Ondansetron for pediatric concussion; a pilot study for a randomized controlled trial

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ABSTRACT

Objectives: Assess the feasibility of a study evaluating one dose of oral ondansetron to decrease post-concussion symptoms at one week and one month following concussion in children aged 8 to 17 years old.

Method: This was a pilot study for a randomized, triple-blind controlled trial of one dose of either ondansetron or placebo performed in a tertiary care pediatric emergency department. Participants were children aged 8 to 17 years who sustained a concussion in the previous 24 hours and visited a single emergency department. The outcome of interest was an increase from pre-concussion baseline of at least 3 symptoms from the Post-Concussion Symptom Inventory, measured at one week and at one month following concussion. The primary outcome was to determine the proportion of children who completed the assessment at one week following the intervention. Secondary outcome was the proportion of children who completed the assessment at one month following the intervention. All children, care givers, and those assessing the outcomes were blinded to the group assignment.

Results: Of the 218 children presenting with a concussion during the study period, we screened 108 and found 36/108 (33%) eligible to participate and 16/108 (14.8%) agreed to participate. All enrolled patients were compliant with the intervention and follow-up.

Conclusion: In our study population, approximately one-third of the screened concussion patients were eligible to participate and approximately one half of those eligible agreed to participate. Our study found that most enrolled patients preferred electronic follow-up; the noncompliance rate was minimal.

RÉSUMÉ

Objectifs: L'étude visait à évaluer la faisabilité d'un essai d'une seule dose d'ondansétron par voie orale afin de diminuer les symptômes postcommotionnels au bout de 1 semaine et de 1 mois après l'accident, chez des enfants âgés de 8 à 17ans.

Méthode: Il s'agit d'une étude pilote préalable à un essai comparatif, à répartition aléatoire et à triple insu d'une seule dose soit d'ondansétron, soit d'un placébo, menée dans un service des urgences pédiatriques de soins tertiaires. Les participants étaient des enfants âgés de 8 à 17 ans, qui avaient subi une commotion cérébrale au cours des 24 heures précédentes et qui avaient consulté un médecin dans un seul service des urgences. Le critère d'intérêt de l'essai clinique définitif sera la persistance d'au moins 3 symptômes indiqués dans l'inventaire des symptômes postcommotionnels, au bout de 1 semaine et de 1 mois après la commotion, comparativement à la période antérieure à l'accident. Le principal critère d'évaluation de l'étude pilote consistait en la proportion d'enfants ayant rempli le questionnaire d'évaluation 1 semaine après l'intervention et le critère d'évaluation secondaire, en la proportion d'enfants ayant rempli le questionnaire d'évaluation 1 mois après l'intervention. Toutes les parties – enfants, aidants et évaluateurs des résultats – étaient tenues dans l'ignorance de la répartition des sujets dans les groupes.

Résultats: Sur 218 enfants qui ont consulté pour une commotion cérébrale durant la période à l'étude, 108 ont été présélectionnés; sur ce dernier nombre, 36 (33 %) étaient admissibles à l'étude et 16 (14,8 %) ont accepté d'y participer. Tous les sujets retenus ont observé l'intervention et respecté le suivi.

Conclusion: D'après les résultats obtenus dans la population étudiée, environ un tiers des patients présélectionnés ayant subi une commotion cérébrale sont admissibles à l'étude et à peu près la moitié d'entre eux acceptent d'y participer. La plupart des sujets retenus choisissent le suivi électronique, et le taux de non-respect est minime.

Keywords: children, mTBI, concussion, ondansetron

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BACKGROUND

Concussions were reported to be responsible for 133,000 visits to Ontario's Emergency Departments (EDs) in 2009.[1] Children with concussions represented 90% of the hospitalization days among all children admitted for all levels of traumatic brain injury.[2] Between 55% to 90% of patients who sustained a concussion, also suffered from post-concussion symptoms at one week following the concussion, and approximately 30% had symptoms at one month.[3-7] These symptoms include cognitive (memory loss, attention deficit, etc.), somatic (headache, fatigue, nausea) or psychological (depression, irritability, etc.) in nature.

Most patients requiring medical attention following a concussion are initially evaluated in the ED. According to current guidelines, the standard of care for concussion is limited to the recommendation of a period of activity restriction (physical and cognitive rest) until full resolution of symptoms related to the injury.[8-13]

Over the past few years, there has been a growing trend among pediatric ED physicians to prescribe ondansetron for children with concussions who present with vomiting.[14,15] A retrospective study reported that in children who sustained a mild traumatic brain injury and had normal head computed tomography (CT), the use of was associated with a significantly reduced risk of a return visit to the ED in the following 72 hours.[16] Reduction in nausea and vomiting symptoms in the first hours could improve rest in the early days following concussion and promote faster recovery. Clinical practice is changing and, despite the lack of clear supporting evidence, ondansetron is more frequently used in the management of children with concussion. For example, one ED in the USA reported an increase in the use of ondansetron in children with concussion form 3% to 23% between 2003 and 2010.[14] Considering its increased use over the past 10 years,[14] the presumed positive effect of ondansetron needs to be properly evaluated in a quantitative manner before it becomes commonly used.

The primary objective of this pilot study was to evaluate the feasibility of a randomized controlled trial (RCT) evaluating the effect of ondansetron in comparison to placebo on the persistence of post-concussion symptoms at one week and one month following concussion in children.

METHODS

Ethics

The study protocol was approved by the Sainte-Justine Research Institute review board and received a non-objection letter form Health Canada. To participate, all children and a parental authority provided written informed consent before randomisation. The study was registered at the ClinicalTrials.gov website (#NCT01815125).

Design

This was a pilot study for a blinded, randomized controlled trial of one dose of either ondansetron or placebo in children who visited a single ED in the 24 hours following a concussion.

Setting

The study was conducted at Sainte-Justine University Health Centre, a tertiary care pediatric hospital with approximately 70,000 visits annually. Recruitment occurred during the presence of research assistants or nurses in 2013 and 2014. Research assistants were present from 9 AM to 4 PM during week days and uncommonly present during week-end at the same schedule.

Participants

To be included in the study, children had to meet all inclusion criteria and have none of the exclusion criteria.

Inclusion criteria (all needed):

1) Children aged between 8 and 17 years old. We limited our study to this small spectrum of age because this is the age group for which our measurement tool was validated.
2) Occurrence of a concussion as defined by the presence of a head trauma, a Glasgow Coma Scale of 13 to 15 and at least one of the three following criteria[17,18]:

- Any period of loss of consciousness.
- Any loss of memory for events immediately before or after the accident.
- Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented).

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And the absence of the following criteria:

- Glasgow Coma Scale <13, 30 minutes post-accident.

3) The trauma occurred in the preceding 24 hours.

Exclusion criteria (none present):

1) Inability to obtain proper written informed consent (language barrier, absence of a parental authority, developmental delay, intoxication, patient too confused to consent according to the treating physician).
2) Known allergic reaction or intolerance to ondansetron.
3) Known rhythm disturbance or cardiac pathology, or history of sudden death in the proximal family.
4) Patients who were taking medication which could increase the QT interval.
5) Patients who received ondansetron in the previous 24 hours.
6) Any abnormality on radiological studies, including any bleeding in the brain or skull fracture.
7) Multi-system injuries with treatment requiring admission to hospital or procedural sedation in the ED.

Intervention

The intervention of interest was the administration of one dose of 8 mg of oral ondansetron.[19] There was no previous study to determine the optimal duration of treatment. Previous studies have failed to show an impact of multiple doses in comparison to a single dose for other disease.[20] The control group received an identical looking/tasting pill as placebo.

Randomization

A biostatistician not involved in the analysis generated a randomization table using a computer generated sequence according to the following request: children were stratified by the presence or absence of vomiting and by the delay between trauma and intervention (<12 hours, 12 to 23 hours).

Blinding

A research pharmacist, not involved in the treatment of the patients, prepared the study medication by putting either ondansetron or placebo in an opaque capsule. The study medication was coded in advance according to the list generated by the biostatistician.

Outcomes of the pilot study

Outcomes for the pilot study included: the proportion of concussed children who were screened and found eligible to participate, the proportion of eligible patients who were invited to participate and agreed to participate, and the proportion of study participants who were compliant with the intervention. Of those participants who were compliant with the intervention, the proportion who chose electronic follow-up and completed the one-week and one-month follow-up questionnaire.

Outcomes of the randomized controlled trial

The primary clinical outcome was the persistence of post-concussive symptoms at one week and one month following the injury. In our study, persistence of post-concussive symptoms was defined as an increase from pre-concussion baseline of at least three symptoms of the Post-Concussion Symptom Inventory (PCSI). The PCSI is a self-reporting tool evaluating the presence of 25 symptoms (on a 3-point Likert scale) for children 8-12 years of age or 26 symptoms (on a 7-point Likert scale) for children 13-17 years of age. An increase of two points or more from pre-injury in any symptom was considered clinically significant.[21] Secondary outcomes were the mean number of PCSI symptoms, the mean number of school days missed, the number of days of sport activity restriction, the time before full recovery, health care utilization, and side effects. PCSI scores were calculated differently for the 8-12 years and 13-17 years age groups. PCSI scores were standardized using percentage in order to be able to compare results from both age groups. Side effects included diarrhea and constipation, in addition to symptoms related to concussion (worsening headache, dizziness, sleepiness, etc.), abdominal pain on palpitation. All outcomes were measured at one week and one month following concussion.

Several independent variables were measured at baseline related to the patients' age, sex, past medical history of traumatic brain injury (TBI) using the brain injury questionnaire, the type of accident (road, sports, fall, non-accidental, other) and the symptoms at time of randomisation (PCSI, vomiting, etc.).

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Compliance and quality control

Compliance was measured by asking the parents/patients how many pills of the study medication were consumed. Several precautions were taken in order to minimize potential biases. A screening log was maintained to record the number of patients screened, excluded, missed, or not randomized for any other reason. The diagnosis and reason for exclusion (ineligible or refused patients) were recorded in order to detect any selection bias.

Procedure

All children who fulfilled all of the inclusion criteria and met none of the exclusion criteria were invited to participate. After informed consent was obtained, children and parents were invited to complete a computerized questionnaire in order to provide baseline data (status pre-injury using the PCSI). Then they were asked to complete another standardized questionnaire to evaluate symptoms secondary to the concussion (PCSI at the moment of randomisation). Children received the study medication and standardized instruction regarding management of concussion at home. Study medication was provided as two pills of 4 mg of ondansetron/placebo per sample. The standardized instructions followed guidelines provided by the Canadian Pediatric Society based on the world consensus on concussion.[22]

Patients and parents were asked to provide contact information, including phone numbers and email addresses prior to ED departure. Depending on their preferences and the availability of computer access at home, patients were contacted one week later to complete the follow-up questionnaire. Electronic follow-up questionnaires were sent to the parental email address one week and then at one month following the concussion. The same schedule and questionnaires were used for the families that opted for telephone follow-up. In the event of incomplete electronic survey within 24 hours of receipt, a second email was sent. In the absence of response, the family was contacted by telephone for a phone interview. The follow-up questionnaire asked children questions related to the persistence of symptoms using the PCSI, school/work absenteeism, duration of symptoms, and any side effects using a standardized datasheet. Answers to the questionnaires were provided by the children with the assistance of a parent.

Statistical analysis

All data were entered in an Excel database (Microsoft Inc., Richmond, WA) and analyzed with SPSS v21 (IBM Software Inc., Armonk, NY). To assess balance across arms, baseline demographic (i.e., gender, age) and clinical data (i.e., presence of vomiting, time from trauma, past history of TBI or other health problems) of patients were compared between arms. The primary analysis was acceptability proportion measured by dividing the number of children/families who accepted participation divided by the total number of children/families invited. Other primary analysis was the proportion of participants who were compliant and provided all necessary information to measure the persistence of post-concussive symptoms at one week and one month following the injury. Another analysis was performed to calculate the proportion of participants who opted for an electronic follow-up.

The exploratory analysis was the comparison between the two groups of the proportion of children who had persistent concussive symptoms at one week and one month post-injury using Fisher's exact test and an intention-to-treat principle. Other analyses included: comparison of the mean duration of symptoms using linear regression; comparison of the mean number of school days missed using linear regression; comparison of the mean PCIS at one week and at one month; and the proportion of patient who presented side effects.

RESULTS

Between April 2013 and January 2014, a total of 281 children visited the ED for a concussion (Figure 1). Among them, 108 were screened for eligibility because they visited the ED during the presence of a research assistant. A total of 36 families were invited to participate in the study because they meet inclusion/exclusion criteria. The main reason for exclusions were: young age and delayed consult. Sixteen children/families (44%) agreed to participate and provided informed consent. The participants were all randomized to the study medication and were all compliant. They all completed the follow-up questionnaires both at one week and one month. Baseline demographics of the study participants were similar between the two study groups (Table 1). The median age of participants was 12 years and the median delay from injury to presentation was 4 hours (range 1-23 hours). The most

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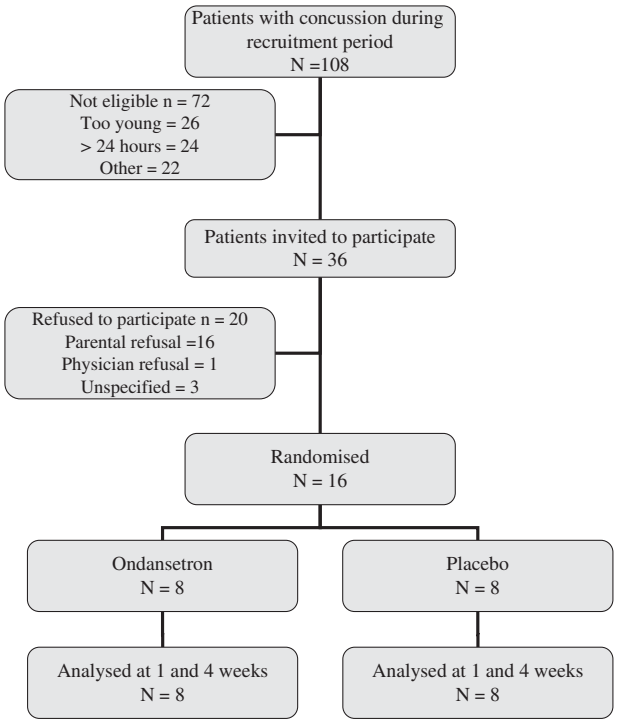

Figure 1. Flow-chart of the study participants in 8 months.

Table 1. Baseline demographics of randomized patients by intervention arm (N = 16)

Characteristics	Ondansetron n = 8 (%)	Placebo n = 8 (%)	*p*-value
Median age (Range)	12.2 (9 to 15)	11.4 (10 to 13)	0.50
Sex male	4 (0.50)	6 (0.75)	0.60
Loss of consciousness	3 (0.38)	2 (0.25)	1.00
Amnesia	6 (0.75)	3 (0.38)	0.31
Confusion	6 (0.75)	7 (0.88)	1.00
Seizure	0 (0.00)	0 (0.00)	1.00
Vomiting	2 (0.25)	3 (0.38)	1.00
Type of accident			0.20
MVA	0	0	
Sport	5 (0.62)	8 (1.00)	
Fall other	2 (0.25)	0	
Other	1 (0.13)	0	
Past medical history			
Migraine	0 (0.00)	1 (0.13)	1.00
Motion Sickness	2 (0.25)	1 (0.13)	1.00
ADHD	1 (0.13)	0 (0.00)	1.00
Concussion	0 (0.00)	2 (0.25)	1.00
Head CT scan	1 (0.13)	0 (0.00)	1.00
Median PCSI before injury (range)			
8-12 years old	1.5 (0 to 5)	3 (0 to 19)	0.91
3-17 years old	8 (0 to 17)	11 (7 to 78)	0.40
Median PCSI at randomization (range)			
8-12 years old	13 (1 to 28)	11 (0 to 12)	0.56
13-17 years old	34 (26 to 71)	42 (31 to 47)	0.63
Patients received medication for pain	6 (0.75)	8 (1.00)	0.47
Delay for intervention (hours) (range)	8.6 (0-21)	9.0 (1-23)	0.45

common cause of concussion was a sport-related accident. Only two participants had had previous concussions and none received medication for vomiting before study recruitment.

Thirteen of the 16 participants (81%) opted for the electronic follow-up questionnaire, and responded to both electronic questionnaires (one week and one month) at the first attempt without electronic or telephone reminder. All participants provided all necessary data for the measurement of the primary outcome at one week and one month (100% follow-up rate).

At one week, 50% of the children who received ondansetron reported persistence of post-concussive symptoms compared to 63% in the placebo group (Table 2). This did not reach statistical significance (difference: 13%; exact 95% CI: –40% to 69%). At one month, 2/8 children in the ondansetron group reported persistent post-concussive symptoms compared to 5/8 in the placebo group, but this failed to reach statistical significance (difference: 37%; exact 95% CI: –15% to 90%).

There were no differences between the groups for multiple secondary outcomes (Table 2). No patient was admitted (re-hospitalized) from either groups and only one patient received an intravenous infusion (normal saline) in the placebo group because he was kept in observation for 17 hours. The mean PCSI at one week and one month and the use of medication (for pain or nausea/vomiting) at home were similar between the two groups. Patients who received the intervention returned to school earlier (median 1 day v. 4 days), but there was no statistical difference for length of stay in the ED (3.5 hours v. 6 hours) and number of missed days of sport (7 days v. 13 days).

DISCUSSION

This study demonstrated the feasibility of a RCT to evaluate the impact of ondansetron for concussion symptoms in children. While the number of participants was small, the follow-up rate of 100% was reassuring in terms of the possibility of conducting a larger study using a similar design. Approximately 45% of the invited families agreed to participate; and this rate of

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Table 2. Outcome measures for randomized patients by intervention arm (N = 16)

Characteristics	Ondansetron n = 8 (%)	Placebo n = 8 (%)	*p*-value
>2 symptoms of PCSI at 1 week	4 (0.50)	5 (0.63)	1.00
>2 symptoms of PCSI at 1 month	2 (0.25)	5 (0.63)	0.32
Median PCSI at 1 week			
8-12 years old	0 (–2 to 17)	0 (–11 to 21)	0.91
13-17 years old	26 (–3 to 55)	27 (–7 to 38)	0.63
Median PCSI at 1 month			
8-12 years old	0.5 (0 to 1)	2 (-17 to 9)	0.29
13-17 years old	–3.5 (–8 to 17)	–2 (–7 to 3)	0.86
Intravenous rehydration	0 (0.00)	1 (0.25)	1.00
Hospitalisation	0 (0.00)	0 (0.00)	-
Length of stay in the ED (in hours)	3.5 (1 to 5)	6.0 (2 to 17)	0.20
Medication for pain at home	5 (0.62)	3 (0.38)	0.62
Medication for nausea at home	1 (0.13)	0 (0.00)	1.00
Return to normal at one week	4 (0.50)	2 (0.25)	1.00
Return to normal at one month	8 (1.00)	6 (0.75)	0.47
Median number of missed school days	1	4	0.13
Median number of missed days of sport	7	13	0.33

participation should be considered when estimating sample size and feasibility of the study. The fact that 81% of the families decided to use the electronic follow-up method and that we had excellent response rates also supports the usefulness of this follow-up strategy. Because this was a pilot study, it was not powered to detect a statistical difference between the two groups.

In the past, few studies have evaluated potential treatments for patients suffering from concussion. Three systematic reviews reported only one clinical trial of a pharmacological intervention for concussion.[23-25] One study showed no effect of nasal vasopressin on cognitive symptoms secondary to mild TBI.[26] A systematic review identified studies investigating interventions initiated in the ED for short-term (one week) and medium term (one month) outcomes in adults and children who sustained mild TBI.[24] The review identified 15 randomized controlled trials. Among them, one evaluated a pharmacological intervention (DDAVP),[27] two evaluated activity restriction (full bed rest,[28] hospitalization[29]), one evaluated head tomodensitometry v. admission,[30] four evaluated an information intervention (pamphlet, information session at the ED)[31-34] and seven evaluated diverse follow-up interventions (in neuropsychology, phone follow-up, etc.).[33,35-40] Since the publication of the last systematic review, a small randomized controlled trial reported fewer headaches associated with hypertonic intravenous saline v. normal saline for 44 concussed children who needed intravenous access for CT-scan.[41]

Ondansetron usage remained limited to patients who suffered from nausea following chemotherapy until a decade ago when research began to emerge supporting its use in children with acute gastroenteritis.[19,42] Although it is primarily used for children visiting the ED for gastroenteritis,[43] it is not constrained to that group of children. A retrospective study of ondansetron in the ED reported that 38% (n = 12,620) of prescriptions were for reasons other than gastroenteritis in the ED.[15] Other indications of ondansetron are post-operativem,[44-46] chemotherapy, radiotherapy,[47,48] sedation,[49] or during pregnancy.[50] Recently, ondansetron has been prescribed for brain-related diseases like obsessive-compulsive disorders[51] or drug/alcohol addictions,[52-54] suggesting that it may influence other symptoms than vomiting. Ondansetron may improve recovery from concussion by decreasing early symptoms of nausea and vomiting, decreasing energy demands, and enhancing brain rest. Nausea and vomiting at initial presentation is associated with persistence of post-concussion symptoms at three months.[55] Limitation of vomiting, therefore, may theoretically decrease energy demands and improve rest. This could improve recovery because it has been previously demonstrated that persistence of concussion symptoms is inversely related to rest quality.[56,57] Although there is a paucity of literature specifically

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describing the use of ondansetron for patients with head trauma, there is evidence for two patients successfully treated with ondansetron for vomiting following neurosurgical brain trauma.[58]

Our study demonstrated the willingness of families to respond to an electronic follow-up questionnaire. This is consistent with previous studies using a similar follow-up strategy for concussed children,[7,59,60] Using this strategy has many advantages including the option for children to answer the questionnaire when they desire, the immediate transfer of data to a database, and inherent cost savings. However, it may be associated with limitations related to the absence of supervision by a professional to ensure that responses are appropriate. Another important aspect of our study is the promising findings on the persistence of post-concussion symptoms. As mentioned, most children have persistent symptoms at one week post-concussion and one third of children at one month;[5,7] and there is no proven effective treatment for any outcome following concussion.[24] Concussion has clinical, societal, and financial impacts. Our results suggest that ondansetron could potentially be useful to limit persistence of post-concussion symptoms. This would improve quality of life for children while decreasing societal cost resulting from work/school absenteeism.

There are limitations to this study. The study was conducted without financial support, hence research assistant coverage was very low. This explains why only 108/281 children with head trauma were assessed for eligibility. The small sample size limited our ability to show statistical differences or equivalences between the two groups. However, this was not the primary objective of the study. The study was performed in a single setting. The feasibility demonstrated in this setting may not be reproducible in another setting. Children were not evaluated by a physician at follow-up and participants may have under or over-estimated their ability to return to normal activity. Children received only one dose of study medication. While this permitted excellent compliance, more doses may have been a better treatment option to decrease long-term symptoms. Finally, there was no standardization of co-interventions.

CONCLUSION

In conclusion, this pilot study demonstrated the feasibility of a RCTto evaluate the impact of ondansetron for concussion in children. Approximately one-third of children who sustained a head concussion were eligible for the study and one-half of eligible patients agreed to participate. Also, more than 80% chose an electronic follow-up method for the assessment of outcomes. Based on these results, a larger, more statistically powered study is required and feasible.

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REFERENCES

1. Fu TS, Jing R, McFaull SR, et al. Health & economic burden of traumatic brain injury in the emergency department. *Can J Neurol Sci* 2016;43(2):238-47.
2. Kraus JF, Fife D, Conroy C. Pediatric brain injuries: the nature, clinical course, and early outcomes in a defined United States' population. *Pediatrics* 1987;79(4):501-7.
3. King D, Brughelli M, Hume P, et al. Assessment, management and knowledge of sport-related concussion: systematic review. *Sports Med* 2014;44(4):449-71.
4. King NS. Emotional, neuropsychological, and organic factors: their use in the prediction of persisting post-concussion symptoms after moderate and mild head injuries. *J Neurol Neurosurg Psychiatry* 1996;61(1):75-81.
5. 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.
6. Pertab JL, James KM, Bigler ED. Limitations of mild traumatic brain injury meta-analyses. *Brain Inj* 2009; 23(6):498-508.
7. 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.
8. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International

https://doi.org/10.1017/cem.2016.369 Published online by Cambridge University Press

Conference on Concussion in Sport held in Zurich, November 2012. *B J Sports Med* 2013;47(5):250-8.

9. 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.
10. Harmon KG, Drezner JA, Gammons M, et al. American Medical Society for Sports Medicine position statement: concussion in sport. *B J Sport Med* 2013;47(1):15-26.
11. 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.
12. 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.
13. Purcell LK, Canadian Paediatric Society HAL, Sports Medicine C. Sport-related concussion: Evaluation and management. *Paediatr Child Health* 2014;19(3): 153-65.
14. Sturm JJ, Simon HK, Khan NS, et al. 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.
15. Sturm JJ, Pierzchala A, Simon HK, et al. Ondansetron use in the pediatric emergency room for diagnoses other than acute gastroenteritis. *Pediatr Emerg Care* 2012; 28(3):247-50.
16. Sturm JJ, Simon HK, Khan NS, et al. 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* 2012, epub.
17. Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation M. Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation. *J Head Trauma Rehabil* 1993;8(3):68-9.
18. McCrory P, Meeuwisse W, Johnston K, et al. Consensus Statement on Concussion in Sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *Br J Sports Med* 2009;43(1Suppl):i76-90.
19. Freedman SB, Adler M, Seshadri R, et al. Oral ondansetron for gastroenteritis in a pediatric emergency department. *N Engl J Med* 2006;354(16):1698-705.
20. Freedman SB, Ali S, Oleszczuk M, et al. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. *Evid Based Child Health* 2013;8(4):1123-37.
21. Barlow KM, Crawford S, Stevenson A, et al. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics* 2010;126(2):e374-81.
22. Society CP. Sport-related concussion: Information for parents, coaches and trainers. 2015. Available at: http://www.caringforkids.cps.ca/handouts/sport_related_concussion.
23. 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.
24. 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.
25. Comper P, Bisschop SM, Carnide N, et al. A systematic review of treatments for mild traumatic brain injury. *Brain Inj* 2005;19(11):863-80.
26. Bohnen NI, Twijnstra A, Jolles J. A controlled trial with vasopressin analogue (DGAVP) on cognitive recovery immediately after head trauma. *Neurology* 1993;43(1):103-6.
27. Filipova M, Jung M, Filip M, et al. Clinical efficacy of 1-desamino-8-D-arginine-vasopressin (DDAVP) in short-term recovery from minor head injury. *Hum Psychopharmacol* 1989;4:47-50.
28. de Kruijk JR, Leffers P, Meerhoff S, et al. Effectiveness of bed rest after mild traumatic brain injury: a randomised trial of no versus six days of bed rest. *J Neurol Neurosurg Psychiatry* 2002;73(2):167-72.
29. Lowdon IM, Briggs M, Cockin J. Post-concussional symptoms following minor head injury. *Injury* 1989;20(4):193-4.
30. af Geijerstam JL, Oredsson S, Britton M. Medical outcome after immediate computed tomography or admission for observation in patients with mild head injury: randomised controlled trial. *BMJ* 2006;333(7566):465.
31. Casey R, Ludwig S, McCormick MC. Minor head trauma in children: an intervention to decrease functional morbidity. *Pediatrics* 1987;80(2):159-64.
32. Mittenberg W, Tremont G, Zielinski RE, et al. Cognitive-behavioral prevention of postconcussion syndrome. *Arch Clin Neuropsychol* 1996;11(2):139-45.
33. Ponsford J, Willmott C, Rothwell A, et al. Impact of early intervention on outcome after mild traumatic brain injury in children. *Pediatrics* 2001;108(6):1297-303.
34. Hinkle JL, Alves WM, Rimell RW, et al. Restoring social competence in minor head-injury patients. *J Neurosci Nurs* 1986;18(5):268-71.
35. Elgmark AE, Emanuelson I, Bjorklund R, et al. Mild traumatic brain injuries: the impact of early intervention on late sequelae. A randomized controlled trial. *Acta Neurochir (Wien)* 2007;149(2):151-9.
36. Bell KR, Hoffman JM, Temkin NR, et al. The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: a randomised trial. *J Neurol Neurosurg Psychiatry* 2008;79(11):1275-81.
37. Ghaffar O, McCullagh S, Ouchterlony D, et al. Randomized treatment trial in mild traumatic brain injury. *J Psychosom Res* 2006;61(2):153-60.
38. Heskestad B, Waterloo K, Baardsen R, et al. No impact of early intervention on late outcome after minimal, mild and moderate head injury. *Scand J Trauma Resusc Emerg Med* 2010;18:10.
39. Paniak C, Toller-Lobe G, Durand A, et al. A randomized trial of two treatments for mild traumatic brain injury. *Brain Inj* 1998;12(12):1011-23.
40. Wade DT, Crawford S, Wenden FJ, et al. Does routine follow up after head injury help? A randomised controlled trial. *J Neurol Neurosurg Psychiatry* 1997; 62(5):478-84.
41. Lumba-Brown A, Harley J, Lucio S, et al. Hypertonic saline as a therapy for pediatric concussive pain: a randomized

https://doi.org/10.1017/cem.2016.369 Published online by Cambridge University Press

controlled trial of symptom treatment in the emergency department. *Pediatric Emerg Care* 2014;30(3):139-45.

42. Reeves JJ, Shannon MW, Fleisher GR. Ondansetron decreases vomiting associated with acute gastroenteritis: a randomized, controlled trial. *Pediatrics* 2002;109(4):e62.
43. Kharbanda AB, Hall M, Shah SS, et al. Variation in resource utilization across a national sample of pediatric emergency departments. *Journal Pediatr* 2013;163(1):230-6.
44. Fujii Y. The benefits and risks of different therapies in preventing postoperative nausea and vomiting in patients undergoing thyroid surgery. *Curr Drug Saf* 2008;3(1):27-34.
45. Fujii Y. Current management of vomiting after tonsillectomy in children. *Curr Drug Saf* 2009;4(1):62-73.
46. Bolton CM, Myles PS, Nolan T, et al. Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth* 2006;97(5):593-604.
47. Lindley C, Goodin S, McCune J, et al. Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy: comparison of ondansetron, prochlorperazine, and dexamethasone. *Am J ClinOncol* 2005;28(3):270-6.
48. Spitzer TR, Friedman CJ, Bushnell W, et al. Double-blind, randomized, parallel-group study on the efficacy and safety of oral granisetron and oral ondansetron in the prophylaxis of nausea and vomiting in patients receiving hyperfractionated total body irradiation. *Bone Marrow Transplant* 2000;26(2):203-10.
49. Langston WT, Wathen JE, Roback MG, et al. Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: a double-blind, randomized, placebo-controlled trial. *Ann Emerg Med* 2008;52(1):30-4.
50. Reichmann JP, Kirkbride MS. Reviewing the evidence for using continuous subcutaneous metoclopramide and ondansetron to treat nausea & vomiting during pregnancy. *Manag Care* 2012;21(5):44-7.
51. Fontenelle LF, Oostermeijer S, Harrison BJ, et al. Obsessive-compulsive disorder, impulse control disorders and drug addiction: common features and potential treatments. *Drugs* 2011;71(7):827-40.
52. Brackins T, Brahm NC, Kissack JC. Treatments for methamphetamine abuse: a literature review for the clinician. *J Pharm Pract* 2011;24(6):541-50.
53. Somaini L, Donnini C, Raggi MA, et al. Promising medications for cocaine dependence treatment. *Recent Pat CNSDrug Discov* 2011;6(2):146-60.
54. Swift R. Medications acting on the dopaminergic system in the treatment of alcoholic patients. *Curr Pharm Des* 2010; 16(19):2136-40.
55. 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.
56. Boutis K, Cogollo W, Fischer J, et al. Parental knowledge of potential cancer risks from exposure to computed tomography. *Pediatr* 2013;132(2):305-11.
57. Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *Journal Pediatr* 2012;161(5): 922-6.
58. Kleinerman KB, Deppe SA, Sargent AI. Use of ondansetron for control of projectile vomiting in patients with neurosurgical trauma: two case reports. *Ann Pharmacother* 1993; 27(5):566-8.
59. Zemek R, Clarkin C, Farion KJ, et al. Parental anxiety at initial acute presentation is not associated with prolonged symptoms following pediatric concussion. *Academic Emerg Med Medicine* 2013;20(10):1041-9.
60. Pasek TA, Locasto LW, Reichard J, et al. The headache electronic diary for children with concussion. *Clin Nurse Spec* 2015;29(2):80-8.

https://doi.org/10.1017/cem.2016.369 Published online by Cambridge University Press