Ketamin vid behandling av kronisk smärta

Patienter med komplexa och långvariga smärttillstånd kan uppleva att konventionell smärtbehandling med exempelvis opioider har otillräcklig effekt. Ketamin används främst för att söva patienter men har i låga doser även använts för smärtlindring vid akut smärta.

Fråga:

Vilket vetenskapligt stöd finns för behandling med lågdosinfusion av ketamin vid kroniska smärttillstånd?

Frågeställare: Verksamhetschef, Verksamhetsområde intensiv- och perioperativ vård, Skånes universitetssjukvård

Sammanfattning

SBU:s upplysningstjänst har identifierat fyra översikter av systematiska översikter och elva systematiska översikter där studier av ketaminbehandling mot kronisk smärta inkluderats i översikterna. De systematiska översikterna inkluderar primärstudier med flera olika populationer med kronisk smärta, där deltagarna fått intravenös infusion med ketamin (men i vissa studier även med andra administrationsvägar), samt där studierna redovisat smärtlindring som primärt utfallsmått. Sammanfattningsvis bedömer vissa författare evidensläget som oklart, medan andra drar slutsatsen att ketamin kan ha en smärtstillande effekt vid kronisk smärta. Fler primärstudier behövs på specifika smärtpopulationer, med upprepade behandlingar, med längre uppföljningstider, och med utförlig biverkningsrapportering.

SBU har inte tagit ställning i sakfrågan eftersom vi inte har bedömt de enskilda studiernas kvalitet eller vägt samman resultaten. Här redovisar vi därför endast de enskilda författarnas slutsatser.

Bakgrund

Långvarig kronisk smärta där konventionell smärtbehandling haft otillräcklig effekt kan ibland ses vid svåra komplexa smärttillstånd, exempelvis ryggmärgsskada, neuropatisk smärta, icke-maligna långvariga smärttillstånd och cancerrelaterad eller cancerbehandlingsrelaterad smärta. Patienter med dessa problem har ofta redan testat flertalet olika behandlingsalternativ, som opioider, antidepressiva läkemedel, antiepileptiska läkemedel eller transkutan elektrisk nervstimulering.

Ketamin har använts kliniskt för nedsövning och smärtstillning i över 50 år [1,2]. I lägre doser används ketamin inom smärtlindring både vid akuta och kroniska tillstånd, både på barn och vuxna. Så kallade subanastetiska doser (0,1–0,3 mg/kg) av ketamin har visats vara av värde vid akut och post-operativ smärta, som prevention av kronisk post-operativ smärta och för att reducera opioidanvändning vid smärta eller vid opioidintolerans [3]. Ketaminbehandling har även använts vid psykiatriska tillstånd, som svårbehandlad depression [4]. Vid högre doser är det välkänt att ketamin ger allvarlig påverkan på centrala nervsystemet i form av så kallade dissociativa eller psykosliknande symptom, hallucinationer och mardrömmar [1,2,3].

Avgränsningar

Vi har gjort sökningar (se avsnittet Litteratursökning) i databaserna Pubmed och Cochrane Library. Vi inkluderade systematiska översikter och översikter över systematiska översikter, alla andra typer av studier exkluderades. Vi exkluderade studier som undersökt behandling av kronisk smärta på grund av migrän och annan huvudvärk, whiplashskada, fibromyalgi eller krigsskada, samt exkluderade studier av ketaminbehandling mot depression i samband med kronisk smärta.

Resultat från sökningen

Upplysningstjänstens litteratursökning genererade totalt 425 träffar. En projektledare på SBU läste alla artikelsammanfattningar och bedömde att 68 artiklar skulle kunna vara relevanta för frågeställningen. Dessa lästes i fulltext av projektledaren och 15 artiklar ingår i svaret. De artiklar som inte ingår i svaret exkluderades på grund av att de inte var relevanta för frågeställningen. Observera att vi inte bedömde kvaliteten på varken översikterna eller de i översikten inkluderade primärstudierna. Det är därför möjligt att flera av studierna kan ha lägre kvalitet än vad SBU inkluderar i sina ordinarie utvärderingar.

Svaret baseras på fyra översikter över systematiska översikter [5–8], och 11 systematiska översikter [9–19], se Tabell 1–3. I de inkluderade översikterna ingick studier på följande populationer: kronisk smärta som är icke-cancerrelaterad, kronisk smärta som är cancerrelaterad, opioidresistent smärta,

postoperativ smärta, prevention av kronisk postoperativ smärta, Complex Regional Pain Syndrome (CRPS), nervskada, neuropatisk smärta, posttraumatisk smärta, traumatisk ryggmärgsskada, ischemisk smärta, whiplash, kronisk migrän, fibromyalgi, och fantomsmärtor (phantom limb pain). Sju översikter inkluderade flera olika smärttillstånd (Tabell 1 och 2) och åtta översikter fokuserade på ett specifikt smärttillstånd (Tabell 3).

I de inkluderade systematiska översikterna ingick primärstudier där ketamin givits som intravenös infusion (olika infusionsprotokoll av subanestetiska doser), men även primärstudier med andra administrationsvägar, inklusive oral, subkutan, epidural, intratekal eller topikal administration. Vissa översikter inkluderade flera olika läkemedelsbehandlingar mot kronisk smärta, däribland ketaminbehandling (Tabell 1–3).

I de inkluderade primärstudier i översikterna angavs utfallsmåtten analgetisk effekt (smärta eller smärtintensitet mätt med olika skattningsinstrument, exempelvis VAS, NRS, MPQ, numerical pain intensity, eller brief pain inventory), andel patienter som uppnådde viss smärtlindringseffekt (pain relief event rate) eller smärtduration. Andra utfall som ingick i översikterna var opioidkonsumtion, rörelseförmåga, smärta vid rörelse, sensoriska tester, risk för att utveckla kronisk smärta, sömn, depression, funktion, livskvalitet, behandlings-tillfredsställelse, och biverkningar (hallucinationer, kognitiva effekter). (Tabell 1–3).

En risk of bias-bedömning, det vill säga en bedömning av risken för systematisk snedvridning, av de inkluderade primärstudierna ingick i fyra systematiska översikter [9,13,15,16], metaanalyser ingick i tre översikter [9,12,15] och evidensgradering (GRADE eller annan) ingick i sex översikter [7,9,8,10,13,17]. De flesta av de systematiska översikterna inkluderade randomiserade kontrollerade studier och prospektiva observationsstudier, men vissa översikter inkluderade även retrospektiva studier, fallstudier och fallserier.

I översikterna som listas i Tabell 1–2 har artikelförfattarna använt delvis olika inklusionskriterier gällande de tillstånd som omfattats i översikterna. Flertalet av de systematiska översikterna, som täckte blandade eller specifika smärttillstånd, ingår även i de översikter av systematiska översikter som listas i Tabell 1. Dessa översikter av översikter omfattade dock även akut smärta, eller annan läkemedelsbehandling vid kronisk smärta. Vilka tillstånd och vilka behandlingar som ingår i respektive översikter listas i tabellerna.

Översikter över systematiska översikter

Tabell 1. Översikter över systematiska översikter/ Table 1. Overviews over systematic reviews

Included studies	Population	Outcome
Bell and Kalso 2018 [5]		
18 systematic reviews	Several populations: chronic noncancer pain, refractory cancer pain, opioid-resistant pain in palliative care, postoperative pain (chronic and acute)	Several assessment tools (pain intensity, overall pain level, pain relief, opioid consumption, adverse effects)
Authors' conclusion: "The evidence for the use of ketamine in palliative care is limited, and it is not possible to recommend any specific treatment regimen. However, despite the limited evidence, a trial of low dose ketamine, adjuvant to opioid (morphine), may be warranted in refractory cancer pain or pain in palliative care. […] The evidence regarding ketamine for chronic noncancer pain is extremely limited, and there is a lack of safety data concerning long-term or repeated treatments. Importantly, there seems to be no strong evidence for the current widespread use of intermittent ketamine infusions."		
Jonkman et al 2017 [6]		
29 systematic reviews, including 8 systematic reviews on chronic pain, including any route of ketamine administration	Several populations: chronic non-cancer pain, cancer pain, prevention of chronic pain following surgery, acute postoperative pain, acute non-postoperative pain	Several assessment tools (analgesic effect, analgesic duration, adverse effects, pain in motion, risk of developing persistent pain)
Authors' conclusion: "Ketamine treatment is most effective for relief of postoperative pain, causing reduced opioid consumption. In contrast, for most other indications (that is, acute pain in the emergency department, prevention of persistent postoperative pain, cancer pain, and chronic non-cancer pain), the efficacy of ketamine is limited. Ketamine's lack of analgesic effect was associated with an increase in side effects, including schizotypical effects."		
Connolly et al 2015 [7]		
6 systematic reviews, 5 RCT, 13 observational studies, 21 case reports, including any route of ketamine administration. Includes evidence levels	Complex Regional Pain Syndrome (CRPS)	Several assessment tools (pain relief, pain intensity, NRS, VAS, MPQ, numerical pain intensity, movement parameters, sensory testing)
Authors' conclusion: "There is no high quality evidence available evaluating the efficacy of ketamine for CRPS and all manuscripts examined in this review were of moderate to low quality. Therefore, we conclude there is currently only weak evidence supporting the efficacy of ketamine for CRPS, yet there is clearly a rationale for definitive study."		

Included studies	Population	Outcome
"Based on the literature identified and the extent of evidence found for ketamine for CRPS, we find the evidence to date to be inconclusive. The quality of the research to date is low, in small "n" studies, with methodological flaws; thus there we conclude there is only weak evidence for the efficacy of ketamine for CRPS, and it cannot be considered a first line option. Nonetheless, CRPS is a significant clinical problem with limited therapeutic options, and therefore, any intervention able to produce improvements should be studied properly, and our review suggests subanesthetic dose ketamine holds promise. There is a critical need for "high quality, randomized, controlled trials with larger numbers of patients and standardized, clinically relevant routes of administration".		
O'Connell et al 2013 [8]		
19 systematic reviews, including 1 SR on iv ketamine	CPRS	Pain (NRS)
Authors' conclusion: "GRADE quality judgement: There was low quality evidence (evidence from RCTs: downgrade twice for sample size) that a course of intravenous ketamine may be effective for CRPS-related pain. The effects did not appear to be sustained beyond four to 11 weeks post-treatment."		

Systematiska översikter

De identifierade systematiska översikterna omfattande antingen flera olika smärttillstånd (Tabell 2), eller specifika smärttillstånd (Tabell 3).

Tabell 2. Systematiska översikter över flera smärttillstånd/ Table 2. Systematic reviews over several pain conditions

Included studies	Population	Outcome
Michelet et al 2018 [9]		
6 RCT All studies on ketamine, 4 studies on iv infusion. Includes risk of bias assessment, meta-analysis and evidence grading.	Chronic non-cancer pain [Several populations: CPRS, neuropathic pain]	Pain score (VAS, NRS, Brief Pain Inventory)
Authors' conclusion: "Results of this meta-analysis found moderate evidence suggesting the efficacy of ketamine during chronic pain. Further studies are warranted to conclude about the effect of ketamine during chronic pain conditions and to determine optimal administration regimes of this agent during this condition."		

Maher et al 2017 [10]		
26 studies: 11 RCT, 4 prospective observational, 4 retrospective studies. All studies on iv ketamine, multiple infusion protocols. Includes evidence levels.	Neuropathic pain [Several populations: Complex Regional Pain Syndrome (CPRS), Fibromyalgia, traumatic spinal cord injury	Pain relief (several assessment tools)

Authors' conclusion:

"Given a relative paucity of evidence in the current literature to guide ketamine infusion therapy for the treatment of various neuropathic pain conditions, such as CRPS, postherpetic neuralgia, traumatic spinal cord injury, and phantom limb pain, further well-conducted prospective comparative effectiveness studies are needed to analyze different ketamine infusion protocols in discreet neuropathic pain states."

Noppers et al 2010 [11]		
36 RCT All studies on ketamine, 21 studies on iv infusion.	Chronic non-cancer pain [Several populations: CPRS, nerve injury, chronic neuropathic pain, peripheral neuropathic pain, neuropathic pain from spinal cord injury, post-traumatic pain, post-nerve injury, whiplash, postherpeutic neuralgia, painful limb ischemia, arterio-sclerosis of lower limb, chronic migraine, fibromyalgia, phantom limb	Analgesic effect

Authors' conclusion:

"While most studies on intravenous ketamine show acute analgesic effects, three recent trials on long-term ketamine treatment (days to weeks) demonstrate the effectiveness of ketamine in causing longterm (months) relief of chronic pain. […] Other administration modes are less effective in causing long-term pain relief. There is now evidence from a limited number of studies that pain relief lasting for months is observed after long-term intravenous ketamine infusion, suggesting a modulatory effect of ketamine in the process of chronic pain, possibly via blockade of upregulated NMDAR."

Tabell 3. Systematiska översikter över specifika smärttillstånd/ Table 3. Systematic reviews over specific pain conditions

Included studies	Population	Outcome
Zhao et al 2018 [12]		
15 studies: RCT, cohort studies. All ketamine iv infusions, includes meta-analysis.	Complex Regional Pain Syndrome (CRPS)	Pain relief (several assessment tools), pain relief event rate (percentage of patients who achieved 30% or higher pain relief)
Authors' conclusion: "Our findings suggested that ketamine infusion can provide clinically effective pain relief in short term for less than 3 months. However, because of the high heterogeneity of the included studies and publication bias, additional random controlled trials and standardized multicenter studies are needed to confirm this conclusion. Furthermore, studies are needed to prove long-term efficacy of ketamine infusion in the treatment of CRPS."		
Azari et al 2012 [13]		
3 RCT, 7 observational studies, 9 case studies. All ketamine studies, multiple routes of administration. Includes risk of bias assessment and evidence levels.	Complex Regional Pain Syndrome (CRPS)	Pain relief (several assessment tools)
Authors' conclusion: "In aggregate, the data available reveal ketamine as a promising treatment for CRPS. […] The current level of evidence is 2B (i.e. weak recommendation, moderate-quality evidence) for the use of ketamine in the treatment of CRPS pain. We do not have sufficient evidence to recommend routine use of ketamine in CRPS. Within the context of this limited evidence for use of ketamine, there are limited data about the optimal dose, route and timing of administration. Although ketamine demonstrates promise for safe and effective use in the treatment of CRPS, the need for large, well designed, randomized controlled trials is evident."		
Humble et al 2015 [14]		
32 studies. (Several interventions: including 6 studies on ketamine, iv or epidural).	Post-surgical pain (after amputation, thoracotomy or mastectomy)	Pain (VAS, NRS, verbal rating score), pain at rest, pain at movement, sensory testing
Authors' conclusion: "Ketamine was not effective at reducing chronic pain. […] This systematic review was limited to amputation, mastectomy and thoracotomy because these operations are considered to […] be associated with a combination of nociceptive and neuropathic symptoms and carry a high risk of chronic pain. If it is accepted that the severity of acute pain is correlated with the risk of developing chronic pain, then it follows that the perioperative period is a logical target for interventions aimed at reducing or preventing the phenomenon."		

McNicol et al 2014 [15]		
17 RCT All ketamine studies, administered peri-operatively via any route. Includes risk of bias assessment and meta-analysis.	Persistant post-surgery pain (PPSP)	Risk of developing PPSP

Authors' conclusion:

”In this meta-analysis of all eligible studies, combining intravenous and epidural administration, ketamine did not provide a significant reduction of PPSP at 3 and 6 months . In common with systematic reviews of short-term effects of ketamine on acute pain outcomes, the study data from our review of outcomes at 3 months or later are heterogeneous and suggest efficacy of intravenous ketamine only in comparison with placebo in preventing PPSP at 3 and 6 months. There was no evidence to support epidural ketamine administration for PPSP prevention.”

Alviar et al 2016 [16]		
14 studies (Several interventions, including 2 studies on ketamine)	Phantom Limb Pain	Pain intensity, sleep, depression/mood, function, quality of life, adverse events, satisfaction with treatment, withdrawals

Authors' conclusion:

”The N-methyl D-aspartate (NMDA) receptor antagonists ketamine (versus placebo; versus calcitonin) and dextromethorphan (versus placebo), but not memantine, had analgesic effects. The adverse events of ketamine were more serious than placebo and calcitonin and included loss of consciousness, sedation, hallucinations, hearing and position impairment, and insobriety.”

McCormick et al 2014 [17]		
27 studies. (Several interventions: including 5 RCT on ketamine, iv or epidural administration. Includes evidence levels.)	Phantom Limb Pain	Pain

Authors' conclusion:

”Level 2 evidence exists for the perioperative use of ketamine (IV or epidural), which non-competitively blocks NMDA receptors, for acute pain reduction but little for a prolonged duration of treatment effect [124–128]. Currently, the best evidence (level 2) exists for the use of IV ketamine and IV morphine perioperatively for short-term treatment of PLP and PO morphine for an intermediate to long-term treatment effect (8 weeks to 1 year).”

Laoire et al 2017 [18]		
6 RCT, including 2 RCT on ketamine	Ischemic pain. Patients with non-reconstructable critical limb ischemia	Pain (VAS, Brief Pain Inventory)
Authors' conclusion:		
"Two RCTs comparing ketamine with normal saline and morphine sulfate showed significantly reduced pain scores in the intervention groups. […] However, the side effect profile continues to be the limiting factor in its use. The overall benefit of ketamine to treat pain secondary to CLI is, therefore, still questionable."		
Bredlau et al 2013 [19]		
5 randomized, double-blind, controlled trials, 6 prospective uncontrolled trials, 0 randomized controlled trials in children. All ketamine studies, administered via any route. 1 RCT on iv infusion.	Chronic cancer pain (adults and children)	Pain relief (several assessment tools)
Authors' conclusion:		
"Despite limitations in the breadth and depth of data available, there is evidence that ketamine may be a viable option for treatment-refractory cancer pain. […] In children and adults with cancer pain that has not responded adequately to standard therapy, the literature supports considering ketamine as an adjuvant therapy. Recommended ketamine infusion dosages are from 0.05 to 0.5 mg/kg/h (intravenous or subcutaneous). Recommended oral dosages of ketamine are 0.2-0.5 mg/kg/dose two to three times daily with a maximum of 50 mg/dose three times daily ."		

Förkortningar:

CLI = Chronic limb ischemia; CRPS = Complex regional pain syndrome; IV = Intravenous; MPQ = McGill Pain Questionnaire; NMDA = N-methyl D-aspartate; NMDAR = N-methyl D-aspartate receptor; NRS = Numerical rating scale; PLP = Phantom limb pain; PO = Per oral; PPSP = Persistent post-surgery pain, RCT = Randomized controlled trial; VAS = Visual analogue scale

Projektgrupp

Detta svar är sammanställt av Malin Höistad, Sally Saad, Irene Edebert och Pernilla Östlund vid SBU.

Litteratursökning

PubMed via NLM 2018-10-18 **Ketamine for chronic pain**		
	Search terms	**Items found**
Population:		
1.	((pain[MeSH] OR pain[Title/Abstract]) AND (chronic[Title/Abstract] OR persistent[Title/Abstract])) OR (”chronic pain”[Mesh]	113 749
Intervention:		
2.	(ketamine[Title/Abstract] OR ketamine[All Fields]) OR (ketanest[Title/Abstract] OR ketanest[All Fields]) OR (ketalar[Title/Abstract] OR ketalar[All Fields]) OR (esketamine[Title/Abstract] OR esketamine[All Fields]) OR ("(RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone"[All Fields])	18144
Limits:		
3.	(animals [mh] NOT humans [mh])	4508299
Combined sets		
4.	#1 AND #2	544
5.	#4 NOT #3	456
Final		456

The search result, usually found at the end of the documentation, forms the list of abstracts

[MeSH] = Term from the Medline controlled vocabulary, including terms found below this term in the MeSH hierarchy
[MeSH:NoExp] = Does not include terms found below this term in the MeSH hierarchy
[MAJR] = MeSH Major Topic
[TIAB] = Title or abstract
[TI] = Title
[AU] = Author
[TW] = Text Word
Systematic[SB] = Filter for retrieving systematic reviews
* = Truncation
“ “ = Citation Marks; searches for an exact phrase

Cohrane Library via Wiley 2018-10-18 **Ketamine for chronic pain**		
	Search terms	**Items found**
Population:		
1.	Pain	
Intervention:		
2.	Ketamine	
Final		12

The search result, usually found at the end of the documentation, forms the list of abstracts
[AU] = Author
[MAJR] = MeSH Major Topic
[MeSH] = Term from the Medline controlled vocabulary, including terms found below this term in the MeSH hierarchy
[MeSH:NoExp] = Does not include terms found below this term in the MeSH hierarchy
Systematic[SB] = Filter for retrieving systematic reviews
[TI] = Title
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[TW] = Text Word
* = Truncation
" " = Citation Marks; searches for an exact phrase
CDSR = Cochrane Database of Systematic Review
CENTRAL = Cochrane Central Register of Controlled Trials, "trials"
CRM = Method Studies
DARE = Database Abstracts of Reviews of Effects, "other reviews"
EED = Economic Evaluations
HTA = Health Technology Assessments

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