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

Reference: *J. Clin Oncol* 2012; 30: 3611-3617. Janet Hardy, Stephen Quinn, Belinda Fazekas, John Plummer, Simon Eckermann, Meera Agar, Odette Spruyt, Debra Rowett and David C. Currow

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Abstract: The anesthetic ketamine is widely used for pain related to cancer, but the evidence to support its use in this setting is weak. This study aimed to determine whether ketamine is more effective than placebo when used in conjunction with opioids and standard adjuvant therapy in the management of chronic uncontrolled cancer pain. Ketamine would be considered of net benefit if it provided clinically relevant improvement in pain with limited breakthrough analgesia and acceptable toxicity. **Patients and Methods** In this multisite, dose-escalation, double-blind, randomized, placebo-controlled phase III trial, ketamine or placebo was delivered subcutaneously over 3 to 5 days. **Results** In all, 185 participants were included in the primary analysis. There was no significant difference between the proportion of positive outcomes (0.04; 95% CI, −0.10 to 0.18; $P = .55$) in the placebo and intervention arms (response rates, 27% [25 of 92] and 31% [29 of 93]). Pain type (nociceptive *v* neuropathic) was not a predictor of response. There was almost twice the incidence of adverse events worse than baseline in the ketamine group after day 1 (incidence rate ratio, 1.95; 95% CI, 1.46 to 2.61; $P < .001$) and throughout the study. Those receiving ketamine were more likely to experience a more severe grade of adverse event per day (odds ratio, 1.09; 95% CI, 1.00 to 1.18; $P = .039$). The number of patients needed to treat for one additional patient to have a positive outcome from ketamine was 25 (95% CI, six to ∞). The number needed to harm, because of toxicity-related withdrawal, was six (95% CI, four to 13).

Conclusion Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard coanalgesics in cancer pain.

Strengths: Largest randomized, double-blinded, multi-centre placebo-controlled study regarding ketamine use in difficult to control pain. Is the most objective data available regarding efficacy of ketamine as adjuvant to opioid and co-analgesics for refractory pain. Study group typical of patients typically referred to the palliative care service. Patient subgroups were for the most part similar. Consistency of results across secondary outcomes and the adequate power to detect prespecified differences in response suggests that there is no type II error.

Weaknesses: Heterogeneity of the population. High placebo response rate (27%). Patients who enter trials are generally of better performance status and may not represent the real patient population.

Relevance to Palliative Care: Ketamine is a dissociative analgesic that has been used as an adjuvant for difficult to control pain or refractory pain in other palliative care centres. With the increased incidence of toxicity and harm compared to clinic benefit, ketamine should not be used as an adjuvant for refractory or difficult to control pain.