Profylaktisk behandling av cluster hodepine

Notat
Litteratursøk med sortering
September 2009

kunnskapssenteret

Bakgrunn: Dette litteratursøket er utført på oppdrag fra Helseøkonomiforvaltningen HELFO. Bestillingen var en oversikt over studier av den forebyggende effekten av prednisolon og andre steroider, og av verapamil, på cluster hodepine. **Metode:** Vi søkte systematisk i internasjonale vitenskapelige databaser etter systematiske oversiktsartikler, randomiserte kontrollerte studier (RCTer) og observasjonsstudier som undersøkte nytten av de aktuelle legemidlene. **Resultat:** Søkeresultatet var 204 unike referanser som vi gikk gjennom sammendragene til. Vi vurderte 17 publikasjoner som relevante for bestillingen. Publikasjonene ble kategorisert etter type legemiddel og studiedesign.

Nasjonalt kunnskapssenter for helsetjenesten
Postboks 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
Notat: ISBN 978-82-1821-289-3

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Nasjonalt kunnskapssenter for helsetjenesten

Tittel	Profylaktisk behandling av cluster hodepine - litteratursøk
Institusjon	Nasjonalt kunnskapssenter for helsetjenesten
Ansvarlig	John-Arne Røttingen, *direktør*
Forfattere	Hege Kornør, Ingrid Harboe, Kristin Kamilla Linnestad, Marianne Klemp
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Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Senteret er formelt et forvaltningsorgan under Sosial- og helsedirektoratet, uten myndighetsfunksjoner. Kunnskapssenteret kan ikke instrueres i faglige spørsmål.

Nasjonalt kunnskapssenter for helsetjenesten
Oslo, august 2009

Oppsummering

Dette litteratursøket er utført på oppdrag fra Helseøkonomiforvaltningen HELFO. Bestillingen var en oversikt over studier av den forebyggende effekten av prednisolon og andre steroider, og av verapamil, på cluster hodepine.

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Forord

Nasjonalt kunnskapssenter for helsetjenesten fikk den 22. juni 2009 i oppdrag fra Helseøkonomiforvaltningen HELFO å levere en oversikt over studier av den forebyggende effekten av prednisolon og andre steroider, og av verapamil, på cluster hodepine.

Når vi bruker forskning som beslutningsgrunnlag, bør vi ta utgangspunkt i tilgjengelig forskning av høyest mulig kvalitet. Studiedesign, utførelse og analyser påvirker vår tillit til studienes resultat. I denne rapporten har vi ikke vurdert inkluderte studier med henblikk på metodisk kvalitet. I vedlegg til Kunnskapssenterets håndbok "Slik oppsummerer vi forskning" finnes det sjekklister som kan brukes til å vurdere kvaliteten av ulike typer studier. Sjekklistene kan være gode hjelpemidler i det videre arbeidet med å ta stilling til forskningens verdi, gyldighet og overførbarhet. Håndboken er tilgjengelig på www.kunnskapssenteret.no/Verktoy/2139.cms.

Gro Jamtvedt	Marianne Klemp	Hege Kornør
Avdelingsdirektør	*Forskningsleder*	*Seniorforsker*

Bakgrunn/problemstilling

HELFO mottar søknader om individuell refusjon på blå resept for personer som får profylaktisk behandling med prednisolon, andre steroider eller verapamil. Saksbehandlerne ved HELFO kjenner imidlertid ikke til dokumentasjon som er god nok til å støtte denne type behandling. Den dokumentasjonen de kjenner til er en systematisk oversikt i Clinical Evidence (1) som refererer til en tidligere publisert systematisk oversikt med litteratursøk fra 1998 (2). Clinical Evidence-oversikten konkluderer med at steroider og verapamil muligens har en forebyggende effekt på cluster hodepine, men effekten er usikker. Dokumentasjonen fra Clinical Evidence har ikke tatt med andre studiedesign enn systematiske oversikter og randomiserte kontrollerte studier (RCTer), og er basert på et litteratursøk fra september 2006. Det kan hende at relevante studier er publisert de siste årene, og at det fins observasjonsstudier som er gode nok til å dokumentere en eventuell forebyggende effekt.

Problemstillingene for dette litteratursøket er:

- Kan prednisolon forebygge framtidige anfall hos personer med cluster hodepine?
- Kan andre steroider forebygge framtidige anfall hos personer med cluster hodepine?
- Kan verapamil forebygge framtidige anfall hos personer med cluster hodepine?

Innledning

Cluster hodepine er en tilstand som kjennetegnes av sterke smerteanfall på den ene siden av hodet, lokalisert rundt øyehulen og i tinningen (1). Smerteanfallene opptrer i serier som varer i uker eller måneder, avbrutt av smertefrie perioder på måneder eller år. Tilstanden rammer ca én av 500, og forekommer oftere hos menn enn hos kvinner.

Det fins to tilnærminger for behandling av cluster hodepine: smertelindring ved akutte anfall og forebygging av framtidige smerteanfall (1). Blant legemidler brukt som forebyggende intervensjoner har vi lithium, steroider, verapamil, baklofen, klorpromasin, ergotamin/dihydroergotamin, gabapentin, leuprolid, melatonin, metysergid, pizotifen, valproinsyre, sumatriptan, topiramat, trisykliske antidepressiver, betametason og xylokain (nerveinjeksjoner), botulinumtoksin (intramuskulære injeksjoner), capsaicin (nesespray), civamid (nesedråper) og klonidinplaster (1).

Verapamil, som er et av legemidlene i fokus for dette litteratusøket, er en selektiv kalsiumantagonist med direkte virkning på hjertet (3). Preparatet brukes hovedsakelig i behandling av angina pectoris, hypertensjon og hjertearytmier. Prednisolon og de andre steroidene, eller glukokortikoidene, har sterke betennelsesdempende og immunsuppressive egenskaper.

Metode

LITTERATURSØK

En forskningsbibliotekar utførte et systematisk litteratursøk i følgende databaser: Ovid MEDLINE, Ovid EMBASE, Ovid PsycInfo, ISI Web of Knowledge, Cochrane Library og Centre for Reviews and Dissemination (CRD).
Litteratursøket ble utarbeidet i henhold til forhåndsdefinerte inklusjonskriterier. Se vedlegg 1 for søkestrategi.

INKLUSJONSKRITERIER

Publikasjoner som oppfylte følgende kriterier ble inkludert:

Populasjon	personer med episodisk eller kronisk cluster hodepine
Intervensjon	prednisolon, andre steroider (glukokortikoider), verapamil
Sammenlikning	andre legemidler eller placebo
Studiedesign	systematiske oversikter, randomiserte og ikke-randomiserte kontrollerte studier, observasjonsstudier

UTVELGELSE OG SORTERING

To prosjektmedarbeidere gjennomgikk søkeresultatene uavhengig av hverandre. Referansene ble utvalgt på bakgrunn av artiklenes sammendrag og i henhold til inklusjonskriteriene. Der hvor sammendrag manglet, ble referansene inkludert hvis tittel var relevant. Referansene ble sortert etter type legemiddel og studiedesign. Utover dette gjorde vi ingen vurderinger eller analyser av innholdet i studiene. Publikasjonene ble presentert med referanser og sammendrag kopiert fra databasene hvor de ble identifisert. De ble ikke innhentet eller lest i fulltekst.

Resultater

Søket identifiserte 204 unike referanser (268 før dublettkontroll). Vi vurderte 17 publikasjoner som relevante. Fem av publikasjonene handlet om steroider (4-8), sju om verapamil (9-15) og fem om både steroider og verapamil (16-21). Se vedlegg 2 for sammendrag av publikasjonene.

Vi fant to oversiktsartikler, to RCTer og én observasjonsstudie om steroider (tabell 1). Prednisolon var ikke nevnt i noen av sammendragene. Type steroid var uspesifisert i den ene oversiktsartikkelen, mens den andre omtalte prednison. Den ene RCTen brukte prednison som intervensjon, den andre brukte betametason og observasjonsstudien brukte metylprednisolon og prednison.

Tabell 1 Inkluderte publikasjoner om steroider

Førsteforfatter og år	Studiedesign	Type steroid	Sammenlikning
Ailani 2009 (4)	oversikt	uspesifisert	botulinumtoksin
Diener 2006 (6)	oversikt	prednison	migrenemidler
Ambrosini 2005 (5)	RCT	betametason	placebo
Mir 2003 (8)	kohort	metyleprednisolon + prednison	Annen behandling
Jammes 1975 (7)	RCT	prednison	placebo

Blant verapamilpublikasjonene fant vi to oversiktsartikler, tre RCTer og to observasjonsstudier. Begge oversiktsartiklene nevnte varapamil som ett av flere aktuelle legemidler i forebyggende behandling av cluster hodepine. Den ene RCTen var en placebokontrollert studie med verapamil som intervensjon. De to andre RCTene brukte verapamil som sammenlikning med henholdsvis lithium og andre kalsiumblokkere. Den ene observasjonsstudien sammenliknet tidlig igangsetting av verapamilbehandling med sen oppstart, mens den andre sammenliknet verapamil med steroider.

Tabell 2 Inkluderte publikasjoner om verapamil

Førsteforfatter og år	Studiedesign	Sammenlikning
Cohen 2007 (10)	oversikt	oksygen, sumatriptan
Valade 2007 (15)	oversikt	Lithium, topiramat
Schurks 2006 (13)	kohort	steroider
Stallmach 2003 (14)	kohort	tidlig vs sen
Leone 2000 (11)	RCT	placebo

Førsteforfatter og år	Studiedesign	Sammenlikning
Bussone 1990 (9)	RCT	lithium
Meyer 1983 (12)	RCT	nimodipin, nifedipin

Fem oversiktsartikler omhandlet forebyggende behandling med forskjellige legemidler, inkludert steroider og verapamil: Dodick 2003 (16), Ekbom 1995 (17), Jürgens 2009 (18), Leroux 2008 (19) og Matharu 2008 (20).

Diskusjon

De 17 inkluderte publikasjonene fra dette litteratursøket er kun valgt ut etter gjennomgang av sammendrag, og i noen tilfeller kun titler. Denne metoden har sine svakheter. Ettersom vi kun har inkludert publikasjoner hvor det klart gikk fram av sammendrag og/eller tittel at steroider eller verapamil spesifikt var brukt i studien, kan vi ha ekskludert relevante publikasjoner.

Ett av inklusjonskriteriene våre var at studien skulle være en systematisk oversikt, en RCT eller en observasjonsstudie. Når det gjelder de inkluderte oversiktsartiklene har ikke sammendragene inneholdt nok informasjon til å vurdere hvorvidt de var systematiske oversikter. Vi har derfor valgt å bruke ”oversiktsartikkel” i stedet for ”systematisk oversikt”, som forutsetter at visse metodiske prinsipper er fulgt.

KONKLUSJON

Oppdragsgiver for dette litteratursøket, HELFO, kjente allerede til den systematiske oversikten i Clinical Evidence fra 2008 (20), og hadde i grunnen som hensikt med bestillingen å identifisere eventuelle nyere RCTer og gode observasjonsstudier som kan dokumentere den forebyggende effekten av steroider og verapamil på cluster hodepine. Det ser ikke ut til at vi har lykkes i å identifisere slike studier, slik at Clinical Evidence-oversikten er det beste og mest oppdaterte dokumentasjonsgrunnlaget som foreligger.

Referanser

(1) Matharu M, Silver N. Cluster headache. Clinical Evicence 2008; 02(1212).

(2) May A, Leone M, Afra J, Linde M, Sandor PS, Evers S et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. European Journal of Neurology 2006; 13(10):1066-1077.

(3) Statens legemiddelverk. Preparatomtale Verakard. http://www.legemiddelverket.no/custom/Preparatsok/prepSearch___80333.aspx?SearchID=cc01541c-5bcf-4495-81b0-66dd34a0966d . 2009. 31-8-2009.

(4) Ailani J, Young WB. The role of nerve blocks and botulinum toxin injections in the management of cluster headaches. Current Pain and Headache Reports 2009; 13(2):164-167.

(5) Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 2005; 118(1-2):92-96.

(6) Diener H-C, Katsarava Z, Gendolla A. What is new in headache 2004/2005? Aktuelle Neurologie 2006; 33(1):3-10.

(7) Jammes JL. The treatment of cluster headaches with prednisone. Dis Nerv Syst 1975; 36(7):375-376.

(8) Mir P, Alberca R, Navarro A, Montes E, Martinez E, Franco E et al. Prophylactic treatment of episodic cluster headache with intravenous bolus of methylprednisolone. Neurological Sciences 2003; 24(5):318-321.

(9) Bussone G, Leone M, Peccarisi C, Micieli G, Granella F, Magri M et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache 1990; 30(7):411-417.

(10) Cohen AS, Matharu MS, Goadsby PJ. Trigeminal autonomic cephalalgias: Current and future treatments. Headache 2007; 47(6):969-980.

(11) Leone M, D'Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology 2000; 54(6):1382-1385.

(12) Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. Headache 1983; 23(6):266-277.

(13) Schurks M, Kurth T, de Jesus J, Jonjic M, Rosskopf D, Diener HC. Cluster headache: clinical presentation, lifestyle features, and medical treatment. Headache 2006; 46(8):1246-1254.

(14) Stallmach M. [Prophylactic treatment of cluster headache with verapamil]. Praxis 2003; 92(46):1951-1953.

(15) Valade D. Clinical description and treatment of cluster headache. Sang Thrombose Vaisseaux 2007; 19(6):311-317.

(16) Dodick DW, Saper J. Cluster and chronic daily headache. Neurology 2003; 60(7 SUPPL. 2):S31-S37.

(17) Ekbom K. Treatment of cluster headache: clinical trials, design and results. Cephalalgia 1995; 15(suppl. 15):33-36.

(18) Jurgens TP, Schaefer C, May A. Treatment of cluster headache in pregnancy and lactation. Cephalalgia 2009; 29(4):391-400.

(19) Leroux E, Ducros A. Cluster headache. Orphanet Journal of Rare Diseases 2008; 3.

(20) Matharu M, Silver N. Cluster headache. Clinical Evidence 2008; 2008, 2008.

(21) Pradalier A, Baudesson G, Vincent D, Imberty-Campinos C. Treatment of the cluster headache. Rev Med Interne 2001; 22(2):151-162.

Vedlegg 1: søkestrategi

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present

#	Searches	Results
1	Cluster Headache/	2184
2	cluster headache*.tw.	2272
3	or/1-2	2761
4	exp Verapamil/	15891
5	verapamil*.tw.	18810
6	exp Steroids/	614027
7	(prednisolon* or prednison*).tw.	33297
8	(corticosteroid* or glucocorticoid* or steroid*).tw.	232032
9	or/4-8	762674
10	3 and 9	282
11	limit 10 to "reviews (specificity)"	3
12	randomized controlled trial.pt. [filter: RCT]	278504
13	controlled clinical trial.pt.	80262
14	randomized.ab.	194965
15	placebo.ab.	117901
16	clinical trials as topic.sh.	145561
17	randomly.ab.	143935
18	trial.ti.	84500
19	12 or 13 or 14 or 15 or 16 or 17 or 18	664944
20	humans.sh.	10934717
21	19 and 20	586121
22	10 and 21	24
23	Epidemiologic studies/ [filter: Observasjonsstud.]	4556
24	exp case control studies/	438018
25	exp cohort studies/	730674

26	case control.tw.	49017
27	(cohort adj (study or studies)).tw.	44353
28	cohort analy$.tw.	2141
29	(follow up adj (study or studies)).tw.	30069
30	(observational adj (study or studies)).tw.	22191
31	longitudinal.tw.	93000
32	retrospective.tw.	174066
33	cross sectional.tw.	95693
34	Cross-sectional studies/	103083
35	or/23-34	1313826
36	case reports.pt.	1440769
37	comment.pt.	413489
38	letter.pt.	677659
39	editorial.pt.	252875
40	animal/	4462674
41	human/	10934717
42	40 not (40 and 41)	3335973
43	or/36-39,42	5583342
44	35 not 43	1175702
45	10 and 44	24
46	or/11,22,45	48

EMBASE 1980 to 2009 Week 32

#	Searches	Results
1	exp Cluster headache/	2435
2	cluster headache*.tw.	1821
3	or/1-2	2642
4	exp Verapamil/	37756
5	verapamil*.tw.	17978
6	exp Steroid/	620633
7	(prednisolon* or prednison*).tw.	26856
8	(corticosteroid* or glucocorticoid* or steroid*).tw.	189976
9	or/4-8	705677
10	3 and 9	768

11 Clinical Trial/ [Filter: RCT]	551097
12 Randomized Controlled Trial/	172175
13 Randomization/	26979
14 Double Blind Procedure/	73566
15 Single Blind Procedure/	8418
16 Crossover Procedure/	21622
17 PLACEBO/	129835
18 placebo$.tw.	112353
19 randomi?ed controlled trial$.tw.	34431
20 rct.tw.	2869
21 random allocation.tw.	643
22 randomly allocated.tw.	10424
23 allocated randomly.tw.	1361
24 (allocated adj2 random).tw.	563
25 single blind$.tw.	7627
26 double blind$.tw.	86280
27 ((treble or triple) adj blind$).tw.	141
28 Prospective study/	84348
29 or/11-28	723592
30 Case study/	6264
31 case report.tw.	121873
32 Abstract report/	71205
33 Letter/	435728
34 Human/	6578853
35 Nonhuman/	3265067
36 ANIMAL/	18283
37 Animal Experiment/	1308662
38 35 or 36 or 37	3500786
39 38 not (34 and 38)	2947821
40 or/30-33,39	3525814
41 29 not 40	681718
42 10 and 41 [RCT]	156
43 Clinical study/ [Filter: Observasjonsstud.]	18426
44 case control study/	20647

45	Family study/	8224
46	Longitudinal study/	20107
47	Retrospective study/	103015
48	Prospective study/	84348
49	Randomized controlled trials/	172175
50	48 not 49	73678
51	Cohort analysis/	55868
52	(Cohort adj (study or studies)).tw.	38164
53	(Case control adj (study or studies)).tw.	35572
54	(follow up adj (study or studies)).tw.	23088
55	(observational adj (study or studies)).tw.	19443
56	(epidemiologic$ adj (study or studies)).tw.	35910
57	(cross sectional adj (study or studies)).tw.	27208
58	or/43-47,50-57	393989
59	10 and 58 [Observasjonsstudier]	31
60	limit 10 to "(reviews (2 or more terms high specificity)"	3

PsycINFO 1987 to August Week 2 2009

#	Searches	Results
1	cluster headache*.tw.	294
2	verapamil/	94
3	verapamil*.tw.	238
4	exp steroids/	9301
5	(prednisolon* or prednison*).tw.	267
6	(corticosteroid* or glucocorticoid* or steroid*).tw.	6624
7	or/2-6	13345
8	1 and 7	19
9	empirical methods/ [Filter: RCT]	1879
10	Experimental methods/	4334
11	Quasi experimental methods/	51
12	experimental design/	4819
13	between groups design/	96
14	followup studies/	9083
15	repeated measures/	405

16	experiment controls/	374
17	experimental replication/	2146
18	exp "sampling (experimental)"/	1402
19	placebo/	1930
20	clinical trials/	3111
21	treatment effectiveness evaluation/	8741
22	experimental replication.md.	4396
23	followup study.md.	28011
24	prospective study.md.	10054
25	treatment outcome clinical trial.md.	14679
26	placebo$.tw.	18048
27	randomi?ed controlled trial$.tw.	6333
28	rct.tw.	685
29	random allocation.tw.	88
30	(randomly adj1 allocated).tw.	997
31	(allocated adj2 random).tw.	33
32	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	11171
33	(clinic$ adj (trial? or stud$3)).tw.	14428
34	or/9-33	100091
35	comment reply.dt.	57642
36	editorial.dt.	14125
37	letter.dt.	8343
38	clinical case study.md.	33783
39	nonclinical case study.md.	10197
40	animal.po.	146263
41	human.po.	1605172
42	40 not (40 and 41)	135055
43	or/35-39,42	253051
44	34 not 43	91978
45	8 and 44	2
46	meta analysis/ [Filter: SR]	2654
47	(metaanaly$ or (meta adj analy$)).tw.	10023
48	((systematic or comprehensive or literature or quantitative or critical or integrative or evidence$) adj2 (review$1 or overview$1)).tw.	35672

49	literature study.tw.	126
50	(critical adj (appraisal or analysis)).tw.	2240
51	"literature review"/	10911
52	Meta Analysis.md.	6705
53	literature review.md.	54597
54	(cochrane or medline or embase or cinahl og cinhal or psychlit or psyclit or science citation index or bids or cancerlit).ab.	4291
55	reference list$.ab.	670
56	bibliograph$.ab.	3312
57	(handsearch$ or hand search$).ab.	307
58	relevant journals.ab.	55
59	manual search$.ab.	217
60	data extraction.ab.	275
61	selection criteria.ab.	893
62	or/46-61	85982
63	comment reply.dt.	57642
64	editorial.dt.	14125
65	letter.dt.	8343
66	nonclinical case study.md.	10197
67	clinical case study.md.	33783
68	animal.po.	146263
69	human.po.	1605172
70	68 not (68 and 69)	135055
71	or/63-67,70	253051
72	62 not 71	79600
73	8 and 72	2
74	(Cohort adj (study or studies)).tw. [Observ.stud]	4028
75	(Case control adj (study or studies)).tw.	2132
76	(follow up adj (study or studies)).tw.	5325
77	(observational adj (study or studies)).tw.	2223
78	(epidemiologic$ adj (study or studies)).tw.	5788
79	(cross sectional adj (study or studies)).tw.	4828
80	or/74-79	23616
81	8 and 80	0
82	or/45,73,81	4

ISI Web of Knowledge

Topic=(cluster headache*) AND Topic=(verapamil*) AND Document Type=(Review)

Cochrane Library 13.08.09

#1	MeSH descriptor Cluster Headache explode all trees	51
#2	(cluster headache*):ti,ab,kw	102
#3	(#1 OR #2)	102
#4	MeSH descriptor Verapamil, this term only	985
#5	verapamil*:ti,ab,kw	1692
#6	MeSH descriptor Steroids explode all trees	31055
#7	(prednisolon* or prednison*):ti,ab,kw	6931
#8	(corticosteroid* or glucocorticoid* or steroid*):ti,ab,kw	20751
#9	(#4 OR #5 OR #6 OR #7 OR #8)	47782
#10	(#3 AND #9)	10

CRD

# 1	MeSH Cluster Headache EXPLODE 1	6
# 2	"cluster headache*"	12
# 3	#1 or #2	13
# 4	MeSH Verapamil EXPLODE 1	6
# 5	verapamil*	42
# 6	MeSH Steroids EXPLODE 1	856
# 7	prednisolon* OR prednison* OR corticosteroid* OR glucocorticoid* OR steroid*	1646
# 8	#4 or #5 or #6 or #7	2317
# 9	#3 and #8	2

Vedlegg 2: inkluderte sammendrag

STEROIDER

Oversiktsartikler

1. **Ailani J, Young WB. The role of nerve blocks and botulinum toxin injections in the management of cluster headaches. Current Pain and Headache Reports 2009; 13(2):164-167.**
   Cluster headache (CH) is a primary headache syndrome that is classified with the trigeminal autonomic cephalalgias. CH treatment involves three steps: acute attack management, transitional therapy, and preventive therapy. Greater occipital nerve block has been shown to be an effective alternative bridge therapy to oral steroids in CH. Botulinum toxin type A has recently been studied as a new preventive treatment for patients with chronic CH, with limited success.

2. **Diener H-C, Katsarava Z, Gendolla A. What is new in headache 2004/2005? Aktuelle Neurologie 2006; 33(1):3-10.**
   This is a review about new publications on epidemiology, pathophysiology and therapy of headaches published late 2004 and early 2005. Controversial debates about the potential risk of stroke in migraineurs has been going on for years. The Dutch CAMERA Study showed subclinical infarctions in patients with migraine with aura. Some authors discussed intellectual deficits in migraineurs. A Danish twin study showed no differences in cognitive levels in migrainous or nonmigrainous twins. Migraine with aura as a risk factor for stoke has been proven in the Woman's Health Study (n = 39754) and the incidence of vascular risk factors in patients with migraine with aura might be an explanation for the increase risk for stroke in this group. A new locus coding a neuronal modulating sodium channel on chromosome 2q24 has been identified recently. Headache intensity is the best predictor for headache response. This favours treatment when headache is mild or moderate in patients who can distinguish between tension type headache and migraine. Switching from one triptan to another is useful in non-responders to a certain triptan. There is no teratogenic risk according to pregnancy registers on triptans so far. A new pharmacological formulation of ASA has been shown to be as effective as sumatriptan 50 mg in triptan naive patients. Due to high placebo rates in children and adolescents triptans have failed to reach statistical significance over placebo in this group. Treatment guidelines recommend ibuprofen and sumatriptan nasal spray in this subset of migraineurs. Studies on venlafaxin, coenzyme Q, petasides hybridicus as well as topiramate show prophylactic efficacy while lamotrigine seems to be effective especially in reducing aura symptoms. Sham acupuncture and

acupuncture are equally effective in the treatment of migraine according to the first published large trial. Cluster: Stimulation with ventroposterior electrodes in the hypothalamus remains the last choice in absolute refractory patients. Gamma knife irradiation is not effective. Single high dose treatment regimen with prednisone for prophylaxis of cluster headache is ineffective but maybe short time prophylaxis with single doses of long acting triptans is. Treatment of tension type headache with botulinum toxin is as effective as placebo; results of different studies are awaited.

RCTer

1. **Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 2005; 118(1-2):92-96.**
   Oral steroids can interrupt bouts of cluster headache (CH) attacks, but recurrence is frequent and may lead to steroid-dependency. Suboccipital steroid injection may be an effective 'single shot' alternative, but no placebo-controlled trial is available. The aim of our study was to assess in a double-blind placebo-controlled trial the preventative effect on CH attacks of an ipsilateral steroid injection in the region of the greater occipital nerve. Sixteen episodic (ECH) and seven chronic (CCH) CH outpatients were included. ECH patients were in a new bout since no more than 1 week. After a one-week run-in period, patients were allocated by randomization to the placebo or verum arms and received on the side of attacks a suboccipital injection of a mixture of long- and rapid-acting betamethasone (n=13; Verum-group) or physiological saline (n=10; Plac-group). Acute treatment was allowed at any time, additional preventative therapy if attacks persisted after 1 week. Three investigators performed the injections, while four others, blinded to group allocation, followed the patients. Follow-up visits were after 1 and 4 weeks, whereafter patients were followed routinely. Eleven Verum-group patients (3 CCH) (85%) became attack-free in the first week after the injection compared to none in the Plac-group (P=0.0001). Among them eight remained attack-free for 4 weeks (P=0.0026). Remission lasted between 4 and 26 months in five patients. A single suboccipital steroid injection completely suppresses attacks in more than 80% of CH patients. This effect is maintained for at least 4 weeks in the majority of them.

2. **(4-8)Jammes JL. The treatment of cluster headaches with prednisone. Dis Nerv Syst 1975;36(7):375-6.**
   Nineteen patients obstinate with cluster headaches whose pain was not mitigated by standard treatment (Methysergide, caffeine, ergotamine preparation, phenobarbital and analgesics) underwent a double blind control study with single crossover for the evaluation of prednisone therapy. Compared to placebo, a single oral dose of prednisone in 17 cases produced sustained improvement. Maintenance administration of prednisone was also effective in decreasing the frequency of attacks; however a single dose of the steroid when headaches began was effective.

Observasjonsstudier

1. **Mir P, Alberca R, Navarro A, Montes E, Martinez E, Franco E et al. Prophylactic treatment of episodic cluster headache with intravenous bolus of methylprednisolone. Neurological Sciences 2003; 24(5):318-321.**
   We evaluated the efficacy of intravenous boluses of methylprednisolone followed by prednisone as a prophylactic treatment for episodic cluster headache. Fourteen male patients (mean age, 42.54 years) with episodic cluster headache were treated with 250-mg boluses of methylprednisolone on 3 consecutive days, followed by prednisone (90 mg/day orally) with gradual tapering in four weeks. Headache parameters of the active phases treated with methylprednisolone were compared with those of previous active phases in the same patients treated with other prophylactic medications. The primary efficacy criterion was decrease in the frequency of attacks during the first month of treatment. The statistical differences were calculated using Wilcoxon's test. The attacks were significantly less frequent in the active phases treated with methylprednisolone boluses than those treated with other medications ($p<0.05$). This treatment seems to be more effective than the usual prophylactic treatments for episodic cluster headache.

VERAPAMIL

Oversiktsartikler

1. **Cohen AS, Matharu MS, Goadsby PJ. Trigeminal autonomic cephalalgias: Current and future treatments. Headache 2007; 47(6):969-980.**
   The trigeminal autonomic cephalgias include cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). The evidence for the current treatment options for each of these syndromes is considered, including oxygen, sumatriptan, and verapamil in cluster headache, indomethacin in paroxysmal hemicrania, and intravenous lidocaine and lamotrigine in SUNCT. Some treatments such as topiramate have an effect in all of these, as well as in migraine and other pain syndromes. The involvement of the hypothalamus in functional imaging studies implies that this may be a substrate for targeting treatment options in the future.

2. **Valade D. Clinical description and treatment of cluster headache. Sang Thrombose Vaisseaux 2007; 19(6):311-317.**
   Cluster headaches are attacks of severe, strictly unilateral pain that is orbital or temporal, lasting 15 to 180 minutes and occurring from once every other do to eight times a day. The attacks are associated wit least one of the following : lacrimation, nasal congestion, rhinorrhea and most patients are restless or agitated during an attack. Attacks occur in series of weeks or months (cluster periods) separated by remission periods, usually lasting months or years. Cluster headache is most often episodic but about 10 to 15% are chronic. Acute therapy for cluster headache includes oxygen inhalation and triptans (especially sumatriptan by subcutaneous injection). The aim of prevention is to stop all attacks if possible or at least to bring attacks under control and maintain relief with minimal side effects. Preventive drugs commonly advocated are verapamil, lithium and topiramate. Injection of local anesthetic p

corticosteroid around the greater occipital nerve ipsilateral to the pain has been widely used. Hypothalamic stimulation is reserved to intractable chronic cluster headache.

RCTer

1. **Bussone G, Leone M, Peccarisi C, Micieli G, Granella F, Magri M et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache 1990; 30(7):411-417.**

   Chronic Cluster Headache (CCH) treatment is troublesome; since there are no pain-free periods, it must be continuous. The most effective CCH prophylactic drug today is lithium carbonate but long-term use of this drug is limited by the possibility of side effects. Recently, calcium antagonists have been successfully employed to prevent migraine, and preliminary studies also indicate that verapamil in particular is an efficacious treatment for CCH. We have conducted a multicenter trial employing a double-dummy, double blind, cross-over protocol, comparing verapamil with the established efficacy of lithium carbonate, in preventing CCH attacks. Both lithium carbonate and verapamil were effective in preventing CCH but verapamil caused fewer side effects and had a shorter latency period. We did not observe any correlation between plasma levels of the two drugs and their clinical efficacy. Both the drugs tested here may exert their effect by restoring a normal inhibitory tone to the pain modulating pathways from the trigemino-vascular system, a circuit putatively implicated in CCH.

2. **Leone M, D'Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology 2000; 54(6):1382-1385.**

   The authors performed a double-blind, double-dummy study to compare the efficacy of verapamil with placebo in the prophylaxis of episodic cluster headache. After 5 days' run-in, 15 patients received verapamil (120 mg tid) and 15 received placebo (tid) for 14 days. The authors found a significant reduction in attack frequency and abortive agents consumption in the verapamil group. Side effects were mild. These findings provide objective evidence for the effectiveness of verapamil in episodic cluster headache prophylaxis.

3. **Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. Headache 1983; 23(6):266-277.**

   Since Wolff's original proposal regarding the vascular etiology of cyclic head pain, evidence has accumulated that the prodromes of migraine are due to cerebral vasoconstriction and headaches of both cluster and migraine are due to painful dilatation. Theories regarding their pathogenesis include cyclic release of vasoactive substances from platelets and/or other sources (such as serotonin, catecholamines, histamine, acetyl choline, prostaglandins, substance P, endogenous opiates). These substances influence vasomotor receptors bringing about abnormal constriction and/or dilatation. Drugs which modify receptors (such as methysergide, alpha and beta blockers, antihistaminics, anticholinergics, steroids and non-steroidal anti-inflammatory agents) have had some therapeutic success in migraine but provide little benefit for cluster patients. Casup 2sup + entry blockers (including nimodipine,

nifedipine, verapamil) theoretically should diminish cephalic vaso-constriction and -dilatation no matter what their cause. To test this, 35 headache patients with classic (N = 13), common (N = 14) migraine or cluster (N = 8) was evaluated by double-blind, cross-over, randomized assignment to high or low dose nimodipine therapy. Within 10 days migraine prodromes became infrequent and after 2-4 weeks headache frequency was significantly reduced for migraine and within 4-6 weeks for cluster. CBF measurements during oxygen inhalation showed reduced cerebral vasoconstrictive responses after high dose nimodipine. Associated muscular contraction headaches were not altered. Nifedipine and verapamil provided equivalent relief for cluster but produced more side effects, and were less effective than nimodipine in control of migraine.

Observasjonsstudier

1. **Schurks M, Kurth T, de Jesus J, Jonjic M, Rosskopf D, Diener HC. Cluster headache: clinical presentation, lifestyle features, and medical treatment. Headache 2006; 46(8):1246-1254.**

   BACKGROUND: Cluster headache (CH) is a rare but severe headache form with a distinct clinical presentation. Misdiagnoses and mismanagement among these patients are high. OBJECTIVE: To characterize clinical features and medical treatment in patients with CH. METHODS: We established a cohort of 246 clinic-based and non-clinic-based CH patients. The diagnosis of CH was verified according to International Headache Society (IHS) criteria. We used standardized questionnaires to assess associated factors as well as success or failure of treatments. RESULTS: The majority (75.6%) was not treated before at our clinic-77.6% were males; 74.8% had episodic CH, 16.7% had chronic CH, in the remaining patients, the periodicity was undetermined because they were newly diagnosed. Cranial autonomic features were present in 98.8%, nausea and vomiting in 27.8%, and photophobia or phonophobia in 61.2% of CH patients. Most (67.9%) reported restlessness during attacks and 23% a typical migrainous aura preceding the attacks. The rate of current smoking was high (65.9%). Half of the patients reported that alcohol (red wine in 70%) triggered CH attacks. Eighty-seven percent reported the use of drugs of first choice (triptans 77.6%, oxygen 71.1%) with sumatriptan subcutaneous injection being the most effective drug for acute therapy (81.2%). The most frequently used preventive medications were verapamil (70.3%) and glucocorticoids (57.7%) with equally high effectiveness. CONCLUSIONS: Apart from the IHS criteria additional features like nausea/vomiting and migrainous aura may guide the diagnosis of CH. A large number of CH patients do not receive adequate treatments.

2. **Stallmach M. [Prophylactic treatment of cluster headache with verapamil]. Praxis 2003; 92(46):1951-1953.**

   Verapamil is the preventive therapy of choice for cluster headache. The recommended dose ranges from 240-720 mg/day. In a retrospective study nine patients with episodic and three patients with chronic cluster headache were analyzed. In episodic cluster headache early treatment onset stopped attacks within 20 days in 80%, late treatment onset was successful within ten days in 67%. Early treatment onset shortens episode duration by four times. The recommended dose is 360 mg/day. Chronic cluster headache probably requires higher doses.

OVERSIKTSARTIKLER SOM INKLUDERTE BÅDE STEROIDER OG VERAPAMIL

Oversiktsartikler

1. **Dodick DW, Saper J. Cluster and chronic daily headache. Neurology 2003; 60(7 SUPPL. 2):S31-S37.**

   Cluster headache, although relatively uncommon, is one of the most painful primary headache disorders. Approximately 90% of affected individuals experience daily attacks for several weeks to months (cluster periods) separated by attack-free intervals lasting for months to years (remission periods). The other 10% of sufferers exhibit a more chronic pattern marked by attacks that persist for longer than 1 year with no remission or only short periods of remission. The most striking feature of cluster headache is its circadian and circannual periodicity, which has implicated the hypothalamic pacemaker (the suprachiasmatic nucleus) in the pathogenesis of the disorder. The unique attack profile of cluster headache mandates the use of rapid-acting symptomatic therapy, such as oxygen or subcutaneous sumatriptan. Preventive treatment is two-pronged and consists of transitional treatment, usually with prednisone, to produce rapid suppression of attacks, and maintenance treatment (typically with verapamil) for the expected duration of the cluster period. Chronic daily headache (CDH) is defined as a headache that occurs for at least 15 days per month and for at least 4 hours per day. The prevalence of CDH is only 4% in the general population but is as high as 80% in headache clinic populations. More than three quarters of patients with CDH have chronic (transformed) migraine. The pathophysiologic mechanisms of CDH remain undetermined. Pharmacotherapy is aimed at relieving daily pain and periodic superimposed acute migraine attacks. Aggressive treatment is required for rebound syndromes, and hospitalization is sometimes required for particularly difficult cases.

2. **Ekbom K. Treatment of cluster headache: clinical trials, design and results. Cephalalgia 1995; 15(suppl. 15):33-36.**

   The spontaneous capricious course of cluster headache may give rise to some problems when treatment is being evaluated. This is one of several explanations for there being so few well-designed, randomized, double-blind clinical trials in cluster headache. The standard treatment of acute attacks of cluster headache is inhalation of 100% oxygen. In the prophylaxis of episodic cluster headache, ergotamine, verapamil, lithium, serotonin, inhibitors and steroids are used. In chronic cluster, lithium is the drug of choice, but verapamil may also be tried. Recently, hyperbaric oxygen has been shown to immediately abort acute attacks, and it seems that it may also be useful in the prophylactic treatment. The introduction of the novel 5HT1 agonist sumatriptan as a symptomatic relief of cluster attacks represents further significant progress. Two randomized, double-blind, placebo-controlled, cross-over trials have shown sumatriptan 6 mg sc to be a rapid, effective and well-tolerated acute treatment for cluster headache attacks. Within 15 min of treatment, 74% of attacks on sumatriptan responded compared to 26% of placebo-treated attacks. Functional disability was also significantly improved. Increasing the dose to 12 mg did not offer significantly greater relief compared to sumatriptan 6 mg, but was associated with an increased incidence of adverse

events. Interim analysis of 3 months of data from a recent multinational open trial comprising, 138 patients having treated 6353 attacks with subcutaneous sumatriptan 6 mg revealed a headache relief in 96% of attacks treated. There was no evidence of an increased incidence of adverse events with frequent use of sumatriptan. No tachyphylaxis was seen over the 3 months, suggesting that sumatriptan is effective and well tolerated also in long-term acute treatment for cluster headache.

3. **Jurgens TP, Schaefer C, May A. Treatment of cluster headache in pregnancy and lactation. Cephalalgia 2009; 29(4):391-400.**
   Cluster headache is a rare disorder in women, but has a serious impact on the affected woman's life, especially on family planning. Women with cluster headache who are pregnant need special support, including the expertise of an experienced headache centre, an experienced gynaecologist and possibly a teratology information centre. The patient should be seen through all stages of the pregnancy. A detailed briefing about the risks and safety of various treatment options is mandatory. In general, both the number of medications and the dosage should be kept as low as possible. Preferred treatments include oxygen, subcutaneous or intranasal sumatriptan for acute pain and verapamil and prednisone/prednisolone as preventatives. If there is a compelling reason to treat the patient with another preventative, gabapentin is the drug of choice. While breastfeeding, oxygen, sumatriptan and lidocaine for acute pain and prednisone/prednisolone, verapamil, and lithium as preventatives are the drugs of choice. As the individual pharmacokinetics differ substantially, adverse drug effects should be considered if unexplained symptoms occur in the newborn.

4. **Leroux E, Ducros A. Cluster headache. Orphanet Journal of Rare Diseases 2008; 3.**
   Cluster headache (CH) is a primary headache disease characterized by recurrent short-lasting attacks (15 to 180 minutes) of excruciating unilateral periorbital pain accompanied by ipsilateral autonomic signs (lacrimation, nasal congestion, ptosis, miosis, lid edema, redness of the eye). It affects young adults, predominantly males. Prevalence is estimated at 0.5-1.0/1,000. CH has a circannual and circadian periodicity, attacks being clustered (hence the name) in bouts that can occur during specific months of the year. Alcohol is the only dietary trigger of CH, strong odors (mainly solvents and cigarette smoke) and napping may also trigger CH attacks. During bouts, attacks may happen at precise hours, especially during the night. During the attacks, patients tend to be restless. CH may be episodic or chronic, depending on the presence of remission periods. CH is associated with trigeminovascular activation and neuroendocrine and vegetative disturbances, however, the precise cautive mechanisms remain unknown. Involvement of the hypothalamus (a structure regulating endocrine function and sleep-wake rhythms) has been confirmed, explaining, at least in part, the cyclic aspects of CH. The disease is familial in about 10% of cases. Genetic factors play a role in CH susceptibility, and a causative role has been suggested for the hypocretin receptor gene. Diagnosis is clinical. Differential diagnoses include other primary headache diseases such as migraine, paroxysmal hemicrania and SUNCT syndrome. At present, there is no curative treatment. There are efficient treatments to shorten the painful attacks (acute treatments) and to reduce the number of daily attacks (prophylactic treatments). Acute treatment is based on subcutaneous administration of sumatriptan and high-flow oxygen. Verapamil, lithium, methysergide, prednisone, greater occipital nerve blocks and topiramate

may be used for prophylaxis. In refractory cases, deep-brain stimulation of the hypothalamus and greater occipital nerve stimulators have been tried in experimental settings. The disease course over a lifetime is unpredictable. Some patients have only one period of attacks, while in others the disease evolves from episodic to chronic form.

5. **Matharu M, Silver N. Cluster headache. Clinical Evidence 2008; 2008, 2008.**
INTRODUCTION: The revised International Headache Society (IHS) criteria for cluster headache are: attacks of severe or very severe, strictly unilateral pain, which is orbital, supraorbital, or temporal pain, lasting 15-180 minutes and occurring from once every other day to eight times daily. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to abort and to prevent cluster headache? We searched: Medline, Embase, The Cochrane Library and other important databases up to September 2006 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 29 systematic reviews, RCTs or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: baclofen (oral), botulinum toxin (intramuscular), capsaicin (intranasal), chlorpromazine, civamide (intranasal), clonidine (transdermal), ergotamine and dihydroergotamine (oral or intranasal), gabapentin (oral), greater occipital nerve injections (betamethasone plus xylocaine), high-dose and high-flow-rate oxygen, hyperbaric oxygen, leuprolide, lidocaine (intranasal), lithium (oral), melatonin, methysergide (oral), octreotide (subcutaneous), pizotifen (oral), prednisolone (oral), sodium valproate (oral), sumatriptan (oral, subcutaneous and intranasal), TCAs, topiramate (oral), verapamil, and zolmitriptan (oral).

6. **Pradalier A, Baudesson G, Vincent D, Imberty-Campinos C. Treatment of the cluster headache. Rev Med Interne 2001; 22(2):151-162.**
Introduction. - The cluster headache (CH) is one of the most severe types of head pain. It is a typical example of a periodic disease and the International Headache Society classification recognizes two forms of this disease: Episodic and chronic CH. Its prevalence is about 0.1 to 0.4% in the general population. Current knowledge and key points. - Pathophysiology: A global hypothesis is still lacking to explain the pain, the vasodilation, the autonomic features (ipsilateral lacrimation, conjunctiva injection, rhinorrhea, partial Horner syndrome, etc.) and the periodicity of the CH. Pain and vasodilation seem secondary to an activation of the trigeminal vascular system and the periodicity of the attacks is thought to be due to a dysfunction of hypothalamic biologic clock mechanisms. Treatment of acute CH attacks: The most effective agents are oxygen inhalation and subcutaneous sumatriptan, a 5HT1B and D receptor agonist which has vasoconstrictor and anti-neurogenic inflammation properties by blocking the release from the trigeminal-sensitive fibers of neuropeptides such as CGRP and substance P. With subcutaneous sumatriptan, headache relief is very rapid, within 5 to 10 min. Prophylactic treatment of CH: The number of attacks per day varies from one to three, but some patients can have four to eight per day and acute treatments fail to provide

sufficient relief or give rise to side-effects. Several different regimens have been proven effective. Future prospects and projects. - Contraindications and side-effects of the drugs limit the choice of the prophylactic treatment: Corticosteroids in a tapering course, verapamil and methysergide are the most useful treatments of the episodic form. Lithium carbonate is more effective for the chronic stage of CH, but side-effects are often troublesome. Numerous other medications have been used for prophylaxis: valproate, capsaicin, beta-blockers. Unfortunately, double-blind studies are often lacking and are difficult to realize due to spontaneous variable remission of episodic CH. When adequate trials of drug therapies show a total resistance to the treatments, surgery may be considered. Radiofrequency trigeminal rhizotomy is the treatment of choice with 70% of beneficial effects. Risks and complications have to be discussed in balance with the benefit of the different surgical procedures.