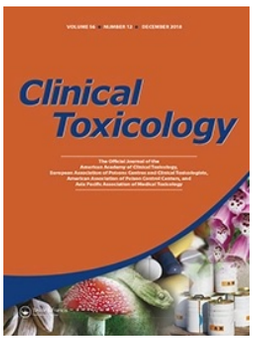

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CLINICAL RESEARCH

Pediatric cannabis intoxication trends in the pre and post-legalization era

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ABSTRACT

Introduction: On April 13, 2017, a bill to legalize cannabis was introduced to the Canadian Parliament and presented to the public. On October 17, 2018, Canada legalized recreational cannabis use. We assessed intoxication severity, reflected by ICU admission rates, risk factors and other characteristics in children who presented to the emergency department (ED) with cannabis intoxication, before and after legalization.

Methods: A retrospective cohort study of children 0–18 years who presented to a pediatric ED between January 1, 2008 and December 31, 2019 with cannabis intoxication. The pre-legalization period was defined from January 1, 2008 to April 12, 2017 and the peri-post legalization period from April 13, 2017 to December 31, 2019.

Results: We identified 298 patients; 232 (77.8%) presented in the pre legalization period and 66 (22.1%) in the peri-post legalization period; median age: 15.9 years (range: 11 months–17.99 years). A higher proportion of children were admitted to the ICU in the peri–post legalization period (13.6% vs. 4.7%, respectively; $p = .02$). While the median monthly number of cannabis-related presentations did not differ between the time periods (2.1 [IQR:1.9–2.5] in the pre legalization period vs. 1.7 [IQR:1.0–3.0] in the peri-post legalization period; $p = .69$), the clinical severity did. The proportions of children with respiratory involvement (65.9% vs. 50.9%; $p = .05$) and altered mental status (28.8% vs. 14.2%; $p < .01$) were higher in the peri-post legalization period. The peri-post legalization period was characterized by more children younger than 12 years (12.1% vs. 3.0%; $p = .04$), unintentional exposures (14.4% vs, 2.8%; $p = .002$) and edibles ingestion (19.7% vs. 7.8%; $p = .01$). Edible ingestion was an independent predictor of ICU admission (adjusted OR: 4.1, 95%CI: 1.2–13.7, $p = .02$).

Conclusions: The recreational cannabis legalization in Canada is associated with increased rates of severe intoxications in children. Edible ingestion is a strong predictor of ICU admission in the pediatric population.

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Cannabis intoxication; Canada; legalization; children; unintentional exposure

Introduction

Cannabis is the most widely misused illicit drug by adults and adolescents [1–4]. According to a national report from the United States (U.S.), approximately 100 million adults have used recreational cannabis at least once, and an estimated 22.2 million (8.3%) individuals aged 12 years or older are current cannabis users [5].

While uncommon in adults, severe cannabis intoxication has been well described in infants and children, with manifestations including behavioural changes, seizures, ataxia, respiratory depression, apnea, and coma [6–9].

As cannabis continues to be legalized or decriminalized in an increasing number of countries and states, the potential for both unintentional and intentional exposure in infants and young children rises [10–12]. At present, in the United States 37 states have legalized cannabis for medical indications since 1996, and 19 states currently allow retail and recreational use [9,13–16]. While conflicting data exist regarding increase in adolescent recreational use following medical cannabis legalization [15,17–19], legalization of recreational cannabis led to increased cannabis commercialization with concurrent introduction of highly concentrated cannabis edibles into the market [20,21]. Several US-based studies demonstrated negative effects of cannabis legalization on the pediatric population [10–14,21–23]. Specifically, pediatric unintentional cannabis exposures [10–12,23], related calls to poison control centers [11], emergency department visits [11,21,22] and hospitalizations [21] have significantly increased in states that passed cannabis legislation. While several states in the U.S. legislated measures to mitigate toxicity from unintentional pediatric ingestions of edibles, such

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as child-resistant and opaque packaging, restrictions on marketing campaigns, and banning of specific edibles [24] pediatric unintentional cannabis exposures continue to rise [25,26]. Poison center calls associated with pediatric cannabis exposures increased in from 2017 to 2019 in states with legalized cannabis use and were largely composed of unintentional edible exposures [26].

In Canada, the use of medical cannabis was legalized in 2001 [27]. The Cannabis Act (Bill C-45), related to recreational use, was introduced to Parliament in April 13, 2017 [28], and anticipated changes regarding cannabis legalization were announced to the public [29,30]. On October 17, 2018 Canada became one of the first countries in the world [27,31], and the first in North America [32] to legalize recreational cannabis use by adults 18 years or older. As of October 17, 2019 cannabis edible products and concentrates are legal for sale [33]. A recent Canadian study [27] reported gradual increase in cannabis use among youth since the beginning of the federal discourse around cannabis legalization. This trend is attributed to the public perception of cannabis use as "sensible" and "socially acceptable" [27]. Pro-cannabis messaging was also associated with increased use [34,35]. For these reasons, we defined the date in which the public was formally notified about cannabis legalization (April 13, 2017), as the start of the peri – legalization period.

These abrupt changes in cannabis legal status in Canada, which represent a natural human experiment, provide a unique opportunity to study, for the first time, the impact of recreational cannabis use on the risk and patterns of cannabis intoxication in children within a national context. Previous research primarily studied cannabis incidence changes following legalization, there is sparse data [10] with respect to legalization impact on outcome severity, such as ICU admission rates and risk factors. The primary objective of this study was to determine the impact of recreational cannabis legalization in Canada on the occurrence of severe outcome following pediatric cannabis intoxication, defined as ICU admission. Secondary objectives included changes in ED presentations, incidence, and patient characteristics, and identifying risk factors for ICU admission.

Methods

Study design

We conducted a retrospective, single center cohort study at the Hospital for Sick Children, Toronto, over a 12-year period from January 1, 2008 to December 31, 2019. Patients, aged 0–18 years, were included if they presented to the ED with presenting symptoms attributed to acute cannabis intoxication. The mean number of annual ED visits in the study hospital was 72,270 between 2017 and 2019.

Cannabis intoxication cases were identified by the following relevant ICD-10 codes: T40.7X, F12, T40.7X1A, X42 X62 Y12, Y49.6. Second, we also reviewed all positive urine samples for cannabinoid metabolites identified during ED visit or hospitalization. These were assessed against study eligibility and inclusion criteria. This complementing method served as an additional layer of quality assurance, to ensure no eligible cases were miscoded.

Urine toxicology tests for cannabinoids were conducted at the local laboratory (Division of Clinical Biochemistry, Department of Paediatric Laboratory Medicine) using the cannabinoids assay performed by the Abbott Architect ci4000 instrument for semi-quantitative detection of cannabinoids (THC) in human urine. Values above 35 ng/mL were reported as positive and those 35 ng/mL and below were considered negative. The study was approved by the local Institutional Research Board.

Data collection

The data was collected from the electronic medical charts by experienced abstractors who were blinded to the study hypothesis, by using a pre-specified, IRB-approved Case Report Form. We, thereafter, sampled 10% of the charts and found no inter-rater discrepancies.

The following parameters were extracted from the medical charts of all patients: (1) demographics: gender, age. (2) medical history and clinical presentation: date and time of exposure to cannabis, date and time of ED presentation, circumstances related to cannabis exposure other-co-ingested substances chief complaint, vital signs, respiratory involvement, Glasgow coma score (GCS) and mental status, meningismus, seizures, urine toxicology screening results. (3) medical management and interventions: administration of medications such as intravenous (IV) saline boluses, vasopressors, mechanical ventilation, lumbar puncture (LP), neuroimaging. (4) outcome: disposition (hospitalization to ICU, to inpatient ward or discharge home from the ED), total length of stay (LOS), mortality, post- hospitalization discharge (home, foster care) and Children's Aid Services (CAS) involvement.

Definitions

Pre and peri-post legalization periods

Two timeframes were defined: the *pre legalization period* – from January 2008 to April 12, 2017, and the *peri-post legalization period* – from April 13, 2017 (when the bill to legalize cannabis was introduced to the Canadian Parliament and the anticipated changes regarding the legalization were published) to December 31, 2019.

Intensive care unit (ICU)

The Department of Critical Care Medicine at the Hospital for Sick Children, Toronto manages the entire spectrum of critical care conditions including all modes of mechanical ventilation, mechanical support of cardiac circulation and other organ systems.

Respiratory involvement

Respiratory involvement was defined as tachypnea or bradypnea as per Pediatric Advanced Life Support (PALS) criteria [36], cyanosis, hypoxia (oxygen saturation $<$ 92% in room

air), bronchospasm (defined as wheezing on auscultation or use of bronchodilator agents) or need for supplemental oxygen.

Outcomes

Our primary outcome was ICU admission. We compared the proportions of ICU admission for cannabis intoxication in children in the peri-post legalization period vs. the pre legalization period. Because overall ward hospitalization is impacted by multiple clinical and non-clinical factors, such as institutional policies, the patient's home environment safety and access to care, we opted to focus our study on ICU admissions, which represent a severe, clinically grounded primary outcome. Our secondary outcomes were monthly number of cannabis related ED visits, circumstances of cannabis intoxication, clinical presentation and ED interventions in the peri-post legalization compared to the pre-legalization period. We defined 12 years of age as a cut-off, as previously done [14].

Predictors for ICU admission

In a secondary analysis, we explored risk factors for ICU admission among all cohort patients, regardless of the period of ED presentation. We compared relevant variables between patients who were admitted to the ICU versus those who were not.

Statistical analysis

Baseline characteristics were compared between patients who presented in the pre legalization period versus the peri-post legalization period using the Chi square or Fisher exact test for categorical variables and two tailed T test or Mann Whitney U test for continuous variables. A comparison of median cannabis- related monthly visits per year was performed between the pre and peri-post legalization period using the Mann Whitney U test for independent continuous variables. A correlation between cannabis-related visits and the year of presentation was performed using Pearson correlation of coefficients test. Categorial variables were described by the proportion (percentage) and continuous variables by the mean with standard deviation (SD) and by the median with interquartile range (IQR). In a secondary analysis, a univariable analysis using Chi square or Fisher exact test for categorical variable, were performed to compare epidemiological, exposure related and clinical characteristics between patients who were admitted to the ICU and those who were not. A multivariable logistic regression analysis was subsequently performed to explore independent predictors of ICU admission. All analyses were performed using SPSS Statistics, version 26 (SPSS Inc, Chicago, Illinois), and a 2-sided type 1 error rate of 0.05 was used as the threshold for statistical significance.

Results

A total of 298 children (150 males; 50.3%) met the inclusion criteria and comprise the study cohort. The median age was 15.9 years (range 11 months to 17.99 years). There was no correlation between the number of cannabis intoxication-related visits and the year of presentation (Pearson's correlation 0.14, $p = .66$). The epidemiologic characteristics and exposure circumstances of the study cohort are presented in Table 1. The most common mode of exposure was *via* inhalation ($n = 173$, 58.1%), followed by ingestion ($n = 26$, 8.7%). Co- ingested substances were detected in the urine of 136 (45.6%) patients, dominated by benzodiazepines and amphetamines. One hundred and thirty-four patients (45.0%) were hospitalized, with a total median length of hospital stay (LOS) of 3.5 days (IQR 1.0–7.0 days). Twenty patients (6.7%) were admitted to the ICU, with the total median LOS of 3.1 days (IQR 1.8–4.8 days) and the median length of ICU stay of 1.0 (0.9–1.7) days, and 4 (1.3%) children were transferred to rehabilitation centers after ICU discharge. Children's protective services were involved in 35 (11.7%) patients.

Pre versus peri-post legalisation periods

Two hundred and thirty-two patients (77.8%) presented in the pre-legalization period and 66 patients (22.2%) in the

Table 1. Epidemiologic characteristics and exposure circumstances of the study cohort.

Characteristic	All patients $N = 298$ (%)	*Pre – legalization era ($N = 232$)* (%)	*Peri-post legalization era ($N = 66$)* (%)	*p* value
Gender (males) (*n*, %)	150 (50.3)	114 (49.1)	36 (54.4)	.48
Median age (IQR*)	15.9 (15.0–16.8)	15.9 (15.1–16.8)	15.9 (14.8–16.8)	.47
Age < 12 years	15 (5.0)	7 (3.0)	8 (12.1)	<.01
Unintentional exposure	14 (4.7)	5 (2.8)	9 (14.5)	<.01
Mode of exposure				
Inhalation	174 (58.3)	137 (59.1)	37 (56.1)	.77
Ingestion	31 (8.7)	18 (7.8)	13 (19.7)	.01
Other	2 (0.6)	2 (0.8)	0 (0.0)	.77
Unknown	91 (30.5)	73 (31.4)	18 (27.2)	.75
Medical history				
Chronic disease	32 (10.7)	26 (11.2)	6 (9.1)	.82
Mental health history	145 (48.7)	112 (48.3)	33 (50.0)	.88
Disposition from ED				
Hospitalized	134 (45.0)	105 (45.2)	29 (43.9)	.88
Intensive care unit admission	20 (6.9)	11 (4.7)	9 (13.6)	.01
Discharged home	164 (55.0)	127 (54.7)	37 (56.0)	.88

*IQR – inter quartile range.

Table 2. Characteristics of children who presented to the emergency department in the pre versus peri-post cannabis legalization period.

	Pre – legalization era (N = 232) (%)	*Peri-post legalization era (N = 66)* (%)	*p* value
Physical findings			
Central nervous system			
Altered mental status	33 (14.2)	19 (28.8)	<.01
Seizures	7 (3.0)	2 (3.0)	1.00
Lowest Glasgow coma scale**	13.3 ± 3.7	11.6 ± 4.2	.01
Respiratory involvement	118 (50.9)	43 (65.2)	.02
Investigations			
Lumbar puncture	3 (1.3)	6 (9.1)	<.01
Neuroimaging	23 (9.9)	10 (15.2)	.26
Interventions			
Fluid bolus	37 (16.0)	19 (29.2)	.02
Intubation	17 (7.3)	5 (7.6)	>.99
Length of stay – total (days)***	3.5 (1.0–7.0)	3.5 (1.5–6.9)	.46
Intensive care unit - length of stay (days)***	1.0 (1.0–1.6)	1.0 (0.7–4.5)	.89

*Few children had more than one mode of exposure.
**Mean and standard deviation.
***Median and intra quartile range (IQR).

peri-post legalization period. The comparison of epidemiological characteristics and exposure circumstances among children who presented in the pre vs. peri-post legalization period is presented in Table 1. The comparison of clinical characteristics and interventions is presented in Table 2. A higher proportion of children were admitted to the ICU in the peri–post legalization period compared to pre-legalization (13.6% vs. 4.7%, respectively; $p = .02$). The median monthly number of children who presented to the ED with cannabis intoxication did not significantly differ between the two time periods (2.1 [IQR: 1.9–2.5] in the pre legalization period vs. 1.7 [IQR: 1.0–3.0] in the per-post legalization period; $p = .69$). The peri-post legalization period included a greater proportion of unintentional intoxications (14.4% vs 2.8%, respectively; $p < .01$) and of intoxications in children younger than 12 years (12.1% vs. 3.0%, respectively; $p < .01$), compared to the pre-legalization period. Edible ingestion was more common in the peri-post legalization period (19.7% vs. 7.8%, $p = .01$).

Compared to the pre legalization period, a greater proportion of children who presented in the peri-post legalization period had respiratory involvement (65.2% vs. 50.9%, $p = .02$), altered mental status (28.8% vs. 14.2%, $p < .01$), lower GCS

(11.6 ± 4.2 vs. 13.3 ± 3.7, $p = .01$), and diagnostic and therapeutic interventions, such as a lumbar puncture (9.1% vs. 1.3%, $p < .01$) and administration of intravenous fluid boluses (29.2% vs. 16.0%, $p = .02$).

Predictors for ICU admission

In a secondary analysis, we compared patient's age, the presence of chronic disease, psychiatric history, time of presentation with respect to the legalization process, and exposure route throughout the entire study period between patients who were admitted to the ICU and patients who were not. Age < 12 years (4/20 [20.0] % vs.11/278 [4.0%], $p = .01$), presentation during the peri-post legalization period (9/20 [45.0%] vs. 57/278 [20.5%], $p = .02$), and edible ingestion (7/20 [35.0%] vs. 24/278 [8.6%], $p < .01$). were more common among ICU patients (Table 3). In a multivariable logistic regression analysis, using the two strongest risk factors in the binary analysis (age< 12 and edible ingestion), only edible ingestion was an independent predictor of ICU admission (adjusted OR 4.1 [95% CI: 1.2–13.7], $p = .02$).

Table 3. Comparison of pediatric patients following cannabis intoxication according to disposition (Intensive care unit vs. Non – intensive care unit).

	Non – ICU (N = 278) (%)	ICU (N = 20) (%)	*p* value
Age < 12 years	11 (4.0)	4 (20.0)	.01
Gender (males)	137 (49.3)	13 (65.0)	.24
Chronic disease	30 (10.8)	2 (10.0)	>.99
Mental health history	135 (48.6)	10 (50.0)	>.99
Edible product ingestion	24 (8.6)	7 (35.0)	<.01
Peri-post legalization period	57 (20.5)	9 (45.0)	.02

Discussion

In this 12-year long cohort study we found that children with cannabis-related ED visits in the peri-post legalization period experienced significantly higher rates of ICU admission compared to those who presented in the pre-legalization period. Children in the peri-post legalization period were younger, had more severe ED presentations and required more interventions during ED visit.

Our finding of higher ICU admission rates following cannabis legalization is corroborated by previous reports from Washington and Colorado, the first states to decriminalize recreational cannabis use in the U.S. [10,11,25]. Previous research reported 10–18% ICU admission rates among children up to 12 years who present with cannabis intoxication [10,11,14]. Overall, in our cohort ICU admission rate was 6.7%, which amounted to 26.6% in those younger than 12 years, representing higher rates than previously reported. Central nervous system (CNS) involvement, is a common manifestation following cannabis intoxication among young children [10,11,14,37], as is respiratory insufficiency secondary to altered mental status [8,14,23,38].

Young children brought to the ED with undifferentiated altered mental status frequently undergo extensive

diagnostic investigations and interventions [8]. Interestingly, fewer diagnostic tests were conducted in Colorado after cannabis legalization [11]. This finding was attributed to both higher rates of family disclosure of cannabis exposure, and to increased familiarity of healthcare providers with the pediatric cannabis intoxication [11]. In contrast to reports from other jurisdictions [10,11,39], we did not observe an increase in cannabis-related presentations after legalization compared to before, possibly due to the relatively short follow-up period after legalization.

In a secondary analysis, we found that edible cannabis ingestion is a powerful independent predictor of ICU admission, and that their ingestion was more common after cannabis legalization. Policy changes that increase the availability of edible cannabis products are contributing to increased ingestions among children [25,40,41]. Edible products are both highly concentrated and visually attractive to young children [25]. Therefore, ingestion is the most reported and consequential route of pediatric exposures [40], and often leads to severe, delayed and prolonged effects compared to cannabis inhalation [40,42–45]. The observed toxicity of cannabis edible ingestion among children combined with its powerful role as an independent risk factor for ICU admission suggests that the increased availability of edible products in the home following legalization may have contributed to the increased severity and higher rates of pediatric ICU admissions.

Several study limitations merit mention. Several study limitations merit mention. First, due to its retrospective nature, some details in the medical charts may have been incomplete. For example, we lack data on cannabis exposure dosage in most patients, and there may have been changes in voluntary reporting rates throughout the study. In addition, cases where no disclosure was made, and urine testing was not performed may have not been identified. Finally, as our study was performed relatively soon after legalization of recreational cannabis use, the full impact of this policy change may have not yet been apparent.

Conclusion

Recreational cannabis legalization is associated with higher rates of ICU admission for intoxication among children compared with the pre-legalization period. Edible ingestion is a strong predictor of ICU admission in children, and legalization may have increased the availability and accessibility of these products to children. Awareness of these adverse outcomes of cannabis legalization on the pediatric population should inform efforts by clinicians, policy makers and the public to mitigate the risks.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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