Cost-effectiveness of subcutaneous ketamine in the management of chronic cancer pain

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PaCCSC
Palliative Care Clinical Studies Collaborative

Overview

- Context
- Study design
- Main results
- Cost-effectiveness
- Limitations
- Implications

Context

Palliative Care Clinical Studies Collaborative (PaCCSC)

- Pain
- Bowel obstruction
- Delirium
- Anorexia

Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain

Hardy J, Quinn S, Fazekas B, Plummer J, Eckermann S, Agar M, Spruyt O, Rowett D, Currow D

Journal of Clinical Oncology. 2012;30(29):3611

Population

Exclusion criteria

- Ketamine ≤ 6 months
- Radiotherapy for pain ≤ 2 weeks
- Other procedure or therapy likely to affect pain
- Contraindicating comorbidities

Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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Cleeland CS & Ryan KM 1994; Hardy et al 2012

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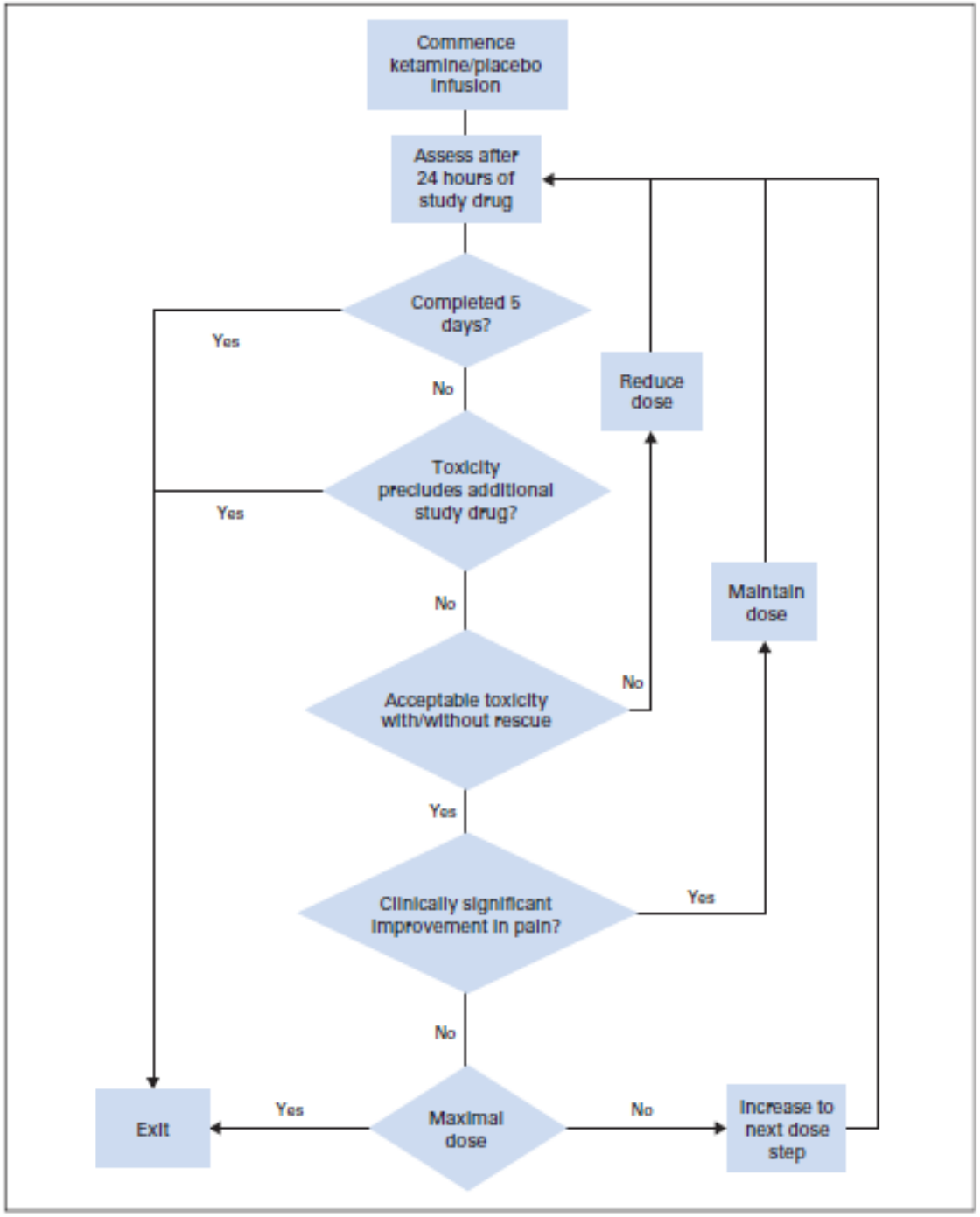
Study diagram



Hardy et al 2012

Cost-effectiveness analysis

Outcomes	Costs (2014 AU$)
Health-related quality of life	Ketamine use
Responder rates*	Hospital admissions
Adverse events	Medication use

* ≥2 points from baseline in the absence of >4 breakthrough doses of analgesia over the previous 24 hours

Groenvold et al. 2006; Lyons et al. 2009;
McCaffrey et al 2014

Baseline characteristics

Characteristic	Ketamine (n=93)	Placebo (n=92)
Age, mean (SD)	63.1 (13.4)	64.4 (9.8)
Male, %	55.1	59.8
Lung, %	23.7	19.6
Prostate, %	14.3	12.1
Colorectal, %	8.8	15.6
AKPS, median (IQR)	60 (50-60)	60 (50-60)
BPI average pain score (SD)	5.4 (1.3)	5.2 (1.4)
FACIT-Pal score[#], mean (SD)	109.9 (18.3)	109.6 (18.9)

[$] 0-100; [#] 0-184;
AKPS = Australian-modified Karnofsky Performance Status;
IQR = interquartile range; SD = standard deviation

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Maximum dose received

Ketamine/ placebo dose (mg)*	Number received ketamine	Number received placebo
<100	6#	7$
100	16	12
300	35	19
500	36	54

* Participants were required to have received at least 80% of planned dose to complete the first dose level; # two patients withdrew before start of treatment and four withdrew during day 1 before 80% of dose step 1; $ two patients withdrew before start of treatment and five withdrew during day 1 before 80% of dose step 1

Results: Outcomes and costs

Treatment arm	Ketamine (n=93)	Placebo (n=92)
Outcomes		
FACIT-Pal score (SD)	108.4 (17.7)	113.4 (18.3)
Responder rates*, %	31.2 (21.5, 39.8)	27.2 (19.6, 38.0)
Adverse events#, n	172	103
Costs		
Ketamine	$476	$0
Hospital stays	$8,295	$8,196
Medication usage	$78	$118
Total	**$8,849**	**$8,314**

*ns, p=0.55; Day 1 incidence rate ratio 1.95 p<0.01 (95% CI 1.46, 2.61)

McCaffrey et al 2014

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Results: Incremental analysis

Outcomes	Increment* (95% CI)
FACIT-Pal score#, mean change	-5.3 (-9.4, -0.8)
Responders, %	4 (-9, 17)
Costs	
Ketamine	$476
Hospital stays	$99 (-$166, $387)
Medication usage	-$40 (-$79, $12)
Total	**$535 ($291, $821)**

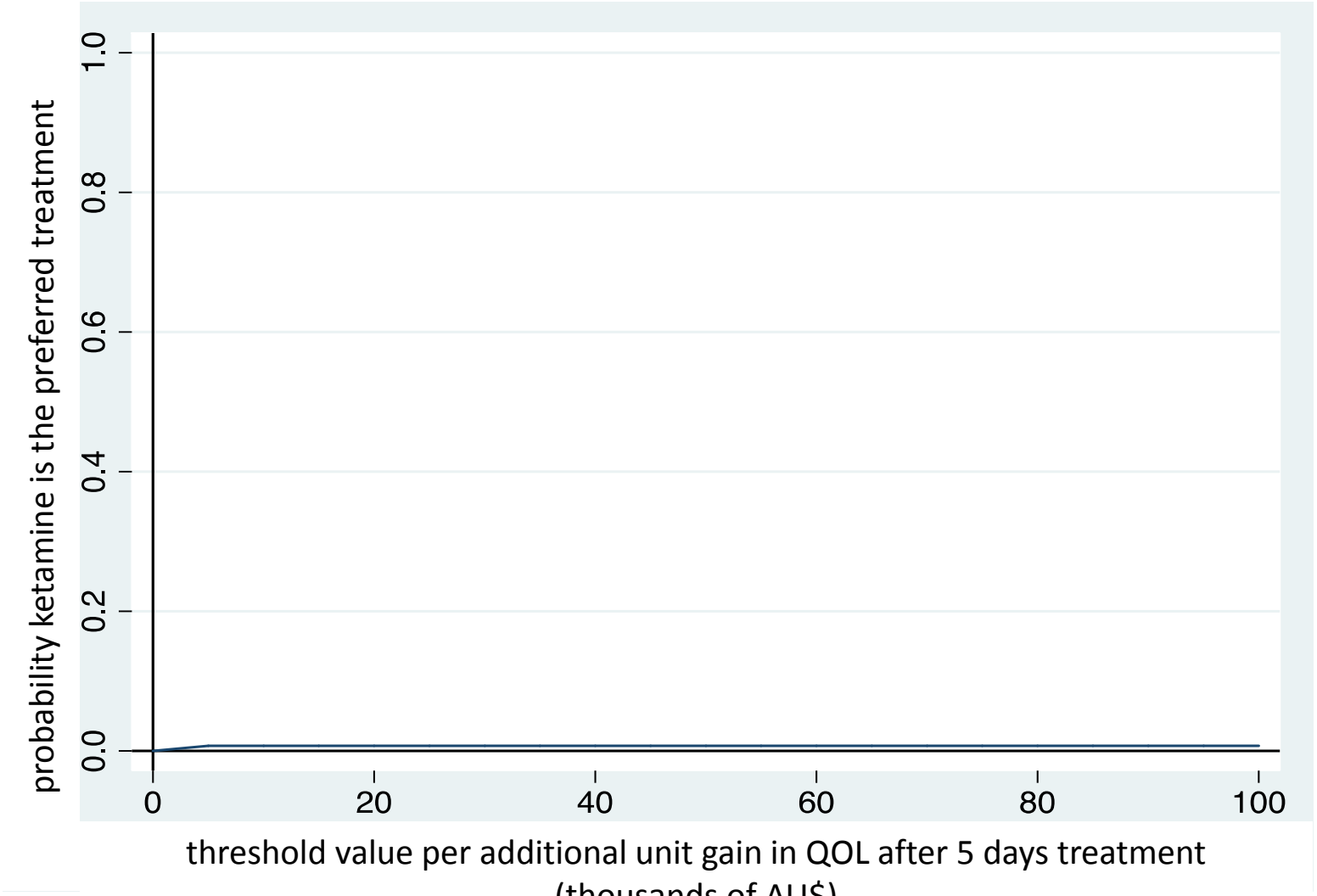
* difference between ketamine and placebo; $ 0-100; # 0-184; SD = standard deviation

Cost-effectiveness acceptability plane

NW quadrant: intervention costs more and gains less

difference in FACIT-Pal QOL score after 5 days treatment

Cost-effectiveness acceptability curve



A few caveats…

- Cost data
  - multiple imputation
- Generalisability
- Other treatment options
  - paucity of evidence

Kaambwa et al 2012; Burton et al 2007

Better informing decision making with multiple outcome cost-effectiveness analysis under uncertainty in cost-disutility space

McCaffrey N, Agar M, Harlum J, Karnon J, Currow D, Eckermann S

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Study implications

- No statistically significant difference in responder rates but higher toxicity and worse QOL
- Higher ketamine costs despite lower costs for other medications
- When costs and QOL are jointly considered, ketamine is neither effective nor cost-effective

References

Afsharimani, B., K. Kindl, P. Good and J. Hardy (2015). "Pharmacological options for the management of refractory cancer pain-what is the evidence?" Support Care Cancer 23(5): 1473-1481.

Ageing, D. o. H. a. (2012) "AR-DRG version 6.0."

Australia, C. o. (2010). National Palliative Care Strategy 2010. Barton, ACT.

Bell, R. F., C. Eccleston and E. A. Kalso (2012). "Ketamine as an adjuvant to opioids for cancer pain." Cochrane Database Syst Rev 11: Cd003351.

Bredlau, A. L., R. Thakur, D. N. Korones and R. H. Dworkin (2013). "Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature." Pain Med 14(10): 1505-1517.

Campbell, M. K. and D. J. Torgerson (1999). "Bootstrapping: estimating confidence intervals for cost-effectiveness ratios." QJM 92(3): 177-182.

Farrar, J. T., J. P. Young, Jr., L. LaMoreaux, J. L. Werth and R. M. Poole (2001). "Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale." Pain 94(2): 149-158.

References

Jackson, K., M. Franco, L. William, P. Poon, M. Pisasale, D. Kenner, D. Brumley, G. Mewett, M. Ashby, M. Viney and D. Kerr (2013). "Ketamine and cancer pain: the reports of my death have been greatly exaggerated." J Clin Oncol 31(10): 1373-1374.

Leppert, W. (2013). "Ketamine in the management of cancer pain." J Clin Oncol 31(10): 1374.

MacKintosh, D. (2012). "Ketamine and cancer pain - an inconvenient truth?" Ann Palliat Med 1(3): 224-226.

Manca, A. and S. Palmer (2005). "Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials." Appl Health Econ Health Policy 4(2): 65-75.

McCaffrey N and C. D (2015). "Separated at birth?" BMJ Supportive & Palliative Care 5(1): 2-3.

McCaffrey, N., M. Agar, J. Harlum, J. Karnon, D. Currow and S. Eckermann (2013). "Is home-based palliative care cost-effective? An economic evaluation of the Palliative Care Extended Packages at Home (PEACH) pilot." BMJ Supportive & Palliative Care 3(4): 431-435.

References

McCaffrey N, A. M., Harlum J, Karnon J, Currow D, Eckermann S (2015). "Better informing decision making with multiple outcomes cost-effectiveness analysis under uncertainty in cost-disutility space." PLoS One 10(3): e0115544

McCaffrey, N., J. Hardy, B. Fazekas, M. Agar, L. Devilee, D. Rowett and D. Currow (2015). "Potential economic impact on hospitalisations of the Palliative Care Clinical Studies Collaborative (PaCCSC) ketamine randomised controlled trial." Aust Health Rev.

McCaffrey N, Skuza P, Breaden K, Eckermann S, Hardy J, Oaten S, Briffa M and C. DC (2014). "Preliminary Development and Validation of a New End-of-Life Patient-Reported Outcome Measure Assessing the Ability of Patients to Finalise Their Affairs at the End of Life." PLoS ONE 9(4): e94316.

Kaambwa B, Bryan S, Billingham L. Do the methods used to analyse missing data really matter? An examination of data from an observational study of Intermediate Care patients. BMC research notes 2012;5:330.

Mercadante, S. (2013). "Ketamine: to be or not to be." Annals of Palliative Medicine 2(1): 37-39.

References

Moher, D., S. Hopewell, K. F. Schulz, V. Montori, P. C. Gøtzsche, P. J. Devereaux, D. Elbourne, M. Egger and D. G. Altman (2010). "CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials." Journal of Clinical Epidemiology 63(8): e1-e37.Pharmaceutical Benefits Advisory Committee (2009). Manual of resource items and their associated costs. Canberra, Australia, The Australian Government, Department of Health & Ageing.

Ramsey, S. D., R. J. Willke, H. Glick, S. D. Reed, F. Augustovski, B. Jonsson, A. Briggs and S. D. Sullivan (2015). "Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report." Value in Health 18(2): 161-172.

Schulz, K. F., D. G. Altman and D. Moher (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.

Spruyt, O., B. Le and J. Philip (2013). "Integrating New Evidence About an Old Drug: Growing Pains as Palliative Medicine Matures." Journal of Pain and Symptom Management 46(5): e3-e5.

References

Spruyt, O., B. H. Le and J. Philip (2014). "Integrating new evidence about an old drug: authors' reply to Franco et al. and Bell et al." J Pain Symptom Manage 47(4): e4-5.

StataCorp (2013). Stata statistical software: release 13. StataCorp LP. College Station, Texas, USA.

Welfare, A. I. o. H. a. (2013) "Australian refined diagnosis-related groups (AR-DRG) data cubes."

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