Treatment of Children With Migraine in the Emergency Department

A Qualitative Systematic Review

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Objective: To evaluate which treatment could be effective in the emergency department (ED) for children with migraine and status migrainosus, we carried out a qualitative systematic review of randomized controlled trials (RCTs) that evaluated treatment that could be used for those conditions.

Methods: Databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Controlled Trials Register, MedLine, and EMBASE) were searched for RCTs that evaluated treatment of migraine in children (<18 years of age). Guidelines published on the subject were checked for missed references. Characteristics of the identified studies as well as primary outcome (headache relief), other recognized primary outcomes, and adverse events were abstracted. Quality of the RCTs was evaluated using the Jadad score.

Results: Of the 14 trials included in the review, only 1 was performed in an ED after other treatments have failed. In that situation, prochlorperazine was more effective than ketorolac in relieving pain at 1 hour. Other treatments were evaluated by neurologists on their outpatients who started the studied drugs early at the beginning of the migraine without previous treatment. In that situation, ibuprofen (n = 3) and acetaminophen (n = 1) were better than placebo for pain relief. The efficacy of intranasal sumatriptan (n = 4), oral rizatriptan (n = 3), and oral zolmitriptan (n = 2) for pain relief was unclear. Oral sumatriptan (n = 1) and oral dihydroergotamine (n = 1) were not effective.

Conclusions: There is a lack of studies addressing the question of treatment in the ED for children experiencing migraine. Although other treatments were found effective in children with migraine, none was evaluated in the ED except prochlorperazine and ketorolac.

Key Words: migraine, status migrainosus, adolescent

Migraine headaches are extremely common during childhood and adolescence. The reported prevalence ranges from 3% to 10%.[1–3] A significant number of children present to the emergency department either during the first episode, or for particularly severe episodes that do not respond to their usual treatments. In fact, migraine represents 8% to 18% of all headaches seen in a pediatric emergency department.[4,5] Despite this, little attention has been given to the treatment that could be administered to children who present to an emergency department with migraine headaches.

Because adolescents have a high rate of success of placebo in the treatment of migraine, it may be difficult to extrapolate results for adult studies to children.[6] The Canadian Headache Society proposed adult guidelines in 1997 based on severity of the attack from mild to ultrasevere attack.[7] In 2004, the French Society for the Study of Migraine Headache also proposed some guidelines for the treatment of migraine in both adults and children.[8] The American Academy of Neurology also published in 2004 pediatric practice parameters.[9] They had previously issued in 2000 practice parameters in adults.[10] However, none of these guidelines were for children who presented to the emergency department. Similarly, a recent systematic review[11] or other reviews on migraine treatment in children do not specifically address the question of emergency department treatment.[12–15] Two recent reviews present most of the available therapies for the acute treatment of migraine that did not respond to outpatient management, but many more recent randomized controlled trials (RCTs) were not mentioned especially concerning the triptans.[16,17] Thus, this lack of evidence-based guidelines can explain the significant variation in practice observed in the management of children with migraine seen in 4 regional emergency departments in 1 Canadian city.[18]

Thus, to evaluate which treatment for children with migraine and status migrainosus could be effective in the emergency department, we carried out a qualitative systematic review of the literature in search of RTCs that evaluated treatment that could be used in that setting.

METHODS

Search Strategy

The literature was searched for potential studies using different strategies with Ovid. Systematic reviews were first searched in the Cochrane Database of Systematic Reviews, second quarter of 2007 (performed February 2, 2007 and updated June 22, 2007), and the Database of Abstracts of

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Reviews of Effects, second quarter of 2007 (performed February 2, 2007 and updated June 22, 2007). These databases were searched using the predefined keywords: migraine or headache and children. The Cochrane Controlled Trials Register, second quarter of 2007 (performed February 2, 2007 and updated June 22, 2007), was also searched for possible RTCs using the same strategies. The MedLine 1950 to June 2007 week 2 (performed February 5, 2007 and updated June 22, 2007) database was searched using the predefined strategies: (1) exp randomized controlled trials/; (2) "randomized controlled trial".pt.; (3) "controlled clinical trial".pt.; (4) (random$ or placebo$).ti,ab,sh.; (5) ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.; (6) or/1–5; (7) (animals not humans).sh.; (8) 6 not 7; (9) exp Migraine Disorders or headache/; (10) limit 9 to "all adult (19 plus years)"; (11) limit 9 to "all child (0 to 18 years)"; (12) 11 not 10; and (13) 8 and 12. The EMBASE 1980 to 2007 week 25 (performed February 5, 2007 and updated June 22, 2007) database was also searched using the predefined strategies: (1) exp randomized controlled trials/; (2) (random$ or placebo$).ti,ab,sh.; (3) ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.; (4) controlled clinical trial$.tw,sh.; (5) or/1–4; (6) (animal$ not human$).sh,hw.; (7) 5 not 6; (8) exp Migraine or headache/; (9) limit 8 to adult <18 to 64 years>; (10) limit 8 to (child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>); (11) 10 not 9; and (12) 7 and 11. The references of all relevant studies were cross-checked for other relevant articles as well as identified systematic reviews, guidelines, or other recent reviews on the subject.[7–14,17,19–23] No attempts were made to obtain unpublished studies.

Study Selection

For this qualitative systematic review, only RTCs were included because of the usual high rate of success of placebo in the treatment of migraine particularly in adolescents.[6] Thus, studies were included for review if they were RTCs of a medication for the treatment of acute migraine attacks in children (<18 years of age) regardless of the setting (emergency department–inpatient or neurology clinic–outpatient). Studies were excluded if they were not RTC, or if they evaluated a medication used for prophylaxis.

Data Extraction and Methodological Quality

Data of all included studies were abstracted in duplicate using a predefined table. Data extraction was done for name of author and year of publication, type of study, setting, how the migraine diagnosis was made, inclusion and exclusion criteria, age range of the enrolled children, treatment evaluated, the number of patients enrolled, what type of measurement tool was used, the primary outcome, rate of pain-free status at 2 hours, rate of recurrence, rate of use of rescue medications, side effects, and author's conclusion. The Jadad score was used to evaluate the internal validity of the studies, from 0 to 5, 5 being the study with the highest quality.[24] We reported the primary outcome, usually pain relief at 2 hours. When this outcome was not the primary

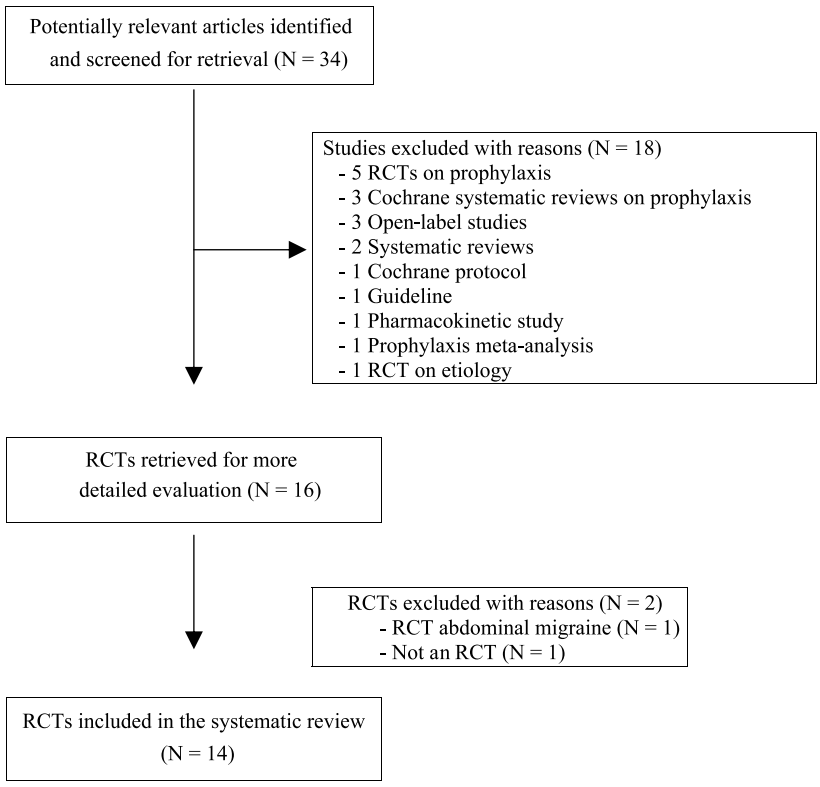

FIGURE 1. Flow of randomized control trials identified in the systematic review by various databases searches.

TABLE 1. Level I Evidence Evaluating Acetaminophen, Ibuprofen, and Zolmitriptan for the Treatment of Migraine Attack in Children

Study	Hamalainen et al[27]	Lewis et al[26]	Evers et al[28]
Type	DBR 3-way XOver	DBR Parallel	DBR XOver
	First-line agent	First-line agent	First-line agent
Setting	Outpatient	Outpatient	Outpatient
	Neurology clinic	Neurology clinic	Neurology clinic
	Multicentric	1-center	1-center
Inclusion/Exclusion criteria	IHSC[40]	Proposed revision IHSC[42]	IHSC[41]
	≥2 attacks/mo lasting ≥2 h		
	Previous medications not effective		
	Patients on prophylaxis excluded		
Age range, y	4–16	6–12	6–18
Treatment	APAP PO 15 mg /kg	IBU PO 7.5 mg/kg	IBU PO 200 or 400 mg
	IBU PO 10 mg/kg	P PO	ZOL PO 2.5
	P PO		P PO
Jadad score[24]	4/5	4/5	3/5
N (enrolled/analyzed)	106/66	138/84	32/29
Measurement	5-face scale (severe to none)	4-point scale (severe to none)	4-point scale (none to severe)
Primary outcome	**↓ in pain by ≥2 grade at 2 h if initial grade ≥ 3**	**↓ in pain from severe or moderate to mild or none at 2 h**	**↓ in pain from severe or moderate to mild or none at 2 h**
	APAP vs. P: OR 2.0 (0.9, 4.3)	IBU vs. P: 34/45 vs. 21/39, $P = 0.006$	IBU vs. P: 20/29 vs. 8/29, $P < 0.05$
	IBU vs. P: OR 2.9 (1.0, 8.1)		ZOL vs. P: 18/29 vs. 8/29, $P < 0.05$
	APAP vs. IBU: 0.7 (0.4, 1.1)*		IBU vs. ZOL: 20/29 vs. 18/29, NS
Pain-free at 2 h	APAP vs. P: OR 2.0 (0.9, 4.3)	IBU vs. P: 20/45 vs. 10/39, $P = 0.07$	IBU vs. P: 14/29 vs. 2/29, $P < 0.01$
	IBU vs. P: OR 3.5 (1.0, 11.9)		ZOL vs. P: 13/29 vs. 2/29, $P < 0.01$
	IBU vs. APAP: OR 2.2 (1.1, 40)		IBU vs. ZOL:14/29 vs. 13/29, NS
Recurrence, %	Within 5 h	4–24 h	Within 24 h
	APAP vs. P: 0/16 vs. 1/12, NS	IBU vs. P: 8/45 vs. 14/39, $P = 0.06$	IBU vs. P: 2/20 vs. 1/8, NS
	IBU vs. P: 1/24 vs. 1/12, NS		ZOL vs. P: 4/18 vs. 1/8, NS
	APAP vs. IBU: 0/16 vs. 1/24, NS		IBU vs. ZOL: 2/20 vs. 4/18, NS
Use of rescue medications	**Within 5 h**	**Within 4 h**	**Within 24 h?**
	APAP vs. P: 8/78 vs. 18/78, NS	IBU vs. P: 1/45 vs. 15/39, $P < 0.001$	IBU vs. P: 5/29 vs. 8/29, NS
	IBU: 13/80 vs. 18/78, NS		ZOL vs. P: 2/29 vs. 8/29, $P < 0.05$
	APAP vs. IBU: 8/78 vs. 13/80, NS		IBU vs. ZOL: 5/29 vs. 2/29, NS
Side effects	No difference	NR	More adverse effects of ZOL vs. P
Authors' conclusion	APAP and IBU are effective	IBU is effective	ZOL and IBU are effective
	IBU gives best relief (see comments)		ZOL has similar efficacy
Comments	Intent to treat analysis was performed with a different outcome (any ↓ in pain), in that situation in both APAP and IBU were better than P, and there was no difference between APAP and IBU	More patients in IBU were receiving prophylactic treatment. IBU dose not optimal	Low placebo response rate

*Estimation from the figure.

DBR indicates double-blind randomized; XOver, crossover; IHSC, International Headache Society Criteria; APAP, acetaminophen; IBU, ibuprofen; P, placebo; ZOL, zolmitriptan; N, number of patients enrolled; NR, not reported; NS, nonsignificant; OR (95% CI), odds ratio and its 95% confidence interval.

outcome, we abstracted it to facilitate comparison as suggested by the International Headache Society Clinical Trial Subcommittee.[25] The 2 important outcomes of migraine trials chosen by the same subcommittee were sustained pain-free defined as pain-free within 2 hours with no use of rescue medication, and recurrence within 48 hours were also

TABLE 2. Level I Evidence Evaluating Intranasal Sumatriptan for the Treatment of Migraine Attack in Children

Study	Ueberall and Wenzel[30]	Winner et al[31]	Ahonen[32]	Winner et al[33]
Type	DBR 2-way XOver	DBR parallel	DBR 2-way XOver	DBR parallel
	1-center	Multicentric	Multicentric	Multicentric
Setting	Outpatient	Outpatient	Outpatient	Outpatient
	Neurology clinic	Neurology clinic	Neurology clinic	Neurologic clinic
	First-line	First-line	First-line	First-line
Inclusion/ Exclusion criteria	IHSC[40]	IHSC[40]	IHSC[40]	IHSC[40]
	≥2 attacks/mo	2–8 moderate-to-severe attacks/mo × 2 mo lasting ≥ 4 h	≥2 attacks/mo	1–8 moderate-to-severe attacks/mo × 2 mo
	Resistant to common medications	Failed ≥1 medication(s)	Lasting ≥4 h	No acute medications from 6 h before and up to 1 h after study drug
	Patients on prophylaxis excluded		Prior no response to APAP or NSAID	
			Patients on prophylaxis excluded	
Age range, y	6–10	12–17	8–17	12–17
Treatment	SUM IN 20 mg	SUM IN 20 mg	SUM IN 5 or 10 mg	SUM IN 20 mg
	P IN	SUM IN 10 mg	P IN	SUM IN 5 mg
		SUM IN 5 mg		P IN
		P IN		
Jadad score[24]	4/5	5/5	5/5	5/5
N (enrolled/ analyzed)	14/14	653/510	129/94	888/731
Measurement	4-point scale (severe to none)	4-point scale (none to severe)	5-face scale (severe to none)	4-point scale (none to severe)
Primary outcome	**↓ in pain of severe or moderate by 2 grade at 2 h**	**↓ in pain from severe or moderate to mild or none at 2 h**	**↓ in pain of severe or moderate by 2 grade at 2 h**	**↓ in pain from severe or moderate to mild or none at 1 h**
	SUM vs. P: 12/14 vs. 6/14, $P = 0.031$	20 vs. P: 74/118 vs. 69/131, $P = 0.059$	SUM vs. P: 53/83 vs. 32/83, $P = 0.003$	20 vs. P: 144/237 vs. 127/244, $P = 0.087$
		10 vs. P: 85/133 vs. 69/131, NS		5 vs. P: 132/250 vs. 127/244, NS
		5 vs. P: 84/128 vs. 69/131, $P < 0.05$		Same but at 2 h
				20 vs. P: 161/237 vs. 142/244, $P = 0.025$
				5 vs. P: 158/250 vs. 142/244, NS
Pain-free at 2 h	SUM vs. P: 9/14 vs. 2/14, $P = 0.016$	20 vs. P: 42/118 vs. 33/131, $P < 0.05$	SUM vs. P: 26/83 vs. 17/83, $P = 0.14$	20 vs. P: 104/237 vs. 73/244, $P < 0.001$
		10 vs. P: 45/133 vs. 33/131, NS*		5 vs. P: NS
		5 vs. P: 33/128 vs. 33/131, NS*		
Recurrence, %	Within 4 h?	2–24 h	Within 7 h	1 to 24 h
	SUM vs. P: 0/9 vs. 0/2	20 vs. P: 19/118 vs. 26/131, NS	SUM vs. P: 4/83 vs. 4/83, NS	20 vs. P: 57/237 vs. 76/244, NS
		10 vs. P: 27/133 vs. 26/131, NS		5 vs. P: 58/250 vs. 76/244, NS
		5 vs. P: 23/128 vs. 26/131, NS		

(continued on next page)

TABLE 2. Continued

Use of rescue medications	Within 4 h? SUM vs. P: 0/14 vs. 6/14, $P = 0.031$	2–24 h 20 vs. P: 31/118 vs. 43/131, NS 10 vs. P: 29/133 vs. 43/131, NS 5 vs. P: 27/128 vs. 43/131, NS	2–7 h SUM vs. P: 29/83 vs. 42/83, $P = 0.10$	1–24 h 20 vs. P: 97/237 vs. 120/244, $P = 0.063$ 5 vs. P: 105/250 vs. 120/244, $P = 0.119$
Side effects	No difference	More taste disturbance with SUM	More taste disturbance with SUM	More taste disturbance with SUM
Authors' conclusion	SUM IN is better than P	SUM IN is effective	SUM IN is effective	SUM may be beneficial to some adolescents
Comments		Unusual results (low dose effective not higher dosages for primary outcome)		

*Estimation from the figure.

DBR indicates double-blind randomized; XOver, crossover; IHSC, International Headache Society Criteria; SUM, sumatriptan; P, placebo; APAP, acetaminophen; NSAID, nonsteroidal anti-inflammatory drugs; N, number of patients enrolled; NS, nonsignificant.

abstracted.[25] Comments on the various studies were made when deemed appropriate.

Data Analysis

Odds ratio was not calculated because for most of the studies, they were impossible to compute considering the crossover design of the study and the absence of raw data presented in the articles. An attempt was made to contact the authors of these studies.

A summary of the RCTs that evaluated efficacy of the medications used to treat children with migraine was produced for each important outcome recommended by the International Headache Society Clinical Trial Subcommittee:[25] pain relief, pain-free, recurrence, and need for rescue medications. Medications considered effective for the outcome were those where the RCTs showed consistent positive results or where one RCT showed a positive result. Medications not considered effective for the outcome were those with RCTs that showed consistent negative results or with one RCT that showed a negative result. Medications that were found inconsistent for the outcome were those that had RCTs that showed both positive and negative results.

RESULTS

The comprehensive search identified a limited number of relevant RTCs (Fig. 1).

One study evaluated ibuprofen against a placebo,[26] another evaluated both acetaminophen and ibuprofen against a placebo,[27] and another compared ibuprofen and zolmitriptan, a triptan, against a placebo.[28] Table 1 summarizes these studies.

Several studies evaluated triptans alone; 1 evaluated oral sumatriptan against a placebo,[29] 4 evaluated intranasal sumatriptan against a placebo,[30–33] 3 evaluated oral rizatriptan against a placebo,[34–36] and 1 evaluated oral zolmitriptan against a placebo.[37] Tables 2 and 3 summarize the 9 studies. The only comparative study with the triptans compared zolmitriptan against ibuprofen and placebo (Table 1).[28]

Another study evaluated oral dihydroergotamine (DHE) against a placebo (Table 4).[38] Finally, 1 study compared intravenous ketorolac to intravenous prochlorperazine (Table 4).[39]

All studies, except one, were neurology clinic-based, and children with migraine that fit the International Headache Society criteria (1988), its second edition (2004), or a proposed revision were treated initially with the study drug or the placebo at home.[40–42] The only study done in a pediatric emergency department compared prochlorperazine versus ketorolac in children that fit the Prensky and Sommer migraine criteria.[39,43] Those patients were likely to have received other medications either at home or in the emergency department before being included in the study.[39] This was not the case in the other identified studies; the studied medications were used first and early after the migraine had started.

The quality of the trials was generally good as evaluated by the Jadad score, but most had large confidence interval. There was an important number of lost to follow-up in most studies. Two studies[29,38] evaluated responses to other treatments in a population initially used for another.[27] Most studies had a priori power calculation: only 2 did not.[26,30]

LIMITATIONS

Like all other systematic reviews or meta-analyses, the quality of this qualitative systematic review is limited by the quantity and quality of the available evidence. Considering that we wanted to evaluate which treatment for children with migraine and status migrainosus would be effective in the emergency department, it was striking to find that in all but 1 study, the patients were treated at home. What does this say for patients seen in the emergency department? In patients studied at home, the studied medication was the first agent

TABLE 3. Level I Evidence Evaluating Oral Triptans for the Treatment of Migraine Attack in Children

Study	Hamalainen et al[29]	Winner et al[34]	Visser et al[35]	Rothner et al[37]	Ahonen et al[36]
Type	DBR 2-way XOver	DBR parallel	DBR parallel	DBR parallel	DBR 3-way XOver
	Multicentric	Multicentric	Multicentric	Multicentric	Multicentric
Setting	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient
	Neurology clinic	Neurology clinic	Neurology clinic	Neurology clinic	Neurology clinic
	First-line	First-line	First-line	First-line	First-line
Inclusion/ Exclusion criteria	IHSC[40]	IHSC[40]	IHSC × 1 y[40]	IHSC[40]	IHSC[40]
	≥2 attacks/mo	≥1 and ≤8 attacks/ mo × 6 mo lasting ≥4 h	≥1 and ≤8 attacks/ mo × 6 mo	≥2 and ≤10 attacks/ mo × 3 mo	≥2 attacks/mo lasting ≥4 h
	No benefit from previous medications	No NSAID as prophylaxis	No NSAID as prophylaxis	Moderate or severe headache	Previous unsatisfactory response to acetaminophen or NSAIDs
	Patients on prophylaxis excluded				No prophylaxis
Age range, y	8–16	12–17	12–17	12–17	6–17
Treatment	SUM PO 50 or 100 mg	RIZ PO 5 mg	RIZ PO 5 mg	ZOL PO 2.5 or 5 or 10 mg	RIZ PO 5 or 10 mg
	P PO	P PO	P PO	P PO	RIZ PO 5 or 10 mg P PO
Jadad score[24]	4/5	3/5	4/5	5/5	5/5
N (enrolled/ analyzed)	31/23	360/291	686/473	850/696	147/96
Measurement	VAS (0–100 mm)	4-point scale (none to severe)	4-point scale (severe to none)	4-point scale (none to severe)	5-point scale (severe to none)
Primary outcome	**↓ by 50% at 2 h**	**Pain-free at 2 h**	**↓ from severe or moderate to mild or none at 2 h**	**↓ from severe or moderate to mild or none at 2 h**	**↓ from severe or moderate (≥3) by at least 2 grade at 2 h**
	SUM vs. P: 7/23 vs. 5/23, NS	See below	RIZ vs. P: 159/233 vs. 165/240, NS	ZOL vs. P: 263/480 vs. 93/160, NS	RIZ vs. P: 71/96 vs. 35/96, $P < 0.001$
		↓ from severe or moderate to mild or none at 2 h			2nd RIZ vs. P: 70/96 vs. 35/96, $P < 0.001$
		RIZ vs. P: 98/148 vs. 79/142, NS			
Pain-free at 2 h	SUM vs. P: 5/23 vs. 2/23, NS	RIZ vs. P: 48/148 vs. 40/142, NS	RIZ vs. P: 91/233 vs. 75/240, $P = 0.053$	ZOL vs. P: 107/480 vs. 32/160, NS	RIZ vs. P: 34/96 vs. 17/96, $P = 0.015$
					2nd RIZ vs. P: 30/96 vs. 17/96, $P = 0.037$
Recurrence, %	**Within 5 h?**	**Within 24 h**	**NR**	**NR**	**NR**
	SUM vs. P: 0/5 vs. 0/2, NS	RIZ vs. P: 11/98 vs. 14/79, NS			
Use of rescue medications	**Within 5 h?**	**Within 24 h**	**2–24 h**	**NR**	**Within 7 h?**
	SUM vs. P: 5/23 vs. 5/23, NR	RIZ vs. P 58/148 vs. 65/142, NS	RIZ vs. P: 84/233 vs. 101/240, NR		RIZ vs. P: 17/96 vs. 38/96, $P = 0.004$
					2nd RIZ vs. P: 21/96 vs. 38/96, $P = 0.017$
Side effects	No difference	No difference	No difference	More adverse events in ZOL group	More adverse events in RIZ groups
Author's conclusion	SUM PO not effective	RIZ effective on some measures	RIZ PO not more effective than P	Similar efficacy of ZOL and P	RIZ PO is effective
Comments			High rate of responders in placebo group	High rate of responders in placebo group	Same results with intent to treat

DBR indicates double-blind randomized; XOver, crossover; IHSC, International Headache Society Criteria; SUM, sumatriptan; RIZ, rizatriptan; ZOL, zolmitriptan; P, placebo; NSAID, nonsteroidal anti-inflammatory drugs; N, number of patients enrolled; NR, not reported; NS, nonsignificant.

TABLE 4. Level I Evidence Evaluating DHE, Ketorolac, and Prochlorperazine for the Treatment of Migraine Attack in Children

Study	Hamalainen et al[38]	Brousseau et al[39]
Type	DBR 4-way XOver	DBR Parallel
	Multicentric	2-center
Setting	Outpatient	PED
	Neurology clinic	Second-line
	First-line	
Inclusion/Exclusion criteria	IHSC[40]	Prensky and Sommer criteria[43]
	≥2 attacks/mo	Enrolled when decision to treat IV
	Patients on prophylaxis excluded	
	Most patients participated previously in a study comparing APAP and IBU to P[27]	
Age range, y	6–15	5–18
Treatment	DHE PO 20 μg/kg	PRO IV 0.15 mg/kg
	P PO	KET IV 0.5 mg/kg
	DHE PO 40 μg/kg	
	P PO	
Jadad score[24]	4/5	5/5
N (enrolled/analyzed)	16/12	62/62
Measurement	5-point scale (severe to none)	9-face pain scale (1-9)
Primary outcome	**↓ of severe or moderate by 2 grade at 2 h**	**↓ by 50% or complete relief at 1 h**
	DHE vs. P: 7/12 vs. 2/12, $P = 0.06$	PRO vs. KET: 28/33 vs. 13/29, Δ30% (95% CI: 8, 52)
Pain-free at 2 h	DHE vs. P: 5/12 vs. 0/12, NR	NR
Recurrence, %	**Within 5 h?**	**Within 48 h**
	DHE vs. P: 2/5 vs. 0/0, NR	PRO vs. KET: 7/26 vs. 4/13, Δ −4% (95% CI: −34, 27)
Use of rescue medications	**Within 5 h?**	**NR**
	DHE vs. P: 6/12 vs. 8/13, NR	
Side effects	No difference	No difference
Author's conclusion	DHE PO may be useful	PRO IV is superior to KET IV
Comments	Unusual low rate of responders in placebo group	Only ED-based study
		Most children received medications before ED visit, but there is no report of medications used before study in the ED

DBR indicates double-blind randomized; XOver, crossover; PED, pediatric emergency department; IHSC, International Headache Society Criteria; KET, ketorolac; P, placebo; PRO, prochlorperazine; APAP, acetaminophen; IBU, ibuprofen; N, number of patients enrolled; NR, not reported; ED, emergency department.

used for a migraine attack and is likely to have been used early after the onset of the headache as per the investigators' instructions. In patients seen in an emergency department, some, if not most, patients have tried other medications that were probably ineffective, and again, some, if not most, patients were seen well after the onset of the migraine. It is unclear if a medication found effective at home can also be effective when another treatment has previously failed. Thus, any conclusions for treatment in an emergency department need to take this limitation into account.

Furthermore, interpretation of the results is somewhat complicated by the outcomes measured. Most studies used pain relief measured 2 hours after the intervention as their primary outcome. This may not be the best outcome for migraine trials according to the International Headache Society Clinical Trials Subcommittee.[25] Instead, they recommend pain-free at 2 hours before any rescue medication as the primary measure of efficacy because patients indicate that they wish and expect to be pain-free after a treatment.[25] Other important outcomes that need to be evaluated are use of rescue medication 2 hours after the intervention and recurrence defined as any severity returns within 48 hours.[25] This is why we reported all 4 relevant outcomes.

Half of the identified RCTs were crossover trials. None of them provided raw data preventing the calculation of odds ratio when not reported and adequate pooling of the data. We chose not to analyze the crossover trials as parallel trials like others have done.[11] This could have led to a debatable conclusion considering the inconsistent results for some medications.

DISCUSSION

Only a limited number of medications proposed in the guidelines of the Canadian Headache Society, the French Society for the Study of Migraine Headache, and the

American Academy of Neurology have been studied by RCTs in children.[7–10] Not surprisingly, the more recently available medications, the triptans, are the most widely studied.

From the studies that evaluated acetaminophen and ibuprofen, it seems that ibuprofen was effective as initial treatment for pain relief (Table 5).[26–28] Acetaminophen also seems to be effective for the same outcome, although the results are not as clear as with ibuprofen because of the way the analysis was done in the study (intent-to-treat analysis not used to report the primary outcome).[27] When the results were analyzed on an intent-to-treat basis, acetaminophen was found effective for pain relief but not pain-free. Neither acetaminophen nor ibuprofen prevented recurrence.[26,27] Ibuprofen decreased the need for rescue medications in one trial,[26] but not in the others.[27,28] Acetaminophen did not decrease the need for rescue medications (Table 5).[27]

Several authors have concluded that oral triptans are not as effective in children as they are in adults.[19,44] However, nasal sumatriptan may be effective.[19,44] Most of the studies that evaluated oral sumatriptan, oral rizatriptan, and oral zolmitriptan found that these medications were not effective for pain relief (Table 5).[29,34,35,37] The exceptions are 2 recent studies that found oral rizatriptan and oral zolmitriptan better than placebo for pain relief, pain-free, and need for rescue medications.[28,36] The difference may be explained by high placebo response rate in previous studies with both medications. Interestingly, zolmitriptan was as effective for pain relief, pain-free, and need for rescue medications but not better than ibuprofen in the only comparative study involving the triptans.[28] None of the oral triptans prevented recurrence (Table 5). Intranasal sumatriptan gave inconsistent results in 4 studies for pain relief, pain-free, and the need for rescue medications (Table 5). However, none decreased recurrence (Table 5). It has been suggested that nasal sumatriptan may be an effective treatment because of its very rapid onset of action compared with the oral formulation (15 minutes compared with 30 to 60 minutes for oral sumatriptan).[44] Furthermore, migraine-associated gastric stasis has also been suggested to explain the difference of efficacy of oral triptans in children compared with adults.[44] This hypothesis seems to be incorrect because acetaminophen, ibuprofen, and zolmitriptan administered orally were found to be effective in children.[26–28]

Oral DHE did not seem to be effective but was evaluated in only 12 children (Table 5).[38] In any case, nausea associated with DHE could limit this option even if it had been effective.[7]

Intravenous prochlorperazine was the only treatment that was evaluated and found effective for pain relief as treatment in the emergency department after other migraine treatment had failed at home (Table 5).[39] If we include patients treated with prochlorperazine after ketorolac had failed, the success of prochlorperazine was 85% (51/60). This was impressive considering that the attacks were present for a median of 24 to 25 hours and that more than 80% of patients received pain medications before the visit to the emergency department including 32% to 35% migraine-specific medications. The rate of success with ketorolac (55%) was close to what might be expected with placebo (30%–50% response rate), although the possibility that ketorolac was effective, keeping in mind the severity of the migraine attack treated in this study, cannot be excluded. We do not know if prochlorperazine is effective for the outcome pain-free or to decrease the need for rescue medications. However, prochlorperazine did not prevent recurrence (Table 5).

From all this, it is difficult to draw conclusion for emergency department treatment of mild or moderate attack in children. In that situation, acetaminophen or ibuprofen may be used to relieve pain, but patients are likely not to become pain-free (Table 5). In these situations, it is unclear if any medications will be effective if the first one was

TABLE 5. Summary of the Efficacy of the Medications Used to Treat Children With Migraine

	Outcome			
	Pain Relief	**Pain-free**	**Recurrence**	**Need for Rescue Medications**
Oral medications				
Acetaminophen (n = 1)	+	−	−	−
DHE (n = 1)	−	−	−	−
Ibuprofen (n = 3)	+	+/−	−	+/−
Rizatriptan (n = 3)	+/−	+/−	−	+/−
Sumatriptan (n = 1)	−	−	−	−
Zolmitriptan (n = 2)	+/−	+/−	−	+
Intranasal medication				
Sumatriptan (n = 4)	+/−	+/−	−	+/−
Intravenous medications				
Prochlorperazine (n = 1)	+	?	−	?
Ketorolac (n = 1)*	?	?	?	?

*Used as a comparative agent against prochlorperazine.

+ indicates studies showing consistent positive results or a study showing positive result; −, studies showing consistent negative results or a study showing negative result; +/−, studies showing inconsistent results; ?, not evaluated.

ineffective. Intranasal sumatriptan may be considered, but because of the discrepancy in the different studies, it is unclear if it is really effective for pain relief. The place of oral triptans in the emergency department is unclear, as one study found oral zolmitriptan no better than ibuprofen. For severe or ultrasevere attacks, intravenous prochlorperazine seems to be the medication of choice in the emergency department with a very good chance of success in relieving pain despite previous failure with other treatment (Table 5). The rate of adverse reactions, especially of extrapyramidal symptoms, is unknown with the use of prochlorperazine in children. From a cohort of children treated with intravenous prochlorperazine who received diphenhydramine as prophylaxis of extrapyramidal symptoms published only as an abstract thus far, 6 (12%) of 51 patients developed akathisia within 24 hours of discharge.[45] This will need to be evaluated in the future. Because prochlorperazine do not prevent recurrence, patients should be discharged with additional analgesics.

No study has evaluated whether or not there are any medications or any dosage schedules better than others to prevent recurrence in the next few hours or days after discharge from the emergency department. In the study by Brousseau et al,[39] patients were discharged on naproxen as needed for the next 48 hours after receiving either prochlorperazine or ketorolac. Recurrence rate was 27% to 31% within 48 hours with that regimen.[39]

CONCLUSIONS

There is a lack of studies addressing the question of treatment in the emergency department of children with migraine. Future studies should focus on finding the best first-line agent for mild to moderate attack in the emergency department and to confirm the usefulness of prochlorperazine as treatment for severe attack or status migrainosus. In the latter studies, attention should be given to adverse drug reactions associated with prochlorperazine. Furthermore, treatment to decrease the recurrence of migraine attack and the need for rescue medications after discharge from the emergency department should also be carefully evaluated.

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