Association between ondansetron use and symptom persistence in children with concussions: A 5P substudy

Jocelyn Gravel, MD, MSc*; Kathy Boutis, MD†; Ken Tang, PhD‡; Miriam H. Beauchamp, PhD¶; Stephen B. Freedman, MD**; Alexander Sasha Dubrovsky, MD††; Isabelle Gagnon, PhD‡‡; Frank Momoli, PhD‡§§¶¶; Roger Zemek, MD§on behalf of the Pediatric Emergency Research Canada (PERC) 5P study group

CLINICIAN'S CAPSULE

What is known about the topic?
Most children who sustain a concussion suffer from post-concussion symptoms for many weeks following the accident.

What did this study ask?
Is there an association between ondansetron administration and the presence of persistent post-concussion symptoms at 1 week and 1 month in children?

What did this study find?
This observational study found that the use of ondansetron among children presenting to the emergency department with an acute concussion was associated with a higher risk of persistent symptoms at 1 month.

Why does this study matter to clinicians?
The treatment of short-term symptoms of a concussion should be balanced with the potential long-term harm of ondansetron.

ABSTRACT

Objective: Ondansetron is increasingly administered to children suffering from concussion-associated nausea/vomiting. We examined the association between ondansetron administration and post-concussion symptoms in children at 1 week and 1 month following the concussion.

Methods: This was a secondary analysis of data collected prospectively in a cohort study conducted in nine pediatric emergency departments (EDs) (5P study). Participants were children ages between 5 and 17.99 years who sustained a concussion in the previous 48 hours. For the current study, only 5P participants who reported nausea and/or vomiting in the ED were eligible. The exposure of interest was ondansetron administration; the comparison group included all other participants. The primary outcome was an increase in at least three symptoms of the Post-Concussion Symptom Inventory score at 1 week and 1 month following trauma.

Results: Among the 3,063 children included in the 5P study, 1805 (59%) reported nausea and provided data at 1 week and/or 1 month. Among them, 132 (7%) received ondansetron. Multivariable logistic regression adjusted for confounders did not show an association between ondansetron use and the risk of persistent post-concussion symptoms at 1 week (OR: 1.13 [95% CI: 0.86-1.49]), but it was associated with a higher risk at 1 month (OR: 1.33 [95% CI: 1.05-1.97]).

Conclusion: In children presenting to the ED with an acute concussion, ondansetron use was associated with a higher risk of persistent post-concussion symptoms at 1 month. Although this may be related to the limitations of the design, it highlights the importance of evaluating this association using a randomized clinical trial.

RÉSUMÉ

Objectif: On administre de plus en plus souvent de l'ondansétron aux enfants qui souffrent de nausées ou de vomissements associés à une commotion cérébrale. L'étude visait à examiner l'association entre l'utilisation de l'ondansétron et les symptômes liés à une commotion cérébrale chez les enfants, une semaine et un mois suivant le trauma.

From the *Department of Pediatrics, CHU Sainte-Justine, Université de Montréal, Montréal, QC; †Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON; ‡Clinical Research Unit, Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON; §Department of Pediatrics, Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON; ¶Department of Psychology, Université de Montréal, Montréal, QC; **Department of Pediatrics, Alberta's Children Hospital, Calgary, AB; ††Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montréal, QC; ‡‡Research Institute of the McGill University Health Centre, Montréal, QC; §§School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, ON; and the ¶¶Ottawa Hospital Research Institute, Ottawa, ON.

Correspondence to: Dr. Jocelyn Gravel, Department of Pediatrics, CHU Sainte-Justine, 3175 Chemin Côte Sainte-Catherine, Montréal, QC H3T 1C5, Canada; Email: graveljocelyn@hotmail.com

CJEM 2019;21(2):204–210 DOI 10.1017/cem.2018.384

Méthode: Il s'agit d'une analyse secondaire de données recueillies dans le cadre d'une étude prospective de cohorte (étude 5P), menée dans 9 services des urgences (SU) pédiatriques. Les participants étaient des enfants âgés de 5 à 17,99 ans, qui avaient subi une commotion cérébrale au cours des 48 heures précédentes. Seulement les participants de l'étude 5P faisant état de nausées ou de vomissements au SU, étaient admissibles à l'étude en question. Le point d'intérêt était l'administration d'ondansétron; le groupe de comparaison était formé de tous les autres participants. Le principal critère d'évaluation consistait en l'intensification d'au moins 3 symptômes selon l'inventaire des symptômes postcommotionnels, une semaine et un mois suivant le trauma.

Résultats: Sur les 3063 enfants ayant participé à l'étude 5P, 1805 (59 %) avaient fait état de nausées ou de vomissements, et avaient fourni des données au bout d'une semaine et d'un mois. Parmi ceux-ci, 132 enfants (7 %) avaient reçu de l'ondansétron. D'après une analyse de régression logistique à plusieurs variables, rajustée pour tenir compte de facteurs parasites, il n'y avait pas d'association entre l'utilisation de l'ondansétron et le risque de persistance de symptômes postcommotionnels au bout d'une semaine (risque relatif approché [RRA] : 1,13 [IC à 95 % : 0,86-1,49]), mais une association a été établie avec une augmentation du risque au bout d'un mois (RRA : 1,33 [IC à 95 % : 1,05-1,97]).

Conclusions: D'après les résultats de l'étude, l'utilisation de l'ondansétron chez les enfants traités au SU pour une commotion cérébrale en phase aiguë a été associée à une augmentation du risque de persistance de symptômes postcommotionnels au bout d'un mois. Si les constatations peuvent être liées aux limites du plan d'étude, elles font néanmoins ressortir l'importance d'évaluer la relation dans le cadre d'un essai clinique à répartition aléatoire.

Keywords: concussion, children, ondansetron

INTRODUCTION

A concussion is a problem commonly evaluated in the emergency department (ED). Recent studies suggest that children may represent as much as 90% of all concussions[1] with an annual incidence for teenagers, varying between 10.5/1,000 to 16.5/1,000.[2] Between 55% and 90% of patients who sustain a concussion suffer from post-concussion symptoms at 1 week following the accident.[3-5] These symptoms can be cognitive (memory loss, attention deficit, etc.), somatic (headache, fatigue, nausea), or psychological (depression, irritability, etc.) in nature. Moreover, studies report that 40% of concussed patients suffer persistent symptoms at 1 month,[6] and as many as 15% remain symptomatic at 1 year post-injury.[7,8]

Many patients requiring medical attention following a concussion are initially evaluated in the ED.[9] As soon as proper assessment is completed, treatments offered for patients suffering from a concussion are limited and mainly directed at alleviating symptoms. This includes medication given in the acute phase to decrease pain, nausea, or sometimes dehydration secondary to vomiting. Aside from guidelines recommending a period of activity restriction (physical and cognitive rest),[10-14] there is little evidence to inform management of the concussion. Four systematic reviews confirm the paucity of studies evaluating treatment for a concussion,[15-18] concluding that no acute intervention has been shown to improve the recovery and outcome of concussed patients.

Over the past few years, there is a growing trend among pediatric emergency physicians to prescribe ondansetron for children with a concussion who present with vomiting.[19,20] Although being given mainly to relieve symptoms in the acute setting, ondansetron may improve recovery from a concussion by decreasing early symptoms of nausea and vomiting, decreasing energy demands, and enhancing brain rest. However, the clinical impact of ondansetron on time to recovery following a concussion has been poorly evaluated. The primary objective of this study was to evaluate the association between ondansetron administration and the presence of persistent post-concussive symptoms (PPCS) at 1 week and 1 month in children.

METHODS

Design

This was a secondary analysis of the data of the 5P study,[5] a prospective cohort study of children with a concussion evaluated in multiple pediatric EDs in Canada. The idea of this sub-analysis emerged during the recruitment of patients but before the analysis.

Setting

Nine Canadian pediatric hospital EDs were involved in the project and recruited patients in 2013-2015.

These sites are members of the Pediatric Emergency Research Canada (PERC) group. All of their institutional review boards approved the study.

Participants

Study participants were children and adolescents ages 5 to 17.99 years who presented in the first 48 hours following a head trauma and met the Zurich concussion criteria.[10] Patients with a language barrier, abnormal neuroradiological findings, neurosurgical operative intervention, intubation or pediatric intensive care unit (PICU) care required, multisystem injuries with treatment requiring admission to the hospital, operating room or procedural sedation, neurological developmental delay, or intoxication were excluded. All participants/families provided written informed consent to be included in the study.

Participants of the sub-study reported nausea and/or vomiting at recruitment (based on an item from the self-reported version of the Post-Concussion Symptom Inventory [PCSI]).

Outcomes

The primary outcome was PPCS at 1 week following the index traumatic event, as defined in the 5P study.[5] This was defined as an increase from the pre-concussion baseline of at least three symptoms from the PCSI. The PCSI is a symptom scale that queries symptoms reflecting physical, cognitive, emotional, and sleep domains.[21] The decision to evaluate the outcome at 1 week was based on the observation that more than 50% of children who sustain a concussion suffer from persistent symptoms at 1 week,[18,22,23] and that most guidelines recommend rest for at least 1 week.[12,14] Because the outcome may be more important at 1 month for some individuals, persistence of symptoms for 1 month was also included as a primary outcome.

Secondary outcomes included the presence of nausea at 1 week and 1 month.

Treatment

The exposure of interest was a dichotomous variable representing those who received at least a single dose of intravenous or oral ondansetron in the ED. The comparison (reference) group included all other children with nausea and/or vomiting at baseline but did not receive ondansetron.

Demographic and clinical characteristics

Because this was not a randomized trial, other characteristics were considered as covariates in the analyses to minimize the risk of confounding bias when estimating the treatment effect of ondansetron. We considered a broad range of 37 pre-treatment variables measured in the original 5P study as the initial list of candidate confounders, which included demographic characteristics (e.g., age, sex), pre-morbid history (e.g., patient previous history of concussion, migraines, learning disability, depression), initial clinical presentation at the ED (e.g., loss of consciousness, mechanism of injury), extent of a wide range of acute concussion-related symptoms, as well as performance on standardized tests in the ED (e.g., Balance Error Scoring System tandem stance test). The full list of candidate confounders is presented in Table 1.

Analysis

Univariate and multivariable logistic regression analyses were used to estimate the relationship between treatment (receiving or not receiving ondansetron in the ED) and each of the four study outcomes. For each multivariable model, we maximized the number of covariates that were included based on a 15:1 event-per-variable ratio where "events" referred to the number of observations in the outcome level with the smaller proportion of the sample. Because the number of events differed for each of four study outcomes, the number of covariates ultimately included in the respective regression models also varied (see Table A1 in the Online Appendix). To prioritize the inclusion of the maximum number of covariates for regression adjustment, the non-linearity of continuous variables was not considered, and variables with greater than two categories were collapsed into two levels considered the most meaningful or treated as a continuous variable.

Because there was a non-trivial amount of missing values for covariates and outcomes (24.2% of cases had at least one missing value), we initially performed multiple imputation using additive regression, bootstrap, and the predictive mean matching method.[24] Variables in the imputation model included all 38 candidate covariates, the four study outcomes, plus the study site. The imputation procedure was repeated 25 times (i.e., 100x the fraction of cases with incomplete covariates). As soon as these imputed data sets were generated, the proposed multivariable logistic

Table 1. Participants' baseline demographic characteristics (n = 1,805)

		Ondansetron N = 132		No ondansetron N = 1,673	
Variable	Scale range or category	N useable	Mean (SD) or frequency (%)	N useable	Mean (SD) or frequency (%)
Age	0-17.99	132	10.8 (3.4)	1,673	12.2 (3.3)
Sex	Female	132	56 (42.4)	1,673	715 (42.7)
Number of previous concussions	0-6 (6 includes 6+)	132	0.3 (0.7)	1,665	0.4 (0.8)
Prior concussion symptom duration	<1 week	132	117 (88.6)	1,663	1419 (85.3)
	1-2 weeks		5 (3.8)		99 (6.0)
	3-4 weeks		6 (4.5)		55 (3.3)
	5-8 weeks		1 (0.8)		33 (2.0)
	>8 weeks		3 (2.3)		57 (3.4)
Time between head injury and triage	Hours	131	6.8 (9.4)	1,665	9.5 (12.1)
Lost consciousness duration	Minutes	132	0.1 (0.5)	1,662	0.1 (0.7)
Personal history of migraines	Yes	131	18 (13.7)	1,663	243 (14.1)
Family history of migraine	Yes	128	69 (53.9)	1,638	807 (49.3)
Prior diagnosis of learning disability	Yes	132	8 (6.1)	1,665	134 (8.0)
Prior diagnosis of attention deficit disorder	Yes	131	8 (6.1)	1,662	156 (9.4)
Prior diagnosis of anxiety	Yes	132	10 (7.6)	1,668	148 (8.9)
Prior diagnosis of depression	Yes	131	2 (1.5)	1,670	61 (3.7)
Prior diagnosis of sleep disorder	Yes	132	0 (0.0)	1,665	41 (2.5)
Seizure at time of injury	Yes	131	4 (3.1)	1,666	28 (1.7)
Mechanism of injury	Sports/recreational play	132	72 (54.5)	1,672	1172 (70.1)
PCSI-P headache	0-6 (6 = severe)	131	4.1 (1.8)	1,571	3.7 (1.8)
PCSI-P nausea	0-6 (6 = severe)	131	4.9 (1.5)	1,571	3.2 (2.0)
PCSI-P balance	0-6 (6 = severe)	131	2.1 (2.0)	1,570	1.7 (2.0)
PCSI-P dizziness	0-6 (6 = severe)	131	3.3 (2.1)	1,570	2.8 (2.0)
PCSI-P sleep more	0-6 (6 = severe)	131	2.9 (2.6)	1,571	1.5 (2.2)
PCSI-P feeling drowsy	0-6 (6 = severe)	131	4.2 (1.8)	1,571	3.1 (2.1)
PCSI-P sensitivity to light	0-6 (6 = severe)	131	2.3 (2.3)	1,570	1.7 (2.1)
PCSI-P sensitivity to noise	0-6 (6 = severe)	131	1.9 (2.2)	1,571	1.5 (2.0)
PCSI-P irritable	0-6 (6 = severe)	131	1.4 (2.1)	1,571	0.9 (1.6)
PCSI-P feeling sad	0-6 (6 = severe)	131	2.0 (2.2)	1,570	1.3 (1.9)
PCSI-P feeling nervous	0-6 (6 = severe)	131	1.2 (1.7)	1,569	0.8 (1.5)
PCSI-P feeling emotional	0-6 (6 = severe)	130	1.9 (2.1)	1,570	1.3 (1.8)
PCSI-P mental fog	0-6 (6 = severe)	131	2.8 (2.1)	1,569	1.9 (2.0)
PCSI-P difficulty concentrating	0-6 (6 = severe)	131	1.8 (2.1)	1,570	1.3 (1.8)
PCSI-P difficulty remembering	0-6 (6 = severe)	130	1.5 (2.0)	1,571	1.0 (1.7)
PCSI-P vision problems	0-6 (6 = severe)	131	1.4 (2.0)	1,570	1.3 (1.9)
PCSI-P feeling fatigue	0-6 (6 = severe)	131	3.9 (2.0)	1,571	3.0 (2.1)
PCSI-P feeling confused	0-6 (6 = severe)	131	1.4 (2.0)	1,570	0.8 (1.5)
PCSI-P feeling clumsy	0-6 (6 = severe)	131	1.3 (1.8)	1,571	0.9 (1.6)
PCSI-P answers more slowly	0-6 (6 = severe)	131	2.4 (2.1)	1,569	1.6 (1.9)
SAC normalized total score		132	−0.9 (2.1)	1,652	−0.4 (1.6)
BESS tandem stance # of errors	0-10 (10 includes physically unable to do test)	129	6.3 (3.8)	1,645	4.2 (3.8)

All PCSI-P scores are delta scores (difference between current symptom and pre-injury symptom; if a negative value then a score of 0 is given).
PCSI = Post-Concussion Symptom Inventory.

regressions were fitted separately for each of the imputed data sets, where parameter estimates are then averaged across these data sets, and imputation-adjusted variance estimates are computed. Lastly, clustered standard errors for the treatment effect were estimated to account for potential intra-site correlation. All analyses were performed using *R* version 3.3.2 (rms, Hmisc packages).

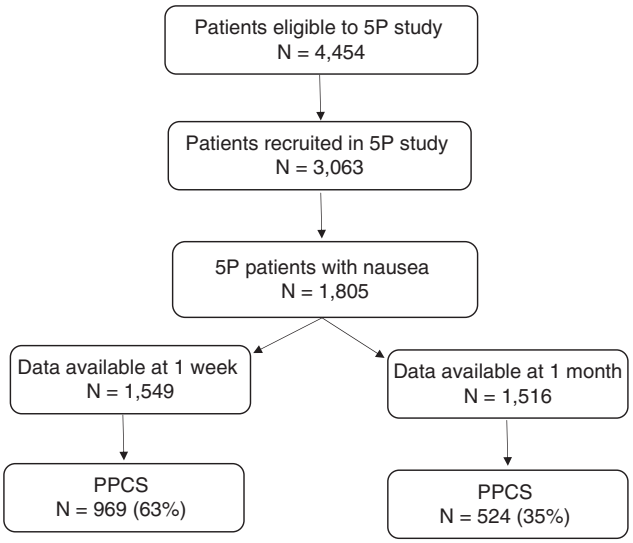

Figure 1. Flow diagram of participant recruitment and selection.

RESULTS

Among the 3,063 children included in the 5P study, 1,805 children were eligible for the current study (Figure 1), the PPCS outcome at week 1 was available for 1,549 children, and it was available for 1,516 children at 4 weeks. Table 1 demonstrates that baseline characteristics of the participants were similar between the two groups with the exception that patients in the ondansetron group received other medications more frequently than controls. Among these participants, 132 (7%) received oral (120) or intravenous (10) ondansetron (2 received it by both routes). PPCS were present in 969/1,549 (63%) at 1 week and 524/1,516 (35%) at 1 month. With respect to the presence of nausea, 480/1,546 (31%) reported this symptom at week 1, and 212/1,518 (14%) at week 4.

In the unadjusted analysis, the use of ondansetron was not statistically associated to the PPCS at 1 week (OR: 1.08 [95% CI: 0.73-1.59]) or 1 month (OR: 1.18 [95% CI: 0.80-1.74]) (Table 2). Once adjusted for covariates, there remained no statistical association between ondansetron use and the risk of PPCS at 1 week (adjusted OR: 1.17 [95% CI: 0.68-2.04]); however, an increase association was observed at 1 month (OR: 1.33 [95% CI: 1.05-1.68]).

Use of ondansetron in the ED was not statistically associated to the presence of nausea at 1 week or 1 month following the ED visit on univariate logistic regression and after adjusting for other predictors (see Table 2).

DISCUSSION

This study failed to identify a decrease in post-concussion symptoms at 1 week and 1 month following a concussion among children ages 5 to 17.99 years who received ondansetron in the ED. However, the use of ondansetron was associated with an increase in the risk of PPCS at 1 month on multiple regression.

There is a paucity of literature specifically describing the use of ondansetron for patients with head trauma and, to our knowledge, no study has evaluated other antiemetics for long-term concussion symptoms. A retrospective cohort study involving 6,311 children with head concussion reported a lower risk of revisit associated with the use of ondansetron in children.[25] However, major differences between the two study populations (use of ondansetron, 25% v. 7%), the proportion of a computed tomography (CT) scan (100% v. 4%) and the number of sites involved may have led to confounding by severity – the sicker patients being more at risk of receiving ondansetron and having PPCS. Another small pilot study conducted to assess the feasibility of a randomized controlled trial of the impact of ondansetron in concussed teenagers[26] reported a trend towards a lower proportion of children with PPCS at 1 week (OR: 0.60 [95% CI: 0.08-4.4]) and 1 month (OR: 0.20 [95% CI: 0.02-1.70]) following oral ondansetron.[27]

From a theoretical perspective, ondansetron holds promise for potentially minimizing post-concussion symptoms. The most commonly cited hypothesis for the pathophysiology of concussion suggests that shear forces experienced at the time of injury lead to ionic fluxes, the releases of excitatory neurotransmitters, and a spreading depression-like phenomenon.[28-32] The decreased cerebral blood flow after injury[31] limits the influx of adenosine triphosphate (ATP) required to restore homeostasis. The mismatch between demand and supply for ATP may prolong concussion symptoms. As such, physical and cognitive rest may improve recovery through conservation of limited ATP supplies following injury to the brain. Ondansetron may improve recovery from concussion by decreasing early symptoms of nausea and vomiting, which has been associated with PPCS at 3 months.[33] Also, this could improve rest and improve recovery because it was previously demonstrated that PPCS is inversely related

Table 2. Association between use of ondansetron and outcomes (n = 1,805)

Outcome	Outcome in ondansetron* (n = 132)	Outcome in control* (n = 1,673)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
PCS at 1 week (%)	77/120 (64.2)	892/1,429 (62.4)	1.08 (0.79-1.47)	1.17 (0.68-2.04)
PCS at 1 month (%)	45/118 (38.1)	479/1,398 (34.3)	1.18 (0.91-1.54)	1.33 (1.05-1.68)
Nausea at 1 week	34/118 (28.8)	446/1,428 (31.2)	0.89 (0.60-1.32)	0.76 (0.42-1.38)
Nausea at 1 month	16/119 (13.4)	196/1,399 (14.0)	0.95 (0.54-1.69)	0.88 (0.47-1.64)

*The denominator changes depending on how many missing values on the outcome (due to loss to follow-up or participant simply not completing question); values reflect raw data prior to performing multiple imputations.
†To prevent from overfitting, the number of model covariables included depended on sample size considerations (i.e., number of observations in a smaller level of binary study outcome). See Table 1 for specific covariables included in each model.

to rest quality.[34,35] On the other hand, ondansetron could also be deleterious to recovery for multiple reasons. By minimizing the initial symptoms, it could hasten return to play and limit brain rehabilitation, as well as increase the risk of a second impact on brain cells. However, a recent study showed that early activity was associated with a lower risk of PPCS.[36] Also, decreasing initial symptoms could modify medication consumption or feeding. Finally, ondansetron's effect on 5HT-3 receptors may interplay with an energy homeostasis of the brain and slow recovery process.

The clinical impact of this study is limited by its exploratory design. However, it raises the question as to whether ondansetron may have a deleterious effect on brain recovery following concussion. Consequently, the treatment of short-term symptoms like nausea and vomiting should be balanced with the potential long-term harm of ondansetron.

There are several limitations inherent to the current study. Among them, the use of an observational design is prone to bias by indication. It is possible that the baseline risk of PPCS was different for children who received ondansetron than for the control group. They may have suffered from a more severe concussion. To account for this, we adjusted the analysis according to multiple factors identified in the 5P study. To balance for unknown risk factor, it would be important to conduct a randomized clinical trial. Missing data limited the precision of our findings. To account for this, we used multiple imputation techniques. Although this permitted to include more patients, there is a risk of unknown biases related to missing data. Another limitation is the absence of a standard dose, number, or route of administration of the ondansetron. This may impact effectiveness of the medication and could be addressed by another study. Also, we did not collect information regarding home medication. Finally, the inclusion of patients who received other antiemetic medication in the control group may have biased the result towards the null hypothesis. However, there were very few patients for whom other antiemetic medication administration was documented.

In conclusion, this exploratory sub-analysis failed to identify a decrease in the risk of PPCS at 1 week among children ages 5 to 17.99 years who suffered a concussion and received ondansetron in the ED. Moreover, as a group, patients who received ondansetron had a worse outcome at 1 month. While this may be related to the design of our study, it highlights the importance of evaluating the impact of this medication on recovery from concussion. Future studies should continue to explore potential therapies to mitigate ongoing concussion symptoms and sequelae.

Competing interests: None declared.

SUPPLEMENTARY MATERIALS

To view supplementary material for this article, please visit https://doi.org/10.1017/cem.2018.384

REFERENCES

1. Amoo-Achampong K, Rosas S, Schmoke N, et al. Trends in sports-related concussion diagnoses in the USA: a population-based analysis using a private-payor database. *Phys Sportsmed* 2017;45(3):239-44.
2. Zhang AL, Sing DC, Rugg CM, et al. The rise of concussions in the adolescent population. *Orthop J Sports Med* 2016;4(8). doi:10.177/2325967116662458.
3. Carroll LJ, Cassidy JD, Peloso PM, et al. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med* 2004;(43 Suppl):84-105.
4. Pertab JL, James KM, Bigler ED. Limitations of mild traumatic brain injury meta-analyses. *Brain Inj* 2009;23 (6):498-508.
5. Zemek R, Barrowman N, Freedman SB, et al. Clinical risk score for persistent postconcussion symptoms among

children with acute concussion in the ED. *JAMA* 2016;315 (10):1014-25.

6. Ingebrigtsen T, Waterloo K, Marup-Jensen S, et al. Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients. *J Neurol* 1998;245(9):609-12.
7. Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology* 1995;45(7):1253-60.
8. Reitan RM, Wolfson D. The two faces of mild head injury. *Arch Clin Neuropsychol* 1999;14(2):191-202.
9. Zemek RL, Grool AM, Rodriguez Duque D, et al. Annual and seasonal trends in ambulatory visits for pediatric concussion in Ontario between 2003 and 2013. *J Pediatr* 2017;181:222-8.e2.
10. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Br J Sports Med* 2013;47(5):250-8.
11. Marshall S, Bayley M, McCullagh S, et al. Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Can Fam Physician* 2012;58(3):257-40.
12. Harmon KG, Drezner JA, Gammons M, et al. American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med* 2013;47(1):15-26.
13. Herring SA, Cantu RC, Guskiewicz KM, et al. Concussion (mild traumatic brain injury) and the team physician: a consensus statement – 2011 update. *Med Sci Sports Exerc* 2011;43(12):2412-22.
14. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013;80(24):2250-7.
15. Borg J, Holm L, Peloso PM, et al. Non-surgical intervention and cost for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med* 2004;(43 Suppl):76-83.
16. Comper P, Bisschop SM, Carnide N, Tricco A. A systematic review of treatments for mild traumatic brain injury. *Brain Inj* 2005;19(11):863-80.
17. Gravel J, D'Angelo A, Carriere B, et al. Interventions provided in the acute phase for mild traumatic brain injury: a systematic review. *Syst Rev* 2013;2:63.
18. King D, Brughelli M, Hume P, Gissane C. Assessment, management, and knowledge of sport-related concussion: systematic review. *Sports Med* 2014;44(4):449-71.
19. Sturm JJ, Pierzchala A, Simon HK, Hirsh DA. Ondansetron use in the pediatric emergency room for diagnoses other than acute gastroenteritis. *Pediatr Emerg Care* 2012;28 (3):247-50.
20. Freedman SB, Uleryk E, Rumantir M, Finkelstein Y. Ondansetron and the risk of cardiac arrhythmias: a systematic review and postmarketing analysis. *Ann Emerg Med* 2014;64(1):19-25.e6.
21. Sady MD, Vaughan CG, Gioia GA. Psychometric characteristics of the postconcussion symptom inventory in children and adolescents. *Arch Clin Neuropsychol* 2014;29(4):348-63.
22. King NS. Emotional, neuropsychological, and organic factors: their use in the prediction of persisting postconcussion symptoms after moderate and mild head injuries. *J Neurol Neurosurg Psychiatry* 1996;61(1):75-81.
23. King NS, Crawford S, Wenden FJ, et al. Early prediction of persisting post-concussion symptoms following mild and moderate head injuries. *Br J Clin Psychol* 1999;38(Pt 1):15-25.
24. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30(4):377-99.
25. Sturm JJ, Simon HK, Khan NS, Hirsh DA. The use of ondansetron for nausea and vomiting after head injury and its effect on return rates from the pediatric ED. *Am J Emerg Med* 2013;31(1):166-72.
26. Gravel J, Carriere B, D'Angelo A, et al. Ondansetron for pediatric concussion; a pilot study for a randomized controlled trial. *CJEM* 2017;19(5):338-46.
27. Gravel J, Carriere B, D'Angelo A, et al. Ondansetron for pediatric concussion; a pilot study for a randomized controlled trial. *CJEM* 2017;19(5):338-46.
28. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train* 2001;36(3):228-35.
29. Yoshino A, Hovda DA, Kawamata T, et al. Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res* 1991;561(1):106-19.
30. Shaw NA. The neurophysiology of concussion. *Prog Neurobiol* 2002;67(4):281-344.
31. Maugans TA, Farley C, Altaye M, et al. Pediatric sports-related concussion produces cerebral blood flow alterations. *Pediatrics* 2012;129(1):28-37.
32. Shrey DW, Griesbach GS, Giza CC. The pathophysiology of concussions in youth. *Phys Med Rehabil Clin N Am* 2011;22(4):577-602; vii.
33. Babcock L, Byczkowski T, Wade SL, et al. Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents who present to the emergency department. *JAMA Pediatr* 2013;167(2):156-61.
34. Boutis K, Cogollo W, Fischer J, et al. Parental knowledge of potential cancer risks from exposure to computed tomography. *Pediatrics* 2013;132(2):305-11.
35. Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *J Pediatr* 2012;161(5):922-6.
36. Grool AM, Aglipay M, Momoli F, et al. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. *JAMA* 2016;316(23):2504-14.