Supplementary Material 1. Morphine/Morphine Milligram Equivalent Use Among Participants During Hospitalization

| Authors | Design; no. of participants; study length | Pain rating on admission | Opioid, dose | Pain response | Major findings |
| --- | --- | --- | --- | --- | --- |
| Al-Anazi et al, 2017[1] | Retrospective cohort study  n = 99  Observation period: 3 days | Mean ± SD where 0 = no pain and 10 = severe pain  5.43 ± 1.73 | Cumulative daily dose of morphine ± SD  Day 1: 215 ± 128 mg (PCA group); 44 ± 25 mg (intermittent IV group)  Day 2: 331 ± 101 mg (PCA group); 45 ± 28 mg (intermittent IV group)  Day 3: 230 ± 84 mg (PCA group); 50 ± 31 mg (intermittent IV group) | Intermittent IV vs. PCA IV groups  Day 1 (P < 0.0004)  2.7% vs. none: no pain  24.3% vs. none: mild pain  60.8% vs. 84%: moderate pain  12.1% vs. 16%: severe pain  Intermittent IV vs. PCA IV groups  Day 2 (P < 0.0008)  8.1% vs. none: no pain  29.7% vs. 12%: mild pain  59.5% vs. 76%: moderate pain  2.7% vs. 12%: severe pain  Intermittent IV vs. PCA IV groups  Day 3 (P < 0.0032)  12.1% vs. 4%: no pain  22.9% vs. 12%: mild pain  60.8% vs. 72%: moderate pain  4.2% vs. 12%: severe pain | Participants in the intermittent IV group experienced a significant reduction (P < 0.0004) in pain compared to those in the PCA group. Participants in the PCA group were administered significantly higher amounts (P < 0.000003) of mean total morphine over 3 days. |
| Ballas et al, 2010[2] | Randomized, double-blind, placebo  n= 299  Observation period in days:  Treatment group  HU: 7.6 ± 6.7  Placebo: 7.8 ± 6.5  HU response group  Responders: 5.9 ± 2.6  Non-responders: 7.7 ± 6.8 | Not reported | Mean daily dose of IV MME (SE)  Treatment group  HU: 42.7 (1.1)  Placebo: 41.3 (1.1)  HU response group  Responders: 54.8 (1.4)  Non-responders: 42.3 (1.1)  Mean daily dose of oral MME ± SE  Treatment group  HU: 34.0 (1.1)  Placebo: 34.2 (1.1)  HU response group  Responders: 50.5 (1.4)  Non-responders: 32.6 (1.1) | Mean number of painful crises  Treatment group  HU: 6.4 ± 8.5  Placebo: 8.5 ± 10.1  HU response group  Responders: 2.1 ± 4.1  Non-responders: 7.2 ± 8.8 | Groups did not differ significantly regarding total opioid amounts used to treat pain. |
| Desai et al, 2013[3] | Randomized, double-blind, placebo  n = 13  Observation period: 7 days | Not reported | Median total dose of MME typically via PCA: 400.2 mg (treatment group); 1,471 mg (placebo group) | Two participants from the treatment group were without pain crisis resolution after 7 days. | There were no significant differences between groups regarding time to crisis resolution, pain intensity, or time to discharge. |
| Lagas et al, 2010[4] | Case report  n = 1  Observation period: 6 days | “Severe” bone pain | Cumulative daily dose of morphine  Days 1 to 5: about 100 mg subcutaneously  Day 6: 10 mg subcutaneously, 29 mg intravenously | No pain resolution | Participant died on day 6 while receiving treatment. |
| van Beers et al, 2007[5] | Randomized  n = 19  Observation period: 12 days | Median pain score (IQR) where 0 = no pain, 100 = worst pain  72 (63 - 84) (PCA group)  59 (51 - 85) (CI group) | Mean daily morphine consumption medians (interquartile ranges)  0.5 (0.3 - 0.6) mg/h (PCA group)  2.4 (1.4 - 4.2) mg/h (CI group) | Mean daily pain where 0 = no pain and 10 = worst pain  4.9 (PCA group)  5.3 (CI group) | During VOC, the median cumulative dose of morphine given to participants in the PCA group was significantly lower (P < 0.018) compared to participants in the CI group. |

SD: standard deviation; SE: standard error; intermittent IV: intermittent intravenous opioid administration; PCA: patient-controlled analgesia; HU: hydroxyurea; MME: morphine milligram equivalent; CI: continuous infusion; IQR: interquartile range.

**References**

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