Caffeine as an Adjuvant Therapy to Opioids in Cancer Pain: A Randomized, Double-Blind, Placebo-Controlled Trial

Presented by: FM R2 Jacky Truong, Dec 12, 2013

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Abstract: Context. Opioid therapy often shows insufficient efficacy and substantial adverse events in patients with advanced cancer.

Objectives. To assess the efficacy of caffeine infusion as an adjuvant analgesic to opioid therapy in patients with advanced cancer.

Methods. A double-blind, randomized, placebo-controlled trial was conducted in the palliative care wards of two teaching hospitals in South Korea. A total of 20 of 41 participants were assigned to the caffeine group and 21 to the placebo group. The participants received caffeine (200 mg) or normal saline intravenously once a day for two days. The primary outcome was pain, which was measured using a 10-point rating scale. Other outcomes included drowsiness, confusion, nausea, sleep disturbance, fatigue, and sadness.

Results. Three participants (two in the caffeine group and one in the placebo group) dropped out after the first intervention because of insomnia; thus, 38 participants completed the trial. Pain score was significantly lower in the caffeine group than in the placebo group after the second trial (P = 0.038). The mean reduction in pain intensity in the caffeine group was 0.833 (95% confidence interval [CI] 0.601–1.066), whereas that in the placebo group was 0.350 (95% CI 0.168–0.532). Considering an improvement higher than 30% from baseline as the threshold value, drowsiness improved significantly in the caffeine group after the first trial (P = 0.041). Adverse event rate did not differ between the two groups.

Conclusion. Caffeine infusion significantly reduced pain and drowsiness, but the reduction did not reach clinical significance in patients with advanced cancer undergoing opioid therapy. Further investigations are warranted.


Strengths:
- Detailed and appropriate randomization process and proper blinding of patients and staff with use of a placebo control group.
- Characteristics of groups fairly balanced including the use of opioids and other adjuvant analgesics taken into account.
- Performed intention to treat analysis (2 dropouts in caffeine vs 1 dropout in placebo group).
- Funded by National Research Foundation of Korea and none of the authors had any conflicts of interest noted.
- It was also useful to assess the other above primary outcomes for which caffeine could have additional beneficial effects.

Weaknesses:
- Small scale study, and furthermore the sample size is insufficient as they predetermined 27 patients were needed in each group to achieve significant power.
- Potential problems with selection of the patient sample given recruitment was based on access to & reading of recruitment posters.
- Excluded patients with pain >6/10 on a numeric rating scale.
- Acknowledged need for future use of crossover study design rather than parallel group design.
- Findings are not clinically meaningful unless 2+ point reduction on a 10 point scale.
- Furthermore, there was inadequate investigation into the nature of the pain experienced by the patients nor information about the use of breakthrough medication.
Relevance to Palliative Care: The study was conducted in a hospital palliative care setting with hopes to improve cancer pain management with use of caffeine; in addition to any additional benefits caffeine may provide. There are posited mechanisms for the role of caffeine in pain regulation but at present are weak with a paucity of studies investigating this. Unfortunately, with the negative results of this study, the use of caffeine is more a topic of interesting discussion than an adjunct to cancer pain management. Further research into the topic with varying dosages and administration frequency in a larger setting maybe useful.