum test. Two-tailed tests were performed, and a P value less than 0.05 was used to determine statistical significance. Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Results

There were 114 total subjects included in the study; 38 patients in the CB^+ group and 76 patients in the CB^- group. *Table 1* describes the characteristics of these patients. There were no statistically significant differences in age or sex, indicating that patients were matched correctly. There were also no differences in race or diabetes status. The mean age for both groups was almost 50 years, the majority of patients were male, black, and did not have diabetes. The mean Body Mass Index (BMI) was higher for the CB^- patients compared to the CB^+ patients (27.86 *vs.* 24.24, P=0.011) while 97.37% of the CB^+ patients smoked cigarettes compared to 63.16% of the CB^- patients (P<0.0001).

There were statistically significant differences in the BUN level, BISAP score and SIRS score between the two groups (*Table 2*). The median BUN level was higher for CB^- patients compared to CB^+ patients (12.00 *vs.* 10.00, P=0.033). Only three patients (7.89%) in the CB^+ group had a BUN ≥20 mg/dL at the time of admission and six (15.79%) had elevation in a BUN within 24 hours while 17 (22.37%) patients in the CB^- group had BUN ≥20 mg/dL at the time of admission and 23 (30.26%) had risen in BUN within 24 hours. A greater percentage of CB^- patients had a BISAP score of two or three compared to CB^+ patients (21.05% *vs.* 5.26%, P=0.031). A greater percentage of CB^- patients also had a SIRS score compared to the CB^+ patients (47.37% *vs.* 26.32%, P=0.043). There were no statistically significant differences in the Balthazar Index or severity of pancreatitis as per modified Atlanta classification.

Outcomes measured during the admission are compared in *Table 3*. There was a nonsignificant trend for a greater percentage of CB^- patients to be in the ICU compared to CB^+ patients (14.47% *vs.* 2.63%, P=0.059). There were no statistically significant differences in length of stay or Charlson's co-morbidity index. Overall, the median length of stay was 4 days, and the majority of patients had a Charlson's score of zero, indicating that they did not have any co-morbidities that increase the risk of mortality. No patient underwent a pancreatitis related procedure in either

Table 2 Severity comparisons between alcoholic acute pancreatitis patients using cannabis (CB^+) and not using cannabis (CB^-)

Severity measure	Overall (N=114) N (%)	CB^+ (N=38) N (%)	CB^- (N=76) N (%)	P value*
BUN level median (IQR)	11.00 (7.00, 16.00)	10.00 (7.00, 12.00)	12.00 (7.00, 18.00)	0.033
BISAP score				0.031
0,1	96 (84.21)	36 (94.74)	60 (78.95)	
2,3	18 (15.79)	2 (5.26)	16 (21.05)	
SIRS score				0.043
Yes	46 (40.35)	10 (26.32)	36 (47.37)	
No	68 (59.65)	28 (73.68)	40 (52.63)	
Balthazar index^				0.29
A,B	27 (24.77)	11 (33.33)	16 (21.05)	
C	46 (42.20)	14 (42.42)	32 (42.11)	
D,E	36 (33.03)	8 (24.24)	28 (36.84)	
Severity of pancreatitis				0.41
Mild	57 (50.00)	22 (57.89)	35 (46.05)	
Moderate	50 (43.86)	15 (39.47)	35 (46.05)	
Severe	7 (6.14)	1 (2.63)	6 (7.89)	

BUN, blood urea nitrogen; BISAP, bedside index for severity of acute pancreatitis; SIRS, systemic inflammatory response syndrome. *, P value generated from Fisher's exact test or Chi-square test for proportions and Wilcoxon rank-sum test for continuous measures; ^, 5 missing a Balthazar index score due to not having a computed tomography (CT) scan. Wilcoxon rank-sum test produces mean scores: mean score for BUN level, 48.08 CB^+, 62.21 CB^-.

Table 3 Admission comparisons between alcoholic acute pancreatitis patients using cannabis (CB^+) and not using cannabis (CB^-)

Outcome measure	Overall (N=114) N (%)	CB^+ (N=38) N (%)	CB^- (N=76) N (%)	P value*
Length of stay in days[a]				0.15
Median (IQR)	4.00 (3.00, 6.00)	3.50 (2.00, 6.00)	4.00 (3.00, 7.00)	
ICU care				0.059
Yes	12 (10.53)	1 (2.63)	11 (14.47)	
No	102 (89.47)	37 (97.37)	65 (85.53)	
Charlson's comorbidity index				1.00
0	95 (83.33)	32 (84.21)	63 (82.89)	
≥1	19 (16.67)	6 (15.79)	13 (17.11)	

IQR, interquartile range; *, P value generated from Fisher's exact test for proportions and Wilcoxon rank-sum test for continuous measures. [a], median (interquartile range) reported; Wilcoxon rank-sum test produces mean scores: mean score for length of stay, 51.20 CB^+, 60.65 CB^-.

group. Only two patients died in the selected cohort and both of them were in CB^- group.

Discussion

Cannabis has been used for medicinal purposes for the treatment of severe cancer pain, chemotherapy-related nausea and vomiting, diarrhea and chronic abdominal pain (1,20). Cannabis has been found to reduce the disease related symptoms in inflammatory bowel diseases (21) and currently research is underway to see if it can modify the disease course as well. Clinical effects of cannabis on the pancreas are unknown although there have been at least 15 cases of cannabis induced pancreatitis reported in PubMed (9-12). It could be possible that cannabis, an antiemetic drug, ameliorates the body's defense mechanism to get rid of alcohol by vomiting, thereby increasing the available amount of alcohol in the body and its side effects. On the contrary, cannabis can also paradoxically cause cyclic nausea and vomiting in the absence of pancreatic inflammation, known as cannabinoid hyperemesis syndrome (1,22). To the best of our knowledge, our study is the first to address the clinical effects of simultaneous cannabis use in AAP.

The role of cannabinoids in AP has been a topic of interest for the last few years but its clinical effects have never been evaluated. Most data of the effect of cannabis on AP comes from mice experimental models but the evidence of this data is conflicting (20). There are two G protein-coupled cannabinoid receptors in the human body, CB1 and CB2 receptors. CB1 receptor is mainly present in the central and peripheral nervous system and CB2 receptor is mainly present in immune cells and the GI tract (23). Both CB1 and CB2 receptors are weakly expressed in the normal pancreas, but this expression increases in the setting of inflammation. CB1 receptor activation has shown to induce fibrosis while activation of CB2 receptor is linked with anti-fibrogenic effects in the pancreas (1,20). Matsuda *et al.* (24) showed that down regulation of endocannabinoid system by AM251 (a CB1 receptor inhibitor) improved survival in rats with severe AP. This finding was later confirmed by another study (25). On the contrary, Michalski *et al.* (26) showed that HU 210, a synthetic agonist of cannabinoid receptors CB1 and CB2, completely abolished the abdominal pain in cerulein induced pancreatitis and simultaneously decreased inflammation of the pancreas, suggesting a potential therapeutic role of cannabinoids in AP. Another study by Li *et al.* (27) also produced similar results, but it was with an atypical cannabinoid (O-1602) and Cannabidiol. We think that these contradictory findings could be the result of the differences in experimental methods, timing of drug administration, and in the types and doses of agonists and antagonists used.

Cannabidiol, the major constituents of plant cannabis has shown anti-inflammatory properties in many organs (28). Cannabinoids decrease Th17 inflammatory autoimmune phenotype and modulate autoimmune cytokines by reducing expression of the pathogenic IL-17 and IL-6 cytokines, while raising the expression of the anti-inflammatory cytokine IL-10 (29). Anandamide, an endogenous cannabinoid, has been shown to hinder proliferation of lymphocytes and macrophage-mediated killing of tumor necrosis factor-sensitive cells (30). On the contrary, alcohol suppresses the immune system and directly affects lymphocyte function (31). It has been proposed that a decrease in activity of antigen presenting cells plays a critical role in the negative effects of alcohol on cell mediated immunity. The effect of alcohol on cytokine and chemokine production is dose and duration dependent. Acute alcohol exposure decreases production of cytokines and chemokines and chronic alcohol exposure is associated with activation of pro-inflammatory cytokines such as TNF-α in experimental models (32-34). In a recent study, Nair *et al.* (30) showed that study participants who abused alcohol had higher levels of inflammatory cytokines such as interleukin (IL)-10, IL-309, IL-12, IL-15, Granulocyte-macrophage colony-stimulating factor, etc. while marijuana abusing patients had lower levels of these cytokines. In a randomized double-blind placebo-controlled study on patients with chronic pancreatitis, it was demonstrated that Namisol (a pure and natural THC) did not affect the levels of pro-inflammatory cytokines TNF-α and IL-8 from their baseline levels. Similarly, levels of anti-inflammatory cytokine IL-10 remained unaffected (35). Recently, in another randomized, double-blind, placebo-controlled two-way crossover study in patients with chronic pancreatitis, a single dose of 8 mg Namisol failed to effectively reduce persistent abdominal pain when compared with diazepam (36). In a study from the National Health and Nutrition Examination Survey (NHANES) 2005–2010, active cannabis smokers had lower serum C-reactive protein (CRP) levels (37). We did not have CRP levels available in our data for most of the patients possibly because measuring and following the CRP levels is not useful for diagnosis and prognosis of pancreatitis. In our study, we found that important markers of disease severity like BUN, SIRS and BISAP scores were significantly lower in CB^+ patients

although the morphological marker of pancreatitis severity, which is the Balthazar score, was not significant. Patients with CB^- had worse outcomes in terms of needing more ICU care but median length of stay for both groups was not statistically significant (P=0.15).

SIRS, & BISAP scores and Balthazar CT severity index have been shown to be reliable indicators in predicting severity of pancreatitis (38-42) and have comparable efficacy in predicting the severity of AP (43,44). We also used the BUN level as a marker of disease severity in our study, as BUN has been shown to be a marker of persistent organ failure in AP (14) and any BUN above 20 mg/dL and any rise in BUN have been associated with mortality (15,45). In our cohort more patients in CB^- group were found to have both of these features.

This study is our effort to determine the effect of cannabis on AP in clinical medicine especially because of conflicting data from experimental AP. We only included patients with AAP because severity and outcome of AP may be related to its origin (46,47). However, we must underline some potential weaknesses in our study. Because of its retrospective nature, we did not have information on type, timing and route of cannabis consumption. There was no way to know if patients used cannabis simultaneously or concomitantly with alcohol. We should also keep in mind that a single positive urine drug screen cannot disclose chronicity of use or evidence of link between cannabis and an event. We did not also have information about amount, type and frequency of alcohol consumed by the patients.

In conclusion, due to increasing decriminalization and legalization of cannabis in many states of the US, consumption of cannabis is poised to increase. Studies are needed to identify and quantify the effects of cannabis on AP. Further, large scale studies are needed to characterize the effect of cannabis on AP.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was reviewed and approved by joint Institutional Review Boards (IRB) of The Medical Center, Navicent Health and Mercer University (protocol no. H1411315).

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