Perspective

# Ketamine and cancer pain - an inconvenient truth?

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"*··· this adequately powered RCT fails to support the current widespread practice of using subcutaneous ketamine as an adjuvant to opioids in the management of refractory pain in patients with advanced cancer*." This is the conclusion of Prof. Janet Hardy and her colleagues following completion of a large and rigorous randomized, double-blind, placebo-controlled trial of subcutaneous ketamine in cancer related pain - 185 patients treated for up to 5 days (1). How does this fit with what is already known about ketamine in pain management and how should this influence future practice?

The Cochrane Collaboration published its original review of ketamine in the management of cancer pain in 2003 and concluded that "*Current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of cancer pain. More randomized controlled trials are needed*." (2). Revisions in 2009 and November 2012 (current to May 2012) have failed to change this conclusion (3).

The original Cochrane review, 2003, was able to identify only two randomized placebo controlled trials of adequate quality for inclusion in the review (2). Mercadante (4) reported improved analgesia in 10 patients with cancer related neuropathic pain from a single intravenous bolus of ketamine (0.25 or 0.5 mg/kg); patients were monitored for up to 3 hours. Yang (5) reported improved analgesia in 20 patients with cancer pain following the intrathecal administration of ketamine. No further trials have been added in either the 2009 or 2012 updates although two additional trials have been excluded on the grounds of small numbers, less than 10 subjects in one group due to dropouts; neither of these trials demonstrated a benefit from ketamine (6,7).

On the basis of the outcomes of included studies, the conclusions of the authors of the Cochrane reviews, Bell and colleagues, have remain unchanged in nearly a decade. They did, however, make note of a significant body of supportive evidence available from open label studies and case reports describing an improvement in analgesia with adjuvant ketamine in refractory cancer pain; a total of 246 patients in 32 reports, 16 of which were said to have shown "dramatic" improvement; again no further reports have been added since 2003 (2). There was then, and is now, a paucity of negative reports.

Since Bell and colleagues' 2009 update this author has identified, up to October 2012, a further 8 reports in adults best described as case series (references can be supplied on request). All of these reports were positive bar one which confessed to having had a mixed experience with ketamine reporting a success rate of only 30% (8). In two additional studies, Okomata (9) in a retrospective review of intravenous ketamine reported a response rate of 69.5% (N=46), and Jackson, using "burst" ketamine, found a response rate of 50% (N=44) (10). Neither of these studies were randomized, placebo controlled or blinded.

By way of contrast, the double blind, placebo controlled studies of Ishizuka (6) and Salas (7), excluded from the 2012 Cochrane review due to inadequate size, both failed to show benefit in the management of cancer pain although Salas reported that there may have been a trend toward benefit that did not reach significance. Salas also expressed concern that the doses of ketamine were possibly too low - 0.5 to 1 mg/kg/day, a charge that cannot be leveled against Hardy and colleagues who used doses ranging from 100 to 500 mg/day (1); approximately 1.5 to 7 mg/kg/day for a hypothetical 70 kg person.

With the one exception noted (8), published open label studies and case reports have been essentially uniformly affirmative of the use of ketamine in the management of refractory cancer pain. That randomized, double blind,

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placebo controlled trials have failed to confirm the findings of case reports and open-label studies opinion is consistent with the observation of Niesters and Dahan that in non-malignant chronic neuropathic pain the benefits of ketamine as described in case reports and open-label studies are often not supported by the findings of systematic review and meta-analysis (11). They offer qualification, however, by saying effectively that lack of evidence is not the same as lack of benefit - just a lack of evidence of benefit. Interestingly, that is also a point of view expressed by Bell, co-author of the Cochrane reviews, in regard to ketamine and cancer pain (12).

At this time the evidence supporting the use of ketamine in cancer pain remains conflicted. In the affirmative is an extensive collection of open label studies and positive case series with one positive randomized control trial (RCT) using peripherally administered ketamine (4) and one trial of intrathecal ketamine (5). On the other hand are three negative RCT's (1,6,7). There is no doubt that the Hardy study is the largest trial published to date, producing sound conclusions based on the evidence presented. Accepting that RCT's are indeed the gold standard, the evidence appears to be shifting in favor of lack of benefit of ketamine in the management of cancer pain bearing in mind the caution noted by Niesters and Dahan (11).

Are the results of the Hardy trial sufficient to change practice given that they are contrary to an extensive body of accumulated non-RCT evidence? It does not seem appropriate to criticize the Hardy trial on technical grounds given its size and apparent rigor. Where it may be susceptible to criticism is in the question of whether or not the study cohort is representative of the patients treated with ketamine in the world outside of clinical trials. Pre-trial oral morphine equivalent opioid consumption of 300 mg to 400 mg/day represents significant daily opioid consumption where pain remains inadequately controlled. Across the whole cohort pain scores ranged from 2.47 to 8.08, with means of 5.43 and 5.21 for treatment and placebo arms respectively. Individual clinicians will have to make their own judgments as to who from such a cohort they might have chosen to treat with ketamine.

It seems unlikely given the conflicting evidence that the work of Hardy and colleagues will sound the death knell for ketamine in the management of cancer pain. It is a substantial achievement, however, and has set a very high standard. There have been repeated calls for high quality RCT's to try to tease out the problem of ketamine in cancer pain and now we have one (1). Despite this, individual clinicians' experiences and case reports are highly influential in shaping practice, and the problem of how we deal with a relatively large body of contrary evidence from open label studies and case series/reports remains to be resolved. Although Hardy and colleagues have demonstrated what can be done with perseverance and confirmed that rigorous trials of this nature can be completed in a palliative care population, we may have a long wait for confirmation of their results.

Ketamine is widely used in pain management in the palliative care population despite the limited evidence and the question must now be asked if Hardy and colleagues have indeed revealed an inconvenient truth. Confusion and uncertainty about the role of ketamine in pain management is not confined to cancer pain (13) and the need to continue to accumulate evidence remains. One consequence of this uncertainty, and a striking feature of the literature on the use of ketamine in cancer pain, is the lack of standardization in methodology making comparison of published reports difficult. Perhaps clinicians should give some thought to the development of uniform dosing and reporting guidelines and for clinicians and journals to publish negative as well as positive experiences with ketamine in the management of cancer pain.

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