Journal Reading

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A Randomized Trial of Intravenous Ketorolac Versus Intravenous Metoclopramide Plus Diphenhydramine for Tension-Type and All Nonmigraine, Noncluster Recurrent Headaches

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Background

- 病人常因急性頭痛發作來急診
  - 包括tension-type, migraine, cluster, 或自行緩解而未歸類的頭痛
- 根據不同形式的頭痛來做治療
  - tension-type headache: NSAID
  - Migraine: dopamine antagonists
- 研究排除migraine及cluster headache, 將nonmigraine, noncluster recurrent headaches與tension-type headache一起討論
  - 之前多數的研究: 急診及 benign headache
  - Convergence hypothesis: 許多的primary headache有不同表現形式,但有相同的neuropathophysiology
- 本篇研究有兩種假設:
  - nonmigraine, noncluster recurrent headaches:
    - metoclopramide(20 mg IV)加上diphenhydramine(25 mg IV) 比 ketorolac(30 mg IV)在1小時後有較佳的疼痛緩解
  - tension-type headache:
    - metoclopramide(20 mg IV)加上diphenhydramine(25 mg IV) 比 ketorolac(30 mg IV)在1小時後有較佳的疼痛緩解

Study objective

- 比較
  - metoclopramide(20 mg IV) 加上 diphenhydramine(25 mg IV)
  - ketorolac(30 mg IV)

  對於成人tension-type headache 以及 nonmigraine, noncluster recurrent headaches 的治療效果

Methods

- 此篇為針對急診的randomized, double-blind研究
  - Montefiore medical center
- 匯集了nonmigraine, noncluster recurrent headaches及tension-type headache的成人病患
  - <65y/o, 之前至少發作一次
  - 排除: 其他因素引起之頭痛, 發燒(>38c), 神經學異常, 過敏, 胃炎,消化道出血, 器官移植, 懷孕, 哺乳…
- Primary outcome:
  - 比較來診時及1小時後pain score的進步程度(0-10分)
    - 兩組間差異scale units 2.0: 訂為臨床上最小的顯著差異值
- Secondary endpoints:
  - 在急診中是否需要救援藥物
  - 在急診中達到疼痛緩解且持續24小時
  - 病患希望再次接受相同的藥物治療

A. At least 10 episodes fulfilling criteria B-E
B. Headache lasting 30 minutes to 7 days
C. Headache has at least two of the following characteristics
   1. Bilateral location
   2. Pressing/ tightening (non-pulsating) quality
   3. Mild or moderate intensity (may inhibit but not prohibit usual activities)
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following
   1. No nausea or vomiting (anorexia may occur)
   2. No more than one of photophobia or phonophobia
E. Not attributed to another disorder

Figure 1. Tension-type headache criteria. From the International Headache Society's *International Classification of Headache Disorders, 2nd Edition*. Tension-type headaches can be further subdivided into infrequent episodic, frequent episodic, or chronic.

2009/11, 35 months

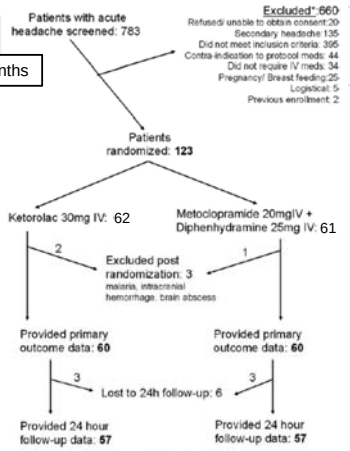

Figure 2. CONSORT flow diagram.

Results

- 在此研究中匯集了120位病患
  - 89位符合tension-type headache criteria
- metoclopramide/diphenhydramine 組別之scale units進步中位數為 5, 而 ketorolac 組別進步中位數為3
- Nonmigraine, noncluster recurrent headaches:
  - 3 secondary outcomes:
    Metoclopramide+diphenhydramine 皆優於ketorolac
    - 不需急診救援藥物使用: NNT= 3 (95% CI 2 to 6)
    - 持續疼痛緩解: NNT= 6 (95% CI 3 to 20)
    - 希望再度接受同種藥物治療: NNT= 7 (95% CI 4 to 65)
- Tension-type headache subgroup 的結果也相似

Table 1. Baseline characteristics of the entire study population.

Characteristic	Ketorolac (n=60)	Metoclopramide+ Diphenhydramine (n=60)
Median age (IQR), y	38 (26, 46)	38 (29, 48)
Female, No. (%)	48 (80)	42 (70)
Race/ethnicity, No. (%)		
Asian	0	0
Black	11 (18)	17 (28)
Latino	40 (67)	34 (57)
White	1 (2)	2 (3)
Mixed	3 (5)	4 (7)
Other	5 (8)	2 (3)
Refused	0	1 (2)
Median duration of headache (IQR), h	72 (48, 168)	72 (24, 144)
Median number of days with headache during the previous 3 mo (IQR)	5 (2, 10)	5 (2, 10)
Medical history of migraine headaches, No. (%)	16 (27)	11 (18)
Median baseline NRS pain score, on a scale from 0–10 with 0=no pain and 10=worst imaginable (IQR)	8 (7, 10)	8 (7, 9)

IQR, interquartile range; *NRS*, numerical rating scale; *h*, hours; *mo*, months; *n*, number.

Table 2. Change in numeric rating scale between baseline and 1 hour postbaseline.

Population	Ketorolac Median Improvement (IQR), N	Metoclopramide+Diphenhydramine Median Improvement (IQR), N	95% CI for Difference Between Medians*
Nonmigraine, noncluster recurrent headache	3 (2, 6), 60	5 (3, 7), 60	0, 3
Tension-type headache	3 (2, 6), 46	5 (3, 7), 43	0, 3

*Independent-samples Hodges-Lehman estimate.

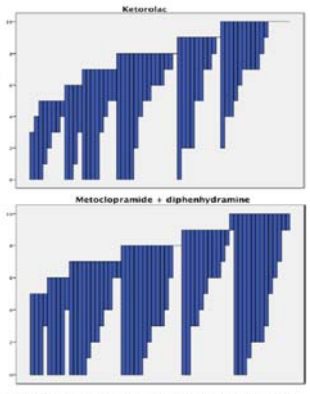

Figure 3. Each line depicts the baseline and 1-hour pain score for an individual. Data are sorted by baseline pain score and then 1-hour pain score, so the patient who worsened after receiving the metoclopramide combination (from 9 to 10) appears in the figure after all of the other patients with a baseline score of 9.

Table 3. Categorical outcomes among all patients with nonmigraine, noncluster recurrent headache

Outcome	Ketorolac (%)	Metoclopramide+ Diphenhydramine (%)	Difference (95% CI), %	Number Needed to Treat (95% CI)
Would want to receive the same medication during the next ED visit for headache	45/57 (79)	53/57 (93)	14 (2 to 27)	7 (4 to 65)
Achieved headache freedom in the ED without requiring rescue medication	16/60 (27)	27/60 (45)	18 (1 to 35)	6 (3 to 67)
Required rescue medication in the ED	27/60 (45)	8/60 (13)	32 (16 to 47)	3 (2 to 6)
Achieved headache freedom in the ED without requiring rescue medication and maintained headache freedom for 24 h	5/60 (8)	16/60 (27)	19 (5 to 32)	6 (3 to 20)
Required analgesic medication within 24 h of ED discharge	27/57 (47)	20/57 (35)	12 (−6 to 30)	Insufficient difference between groups—unable to calculate NNT

NNT, number needed to treat.

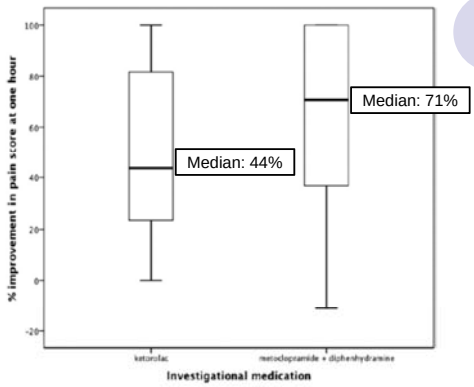

Figure 4. Box plots demonstrating percentage improvement in 0 to 10 pain score 1 hour after medication administration.

Table 4. Categorical outcomes among all patients with tension-type headache.

Outcome	Ketorolac (%)	Metoclopramide+ Diphenhydramine (%)	Difference (95% CI), %	Number Needed to Treat (95% CI)
Would want to receive the same medication during the next ED visit for headache	34/43 (79)	37/40 (93)	14 (−1 to 28)	Insufficient difference between groups—unable to calculate NNT
Achieved headache freedom in the ED without requiring rescue medication	10/46 (22)	20/43 (47)	25 (6 to 44)	5 (2 to 18)
Required rescue medication in the ED	20/46 (44)	6/43 (14)	30 (12 to 47)	4 (2 to 8)
Achieved headache freedom in the ED without requiring rescue medication and maintained headache freedom for 24 h	4/46 (9)	11/43 (26)	17 (2 to 32)	6 (3 to 66)
Required analgesic medication within 24 h of ED discharge	21/43 (49)	16/40 (40)	9 (−12 to 30)	Insufficient difference between groups—unable to calculate NNT

Table 5. Adverse events among entire study population.

Adverse Event	Ketorolac (n=60) (%)	Metoclopramide+ Diphenhydramine (n=60) (%)	Difference (95% CI), %
Drowsy at 1 h			For no drowsiness: 29 (12 to 47)
No	38 (64)	21 (35)	
A little bit drowsy but able to function	18 (31)	38 (63)	
Too drowsy to function	3 (5)	1 (2)	
Not sure/did not answer	1	0	
Restless after receiving intravenous medication			For no restlessness: 1 (−13 to 13)
No	47 (85)	48 (86)	
A little bit restless	7 (13)	6 (11)	
Very restless	1 (2)	2 (4)	
Lost to follow-up	3	3	
Not sure/did not answer	2	1	
Other adverse events			
Dizziness	2	2	
Epigastric pain	1	1	
Nausea	2	1	
Neck/back pain	1	2	
Palpitations*	1	0	
Abnormal olfaction*	0	1	

*One patient who received ketorolac reported a rapid heartbeat after ED discharge, for which the patient did not seek medical attention. One patient who received metoclopramide reported a self-limited change in sense of smell.

16 patients would not want to receive the same medication at the next visit -- lack of efficacy rather than adverse effects

Conclusion

- 針對因tension-type headache或nonmigraine, noncluster recurrent headache來急診之成人病患
  → IV metoclopramide 加上 diphenhydramine 比 IV Ketorolac 有較佳的疼痛緩解效果

Discussion

- Restlessness是metoclopramide常見的副作用
  - 似乎可因同時使用diphenhydramine而成功地預防
- Mild drowsiness:
  - metoclpramide: 2/3
  - Ketorolac:1/3
- 少數病患抱怨"too drowsy to function"
  - 減低metoclpramide的劑量可以降低drowsiness,但效果也較差, 須取得平衡

Discussion

- 事實上, migraine及tension-type headache似乎都對metoclpramide有良好反應
  - 但此藥並無止痛效果
- 也許tension-type headache和migraine有同樣的進程, 共同的 final nociceptive pathway,因而metoclopramide可作用之
  - 兩種headache types有相似的pathophysiology, 只是有多種表徵
  - 但目前無pharmacodynamic或mechanistic數據來解釋metoclopramide在急性頭痛的效用

Discussion

- 作者只排除migraine及cluster headache, 但並未細分其他少見的頭痛形式
  - nummular headache
  - noninfectious rhinosinusitis-like headache
  - hemicrania continua
  - 單就Tension-type headache病患與全部的病患比較 → 對於兩組藥物的反應是相同的
  - 這些較不常見的頭痛形式, 可能在此研究中樣本比例太低, 或對藥物的反應與tension-type headache反應相似

Poor Sensitivity of a Modified Alvarado Score in Adults With Suspected Appendicitis

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Background

- 腹痛是急診很常見的主訴(在美國約10%)
- Appendicitis是最常見的緊急手術適應症
  - 在2009年美國約有250,000例的 appendectomies
- Alvarado score最初是從1986年的研究中衍生出來的
  - 懷疑appendicitis的住院病人
  - 根據病人的症狀, 理學檢查以及實驗室診斷做評估,分數為0-10分
  - 作為病人是否需開刀的指標
- American College of Emergency Physicians clinical guidelines 及 Journal of the American Medical Association: 此score可作為潛在工具來幫助臨床醫師做決定
- Modified Alvarado score: 去除 left shift of leukocytes, 分數為0-9分
- 先前研究指出: modified Alvarado score小於4分只有非常低的機率為appendicitis

Study objective

- 根據臨床診斷標準, 辨認出低機率appendicitis病人, 可減少對CT診斷的依賴
- 比較在急診中懷疑是appendicitis的病人, 用modified Alvarado score 或臨床判斷的評估準確性
- 作者假設低的modified Alvarado score
  - 有足夠的高敏感度來排除appendicitis

Methods

- 前瞻性觀察研究:
  - 2008/3-2009/3
  - 兩個都市大學的急診: Pennsylvania, Copper
  - 懷疑有appendicitis的成人
- 低的modified Alvarado score定義為低於4分
  - 計算sensitivity及specificity
- 最終診斷為appendicitis是根據
  - CT, laparotomy, 或7天追蹤

Results

- 研究包含261位病患
  - 平均年紀35歲, 68% 是女生, 52%是白人
- 53位病患(20%)是acute appendicitis
- modified Alvarado score的sensitivity為72%, specificity為54%
- 臨床判斷appendicitis為第一或第二可能的診斷之 sensitivity為93%, specificity為33%

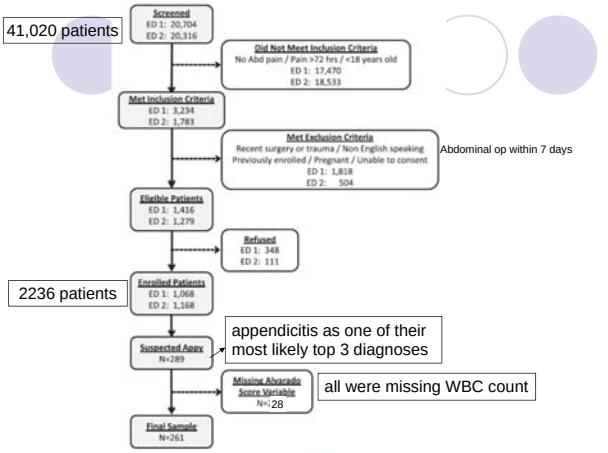

Figure 1. Flow diagram of patient enrollment.

Table 1. Overall patient characteristics (N=261).

Characteristics	Frequency	Percentage
Age, mean, y	35 (range 18–89)	
Sex, male	84	32.2
Race		
White	136	52.1
Black	112	42.9
Asian	8	3.1
Other	5	1.9
Triage classification		
1	1	0.4
2	79	30.3
3	165	63.2
4/5	15	5.7
Abdominopelvic CT	221	84.7
Admission to hospital	110	42.2
Top 5 final diagnoses		
Abdominal pain, NOS	68	26.0
Appendicitis	53	20.3
Ovarian cyst	26	10.0
Ureteral calculus	11	4.2
Pelvic inflammatory disease	10	3.8

NOS, Not otherwise specified.

Table 2. The modified Alvarado score in acute appendicitis (N=261).

Data Category	Data Element	Value	Frequency	Percentage
Symptoms	Migration	1	34	13
	Anorexia-acetone (in the urine)	1	142	54
	Nausea-vomiting	1	164	63
Signs	Tenderness in right lower quadrant	2	197	76
	Rebound pain	1	25	10
	Elevation of temperature (>37.3°C [99°F] measured orally)	1	34	13
Laboratory	Leukocytosis (>10,000/mm^3)	2	84	32
Total score		9		

Score		Frequency	Percentage
1–4	Appendicitis unlikely	177	68
5–6	Appendicitis possible	64	24
7–9	Appendicitis probable	14	5

Adapted from Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med.* 1986;15:557-564, with permission from Elsevier.

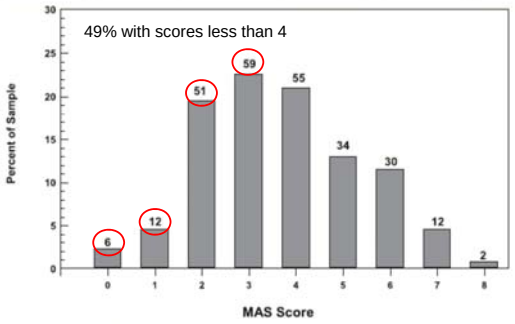

Figure 2. Distribution of modified Alvarado score.

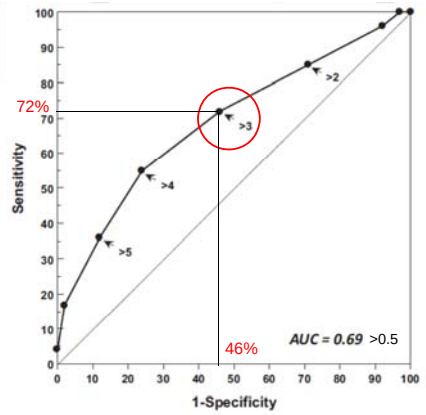

Figure 3. Receiver-operator curve for modified Alvarado score.

Table 3. Comparison of the modified Alvarado score and clinical judgment.

Clinical Decision Rule	Sensitivity (95% CI), %	Specificity (95% CI), %	+LR	–LR
MAS >5	36 (23–50)	88 (83–92)	3.0	0.7
MAS >4	55 (40–68)	76 (70–82)	2.3	0.6
MAS >3	72 (58–83)	54 (47–61)	1.6	0.5
Clinical judgment				
#1 diagnosis is appendicitis	79 (66–89)	68 (61–74)	2.5	0.3
#1 or #2 diagnosis is appendicitis	93 (82–98)	33 (27–40)	1.4	0.2

CI, confidence interval; *MAS*, Modified Alvarado score.

Conclusion

- 低的modified Alvarado score對於排除acute appendicitis之sensitivity為72%, 較臨床判斷更不敏感

Discussion

- modified Alvarado score:
  - 評估懷疑是appendicitis而未做影像學檢查病患之機率分層
  - 可用在資源缺乏地區(無CT)或低機率病患(CT輻射暴露風險>診斷益處)
- 本研究發現modified Alvarado score分數低於4分對於診斷appendicitis敏感度只有72%
  - 不足以排除後續影像檢查的必要性
  - 且低於臨床判斷的敏感度
- 本研究是屬於"high-risk"的腹痛族群, 因appendicitis是前三個鑑別診斷
  - 約12%屬低的modified Alvarado score,但經影像學或外科病理診斷後確診為appendicitis
  - 影像學診斷可增加準確度

Discussion

- 此種診斷方式的挑戰:
  - 造成腹痛得原因很多,可從輕微良性到致死
  - 腹腔構造複雜
  - CT診斷精確且易取得
- 有效益的評估:
  - 資源缺乏地區: 只有少數高度懷疑病患須做影像檢查或開刀
  - 減少CT輻射暴露,減少癌症
  - 減少花費
  - 減少不必要的手術

Discussion

- 低的modified Alvarado score較臨床判斷敏感度低
  - 無法排除急診中腹痛而懷疑appendicitis之病患
  - 無法安全地讓病患出院而不繼續追蹤
- 需要更進一步的研究尋找新的診斷工具, 進而增加臨床診斷的準確度及排除不必要的影像學診斷

Thanks for your attention !!