Update treatment of cluster headache

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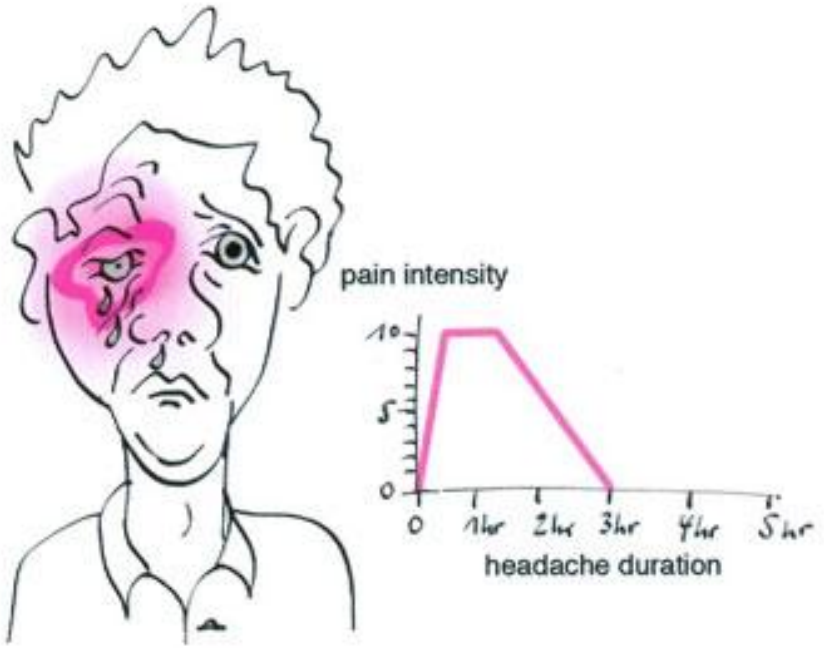
Cluster Headache

- 原發性頭痛中嚴重程度最嚴重的一種



3.1 叢發性頭痛

A. 至少有五次符合基準B-D之發作

B. 位於單側眼眶、上眼眶及/或顳部重度或極重度疼痛，如不治療可持續15至180分鐘

C. 頭痛時至少伴隨下列一項：

1. 同側結膜充血及/或流淚
2. 同側鼻腔充血及/或流鼻水
3. 同側眼皮水腫
4. 同側前額及臉部出汗
5. 同側瞳孔縮小及/或眼皮下垂
6. 不安的感覺或躁動

D. 發作頻率爲每二日一次至每日八次

E. 非歸因於其他疾患

http://www.jawpain.ie/site/index.php/tmj-headaches

3.1.1 陣發性叢發性頭痛

A. 發作符合3.1叢發性頭痛基準A-E

B. 至少有兩次叢發期，爲時7-365日，其中間隔≧1個月無痛的緩解期

3.1.2 慢性叢發性頭痛

A. 發作符合3.1叢發性頭痛基準A-E

B. 反覆發作＞1年而無緩解期，或緩解期持續＜1個月

– 台灣:

- 絕大多數為陣發性叢發性頭痛
- 僅有五成的叢發性頭痛病患出現 “不安的感覺或躁動”

Cluster headache in summary

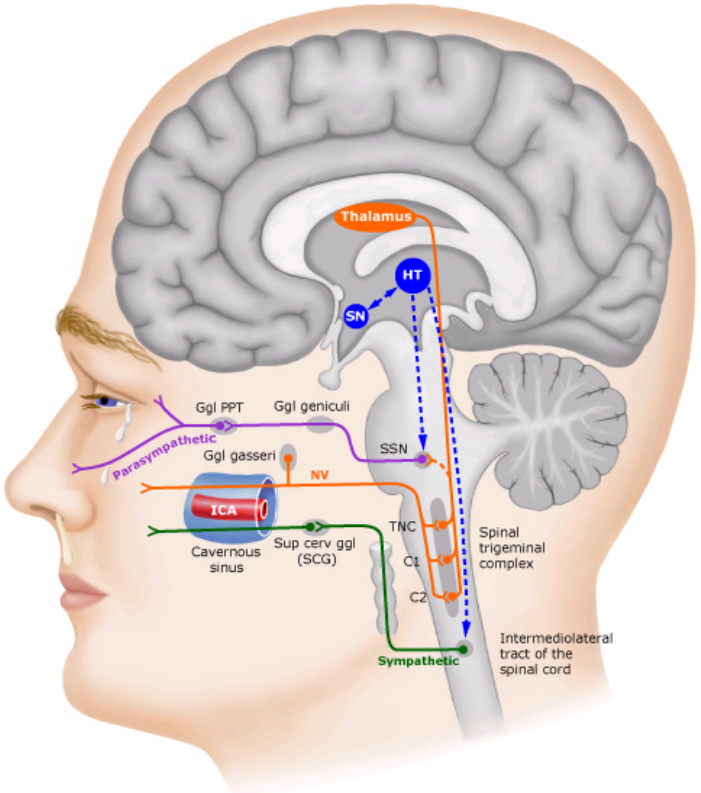
- A trigeminal autonomic cephalagia (TAC)
- Short-lasting, unilateral and severe headache attacks accompanying autonomic symptoms.

Epidemiology of cluster headache

- Lifetime prevalence for adults: 124/100,000, about 0.1%.
- One year prevalence: 53/100,000
- Male: female: 4.3: 1

Cephalalgia. 2008;28(6):614.

Pathogenesis of cluster headache



Schematic model showing most of the putative actors in CH pathogenesis. Pain afferents from the trigeminovascular system synapse on the trigeminocervical complex (TNC), and then project to the thalamus and lead to activation in cortical areas known to be involved in pain transmission. Either a direct influence of the hypothalamus or a reflex activation of the parasympathetic outflow from the superior salivatory nucleus (SSN) predominately through the pterygopalatine (sphenopalatine) ganglion, leads to the parasympathetic symptoms ipsilateral to the pain. A third-order sympathetic nerve lesion, thought to be caused by vascular changes in the cavernous sinus loggia with subsequent irritation of the local plexus of nerve fibers, results in a partial Horner's syndrome. The key site in the CNS for triggering the pain and controlling the cycling aspects is in the posterior hypothalamic grey matter region, modulated by phase-shifting in the suprachiasmatic nuclei.

Abbreviations: Ggl = ganglion, HT = hypothalamus, ICA = internal carotid artery, NV = trigeminal nerve, PPT = pterygopalatine, SCG = superior cervical ganglion, SN = suprachiasmatic nucleus, SSN = superior salivatory nucleus, TNC = trigeminal nucleus caudalis

Modified from: May A. Cluster headache: pathogenesis, diagnosis, and management. Lancet 2005; 366:847.

1.Hypothalamic activation with secondary activation of trigeminal-autonomic reflex.

2. Neurogenic inflammation of the wall of cavernous sinus obliterates venous outflow and injures travelling sympathetic pathway of the intracranial ICA.

急性治療

認識證據等級

- Level **I**: prospective, RCT, masked outcome measures且 clear primary outcome, inclusion/exclusion criteria, drop- out or change trial group do not alter outcome

  Ia : evidence from meta-analysis of RCTs

  Ib: evidence from >=1 RCT

- Level **II**: prospective, matched cohort, masked outcome measures但需求條件中有一項不符合.

  IIa: >=1cohort或case-control且設計嚴謹的試驗, not randomized.

  IIb: 設計嚴謹的 quasi-experimental study

- Level **III**: other controlled trial
- Level **IV**: case series, not controlled, expert opinions.

氧氣 (Ib, A)

- Horton: 首先提出100%氧氣之療效
- Kudrow et al:
  - N=50
  - O2 mask, 7 L/min: 在15分鐘內有82%的發作得到緩解
  - 62%的發作在最初的7分鐘內得到緩解
  - 8-10分鐘與10-15分鐘的緩解率分別為31%與7%
- Forgan et al:
  - N=19, double-blind, cross-over
  - 非再吸式面罩 (NRB), 6 L/min, 15分鐘內, 56%的發作緩解，而吸入空氣的對照組僅7%

氧氣

- Cohen et al:
  - N=109 (病人), n=298 (發作)
  - NRB, 12 L/min 純氧治療
  - 78%的發作可以在15分鐘內達到頭痛停止
  - 對照組僅20%
- Lin KH, et al:
  - 71%病人自行報告使用高流速純氧可使頭痛緩解
- Rozen et al:
  - N=1134 (病人), 70%肯定氧氣的治療效果, 不因年紀、性別、是否抽菸、每日發作頻率等而有差別
  - 陣發 vs. 慢性叢發性頭痛: 73% vs. 62%
  - 52%報告當合併使用triptans, 頭痛於20分鐘內停止

氧氣

- NRB, 7-12 L/min, 連續使用15分鐘以上
  - 越早使用, 效果越好
  - 25%使用純氧治療, 頭痛並未消失, 而是延遲幾分鐘到幾個小時候再度發作
    - 純氧的使用須限制, 否則頭痛發生的頻率會增加
  - 無明顯副作用
  - 但非隨處可得, 限制臨床使用上的可行性
- 高壓氧: 無療效

Triptans

- 血清張力素 (Serotonin, 5-HT) 1B/1D接受器的活化劑
  - Sumatriptan, Imigran®
    - Fast-disintegrating/rapid-release tablet
    - Nasal spray
  - Rizatriptan, Migoff®
  - 健保只給付於急性偏頭痛治療

Sumatriptan

– Sumatriptan 6 mg sc (Ib, A)

- 在兩個隨機雙盲對照試驗, 一共173位病人, 10分鐘內能使36-49%病患頭痛明顯緩解 (至自訴僅輕微頭痛) 或消失, 而15分鐘內達此效果的高達74-75%
- 有兩個大型open-label 研究, 在分別為3個月與1年的急性叢發性頭痛治療追蹤中, 共計138位病人6353次與52位病人2031次從發性發作, 在15分鐘內達到頭痛緩解的比率分別為96%與88%, 且每日使用並無rebound或藥效減退
- 副作用與急性偏頭痛長期使用研究中相似
- 15分鐘達到頭痛完全停止, 慢性vs.陣發: 60% vs. 72.9%
- 台灣無此劑型

Sumatriptan

- Nasal-spray, 20 mg (Ib, A)
  - 一隨機雙盲對照研究, 118位病患, 154次發作, 77次以sumatriptan鼻噴劑20 mg治療, 30分鐘內能使57%的發作達到頭痛緩解, 46%達到頭痛停止, 治療效果明顯優於對照組 (27%緩解, 18%停止)
  - 較皮下注射效果差
  - 建議 20 mg, 24小時最大劑量40 mg

Sumatriptan

- Sumatriptan tablet (III, C)
  - 無設計良好的對照研究
  - Lin et al:
    - 49位病患, 叢發性頭痛發作時使用sumatriptan錠劑50 mg, 高達80%病患頭痛有效緩解
  - Shurks et al:
    - 78位病患 (? dose), 有42.3%頭痛有效緩解
  - 建議劑量 (單次發作): 50-100 mg, 24小時內最大劑量為300 mg
  - 副作用: 噁心、嘔吐、頭暈、倦怠、嗜睡、胸口與頸部緊繃或疼痛、軀幹或四肢感覺異常, 與劑量有關; 不可並用ergot

Ergot Derivatives (III, C)

- 作用於 serotonin 1B/1D receptor, not as specific as triptans.
- Horton in an open-label study: oral ergotamine 1mg/caffeine 100mg in acute attack of cluster HA, 71% (10/14) significantly improved.
- Kudrow: 50 pts, sublingual ergotamine reached 70% remission within 15 minutes.
- Graham et al: good response by ergotamine inhalation.
- Horton, Friedman: relieved by IV DHE in acute attack of cluster HA.

Ergot Derivatives (III, C)

- So far, no well-desinged controlled trial has proved good efficacy of ergotamine in acute attack of cluster HA.
- Oral ergotamine and DHE: slow onset and instability of absorption.
- Not available in Taiwan: sublingual, IN, IV DHE
- Adverse effect: nausea/vomiting, diarrhea, weakness, bradycardia , risk of CAD and CVD.

其他急性治療

- Analgesics: 21% remission in a 60 pts, open-label study.
- Lidocaine (IIa, C)

- 4-10% lidocaine rinsed cotton ball in pterygopalatine fossa, head extend 45^{o} and turn 30^{o} to 40^{o} to headache site: mild to moderate remission.
- Costa et al *(Cephalagia 2000)*: 15 pts, drugs in nasal cavity near sphnopalatine fossa, to compare duration of hedache: 10% lidocaine (31.3 mins), vs. 10% cocaine hydrochloride (37.3 mins), normal saline (59.3 mins).→ onset of effect too late, uncomfortable.

其他急性治療

- Octreotide (Ib, B)

1. Synthetic somatostatin analogue.
2. Sicuteri et al*(Pain, 1984):* IV. and SC. Somatostain rapidly relieve cluster headache.
3. Matharu et al*(Ann Neurol 2004)*: 57 pts by subcutaneous octreotide 100 *u*g vs. control : 52% vs. 36% of remission within 30 minutes.

預防治療

Transitional prophylaxis

- Corticosteroid (III C)

- No large, double blind RCT to prove its effect.
- Some small double blind controlled trial or open-label studies: oral prednisolone (10-80 mg/d) relieved or terminated acute attack of cluster hedache. 79% rebound HA when tapering drug.
- IV. Bolus methylprdnisolone (30mg/kg) for 3 hrs, daily frequency of headache within 7 days.
- Recommendation: oral prednisone from 1mg/Kg/d, max <= 100 mg, then taper 10 mg daily from 6th day. *(Eur J Neurol 2006;13:1066-1077)*
- Short term use!, as risk of femoral head necrosis.

Ergot Derivatives (III, C)

- Marther et al :

Methods: 23 ECH, 31 CCH pts, admitted with repetitive IV. DHE

Results: 22 (34%) HA free by 2nd hospitalized day.

> 90% HA free by day 3.

All HA free by day 5.

At 3 months after discharge, > 90% of ECH and 44% of CCH pts headache free.

Headache 1991;31: 525-532

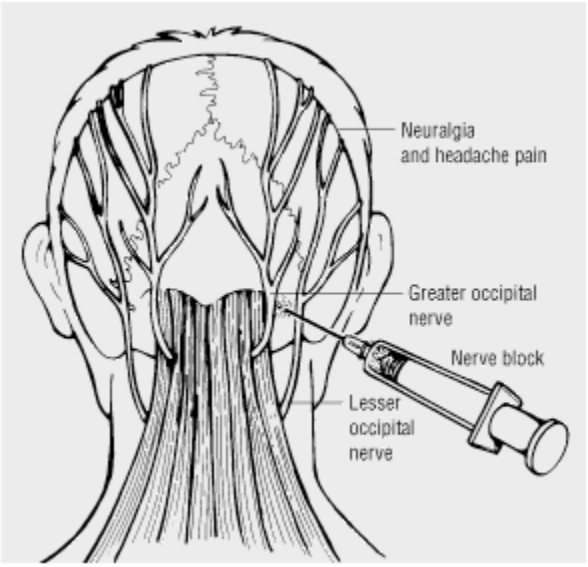
Ergot Derivatives (III, C)

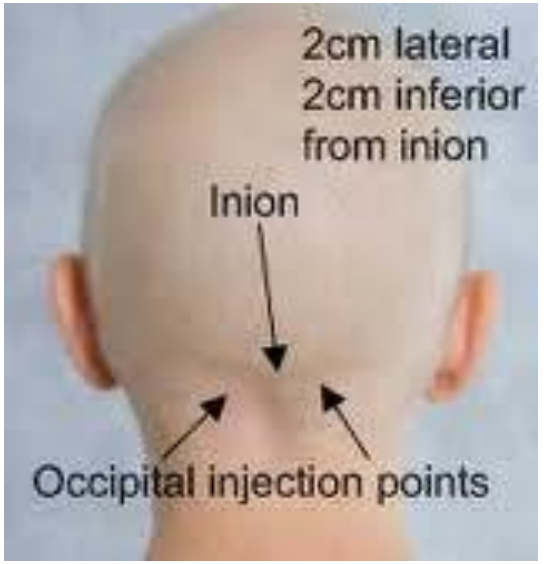
- As risk of ergotamine overuse and adverse effect, not recommended in longterm prophylaxis.
- Halker: ergotamine 3-4 mg/day in divided dose for 2-3 wks for transitional prophylaxis. Administration just before bedtime (2 mg hs) may prevent nighttime attacks.

Semin Neurol. 2010;30:175-185

Greater occipital nerve blockade (IIa, B)

Figure 3. Occipital nerve block. Via a needle inserted at the base of the skull, an anesthetic agent is injected around the origin of the greater occipital nerve.





Greater occipital nerve blockade (IIa, B)

Table 1 Age, gender, temporal pattern, clinical response, number of headache-free days after the greater occipital nerve block, mean intensity, frequency and duration before and 1 week after the block

	Age	Gender	Temporal pattern	Headache-free days after	Response	Intensity before	Intensity after	Frequency before	Frequency (attacks/day) after	Duration before	Duration after
1	30	M	E	0	N	10	10	2	2	60	60
2	68	M	E	21 out of cycle	G	8	0	2	0	45	0
3	47	F	C	0	N	10	7	3	2	40	20
4	52	M	C	70	G	8	0	1	0	30	0
5	65	M	E	14 out of cycle	G	10	0	2	0	15	0
6	29	M	E	0	N	10	10	4	4	40	40
7	33	M	E	2	M	10	7	4	2	45	20
8	40	M	E	2	M	9	0	2	0*	45	0
9	36	M	E	4	M	9	6	3	1	90	60
10	53	F	C	0	N	10	6	5	1	60	60
11	40	M	C	3	M	8	5	5	1	45	15
12	38	M	C	64	G	9	0	6	0	60	0
13	69	M	E	4	M	6	0	2	0*	45	0
14	55	M	E	0	N	10	10	3	3	60	60
Mean ±SD				13.1 ±23.6		9.1 ±1.2	4.3±4.2	3.1±1.4	1.1±1.3	48.5±17.3	23.9±26.3
P-value							0.003		0.003		0.005

E, Episodic; C, chronic; G, good; M, moderate; N, none.
*Patients 8 and 13 had only one attack, 3 and 5 days after the blockade, respectively.

Cephalagia 2002:22:520-522

Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: A double-blind placebo-controlled study

- Methods:

injection with betamethasone (n=13)

injection with normal saline (n=10)

- Results:

11 verum –group pts (3 CCH, 85%) reached attack free in first week after injection.

None had attack free in placebo group (P=0.0001)

8 remained attack free for 4 wks (P=0.0026)

Pain 2005; 118:92-96

Greater occipital nerve blockade (IIa, B)

- Longterm prophylactic effect is still unclear.

Triptans (IIb, D)

- multinational, multicenter, randomized, double-blind, placebo-controlled study in 169 patients with cluster HA.
- Oral sumatriptan 100 mg tid vs. placebo for 1 week.
- Results: did not produce a significant reduction in the number or severity of cluster headache attacks during an established cluster headache period.

Headache 1995;35: 607-613

維持預防治療

Verapamil (Ib, A)

- In episodic CH pts,

  verapamil 120 mg tid (N=15) vs.

  Placebo tid (N=15) x 2 weeks

  Results: verapamil group significantly reduce in attack frequency and abortive agent consumption . Headache intensity decreased > 50% in 80% of pts.

neurology 2000; 54:1382-1385

- Double blind comparison of verapamil 360 mg/d, vs. lithium 900 mg/d x 8 weeks, both were effective in prophylaxis. But verapamil onset earlier and had less adverse effect.
- In Taiwan, 89 episodic CH treated by verapamil got headache remission within 2 months.

Headache 1990; 30:411-417
Cephalagia 2004: 24: 631-638

Verapamil (Ib, A)

- Recommendation:

1. verapamil can combine prednisolone and ergotamine for short term use in prevention of CH.
2. usual dose 240-480 mg/d. Starts from 80 mg tid and gradually titrate per 10-14 days.

Headache 2007; 47:969-980

Lithium (Ib, B)

- Clinical use: cyclic affective disorder, bipolar disorder.
- CH has similar periodic clusters.
- In 19 CH pts treated by lithium with serum level 0.7-1.2 mmol/l. All of 8 CCH pts had immediate partial remission . Headache index improved by 83.5% in 2 week.

In 11 ECH pts, 4 had complete suppression of cluster periods. Overall 63% (12/19) effectiveness.

Headache 1981;21:132-139

Lithium (Ib, B)

- Steiner et al: double-blind controlled trial showed no significance with placebo in 27 episodic CH pts.
- Manzoni et al: 18 chronic CH pts got remission period for 4 years treated by lithium 600-1200 mg/d.

Cephalagia 1997; 17: 673-675

Cephalagia 1983; 3: 109-114

Lithium (Ib, B)

- Comment:

1. Lithium has better response in chronic CH than episodic CH.
2. narrow therapeutic level: 0.6-1.2 mmol/l.
3. many adverse effects: nausea, vomiting, weakness, tremor, ataxia, disorientation and extrapyramidal symptom.

Melatonin (IIa, B)

- Screted by pineal gland, modulated by supraoptic nuclues of hypothalamus.
- Diurnal change of concentration by gene and environmental factors.
- Serum melatonin level decreased in attack period.

Antiepileptic drugs

- Valproic acid: undetermined role in prophylaxis.
- Gabapentin:

- gabapentin started 300 mg/d and titrate to 900 mg/d, all 12 CCH pts headache remission within 8 days.
- another gabapentin study for 8 pts, 6 of them (75%) remission in 4 months. But dose was as high as 2700 mg/d.

Melatonin (IIa, B)

- A double-blind pilot study of 18 ECH and 2 CCH, daily attack frequency and intensity reduced in melatonin 10 mg vs. placebo.
- A pilot add on therapy of melatonin in 6 CCH and 3 ECH for 1 month, days of headache had no significance in both group.

Cehpalagia 1996; 16: 494-496

Headache 2002; 42:787-792

Topiramate (III, C)

- Two studies with sample 10 and 26 pts, topiramate 25-200 mg/d for 1-4 weeks, 58-90% pts stop period clusters.
- One open label study for 33 pts by topiramate 50-200 mg/d, only 21% of pts headache frequency reduction > 50%.
- In Taiwan, 13 pts by 100-400 mg/d, 77% shorten cluster period. 1 CCH needed 400 mg/d for remission.

Surgical intervention

- Radiofrequency block of sphenopalatine ganglion.
- Percutaneous radiofrequency rhizotomy.
- Trigeminal nerve section.
- Gamma knife radiosurgery.
- Diverse effect in all, and potential risk of side effect.

藥物種類	在叢發性頭痛治療中的注意事項	推薦等級	證據等級*	臨床療效**
急性治療藥物				
純氧以非再吸式面罩使用 Oxygen with Non-rebreathing mask	急診與門診使用，注意使用次數，流速須達7-12 L/min，連續15分鐘以上	A	Ib	+++
Triptans	#腦血管疾病、冠狀動脈疾患、高血壓控制不良、肝腎衰竭、雷諾氏症或正處於懷孕或哺乳狀態的婦女，都不適合使用			
Sumatriptan (sc)		A	Ib	+++
Sumatriptan (in)		A	Ib	++
Sumatriptan (po)		C	III	+～++
Ergotamine tartrate (po)	#同上			
	#同時使用心血管藥物和過度使用麥角胺，會增加缺血機會	C	III	++
Lidocaine (in)	#執行此治療步驟常引起病患更加的不舒服	C	IIa	+～+++
Octreotide (sc)		B	Ib	++
過渡預防藥物				
Prednisolone (po)	#僅建議短期使用 #可能增加股骨頭壞死的危險性	C	III	+++
Ergotamine tartrate (po)	#同時使用心血管藥物和過度使用麥角胺，會增加缺血機會	C	III	++
大枕神經阻斷(Greater occipital nerve blockade)	#少數人有禿頭與皮膚萎縮的情形	B	IIa	++～+++
維持預防藥物				
Verapamil	#房室阻斷或心跳過慢的情形	A	Ib	+++
Lithium	#注意無力、噁心、顫抖、視力模糊、白血球增加、神智不清、步態不穩、眼震、外椎體路徑症狀、癲癇	B	Ib	+++
Melatonin		B	IIa	++
Antiepileptic Drugs Valproic acidand derivatives	#掉頭髮、肥胖、顫抖、噁心、嘔吐、嗜睡、肝功能異常。較少見的有胰臟炎與血小板缺乏	C	IV	0～+
Gabapentin	#頭昏，嗜睡與周邊水腫	C	IV	+～++
Topiramate	#頭昏、疲倦、食慾不振、噁心、感覺異常、味覺異	C	III	+～++

Acta Neurologica Taiwanica,20:227, 2011

Summary : treatment of CH according to clinical practice in Taiwan

- Acute (terminating) treatment

  - 1st choice: high flow O_2 or nasal spray triptans.

  - 2nd choice: oral triptans.

- Prophylactic treatment

  - can combine transitional (eg. Steroids) and maintenance prophylaxis (eg. Verapamil). Verapamil should be gradually titrated to avoid adverse effect and tolerance.

  - If maintenance drugs exert effect, slowly stop transitional medication.

  - avoid steriods use >2weeks.

  - gradually taper and stop maintenance drug when cluster bouts cease.