Subcutaneous versus intravenous route switch from oral to parenteral morphine in patients with cancer: randomised controlled trial

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ABSTRACT

Background Subcutaneous (SC) administration is the preferred parenteral opioid route in palliative care, while intravenous infusion may allow faster titration. Comparative evidence remains limited. This study assessed whether intravenous or SC morphine, administered by continuous infusion with bolus doses, offered advantages in (1) time to stable infusion rate and (2) time to pain relief following a bolus dose.

Methods In this double-blind, double-dummy randomised controlled trial, 60 hospitalised palliative care patients with cancer requiring opioid rotation to parenteral morphine were randomised to continuous SC or intravenous infusion with bolus doses over 48 hours.

Results Mean time to final infusion rate was 20.4 hours (95% CI: 15.2 to 25.6) for SC and 16.3 hours (95% CI: 10.5 to 22.2) for intravenous (mean difference: 4.1 hours, 95% CI: –3.6 to 11.7; p=0.293). Median time to effect from bolus doses was 20 min (Q1, Q3: 15, 23) for SC and 15 min (10, 20) for intravenous (HR=1.08, 95% CI: 0.61 to 1.88; p=0.795), indicating no significant difference. NRS scores decreased from 3.9 to 2.1 (SC) and 3.3 to 2.3 (intravenous). Infusion rates increased from 2.4 to 3.3 mg/hour, bolus doses from 4.6 to 6.6 mg. Of 604 boluses, the proportion of effective doses was similar between groups. One intravenous patient developed catheter-related thrombosis and infection post-intervention.

Conclusion No statistically significant or clinically meaningful differences in effectiveness or safety were observed between SC and intravenous morphine administration. Both routes allowed similar titration patterns, supporting the use of either route in palliative care without compromising analgesic efficacy or safety.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Subcutaneous (SC) morphine is preferred in palliative care for its ease and safety, while intravenous morphine is thought to provide faster pain relief.

WHAT THIS STUDY ADDS

⇒ This randomised controlled trial found no statistically or clinically significant differences between SC and intravenous morphine via patient-controlled analgesia in time to stable infusion rate or time to pain relief after bolus dose. Across other outcomes—including bolus effectiveness, opioid use, pain and symptom scores, side effects and quality of life—no meaningful differences were observed during the 48-hour intervention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians can confidently choose either route based on practical considerations. Future research should explore whether subgroups with compromised SC absorption may benefit more from intravenous administration.

INTRODUCTION

Effective pain management is central to palliative care, with opioids routinely used for moderate-to-severe cancer pain. The WHO analgesic ladder provides a structured approach to pain relief.[1] Despite appropriate step 3 management, some patients do not achieve adequate pain relief, experience intolerable side effects with oral opioids or are unable to take oral medication. For these patients, parenteral opioid administration is often considered.[2]

Subcutaneous (SC) administration is recommended as the primary parenteral

route in palliative care due to its ease of use, lower risk of complications and suitability outside hospital settings. Guidelines from the European Society for Medical Oncology (ESMO) and the European Association for Palliative Care support SC opioids as the preferred option, reserving intravenous administration for cases where rapid titration to analgesia is required or when SC administration is contraindicated due to factors such as poor peripheral circulation, oedema or coagulation disorders.[2 3] Intravenous titration has provided a rapid onset of analgesia within minutes in patients with cancer pain.[4] Studies from the postoperative setting further support its fast action, safety and feasibility[5] and its pharmacokinetic advantage.[6] Still, high-quality studies comparing time to pain relief in palliative care patients are lacking.

Traditionally, intravenous opioid infusions are reserved for hospital settings due to the need for venous access and monitoring. However, increasing use of peripherally inserted central catheters (PICC) and midline catheters has improved access and safety, expanding intravenous opioid use beyond hospitals[7 8] and challenging the notion that SC should remain the default route.

Patient-controlled analgesia (PCA), initially developed for postoperative pain management, has been increasingly adopted in palliative care.[9] By combining continuous infusion with bolus dosing, PCA enables individualised pain control and is now widely available in both institutional and home care settings.[10] Despite the widespread use of PCA in palliative care, comparative studies of SC and intravenous routes—including equianalgesic effects and titration strategies—remain limited.[11 12]

In this randomised controlled trial, intravenous and SC routes were compared for initiation of parenteral morphine with continuous infusion and bolus doses in palliative care patients with cancer. The primary outcome was time to achieve a stable infusion rate, and the secondary outcome was time from bolus administration to clinically meaningful pain relief.

METHODS

Design

This phase III double-blind, double-dummy, randomised controlled trial compared morphine infusion combined with bolus doses administered subcutaneously or intravenously. To maintain blinding, each participant received two PCA pumps, one delivering morphine and the other placebo via the alternate route. Data were collected between March 2022 and January 2025. The trial was registered at ClinicalTrials.gov (NCT05236647) and EudraCT (2021-003427-14).

Setting

The study was conducted at the Department of Palliative Medicine, Akershus University Hospital, Norway. Participants were hospitalised during the 48-hour intervention and followed-up through medical records at 1-week and 4-week post-intervention for opioid use, adverse events and survival.

Eligibility criteria for participants

Eligible participants were palliative care patients with cancer (≥18 years) hospitalised with inadequate pain relief despite oral or transdermal opioids, requiring parenteral morphine via PCA, with a planned discharge to home or nursing home, suitable initial morphine dose of 1–8 mg/hour and study initiation between 11:00 and 15:00.

Exclusion criteria were a clear indication for either SC or intravenous administration, inability to report outcomes due to language barriers, cognitive impairment or delirium, contraindications to morphine (eg, allergy, estimated glomerular filtration rate (eGFR)<30), inadequate venous access, significant cachexia, peripheral oedema, expected survival under 2 weeks or opioid therapy other than morphine, oxycodone or fentanyl, or recent (<24 hours) initiation or adjustment of co-analgesics.

Outcomes and measurements

The primary outcome

was time from the start of continuous morphine infusion with titration until a stable infusion rate was reached, defined as no further dose adjustments required. (H_0: no difference between SC and intravenous routes).

The secondary outcome

was time from bolus administration to clinically meaningful pain relief, defined as a reduction of ≥2 on the Numerical Rating Scale (NRS, 0–10).

Additional outcomes included total opioid consumption, total and proportion of effective bolus doses, and pain intensity measured by NRS at 12-hour intervals.[13] Patient-reported treatment benefit was assessed using the Patient Global Impression of Change (PGIC).[14] Symptom burden was evaluated using the Edmonton Symptom Assessment Scale (ESAS). Quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) at baseline and after 48 hours[15] and compared with reference populations.[16 17] Sedation was measured every 2 hours during daytime using the Richmond Agitation-Sedation Scale for Palliative Care (RASS-PAL).[18] Respiratory rate was recorded every 2 hours and other vital signs every 12 hours. Opioid-related side effects were assessed at baseline, 24, and 48 hours using a structured side effect score modelled after the ESAS.[19] Infusion site and line complications were documented throughout the intervention and follow-up.

Infusion procedures

Patients received two identical CADD-Solis PCA (ICU Medical) infusion pumps: one morphine, one placebo

(saline). Pumps were labelled intravenous or SC based on randomisation and connected to respective lines. Infusions and bolus doses were administered simultaneously through both pumps.

Morphine (10 or 20 mg/mL, Oripharm) was diluted in sodium chloride 0.9% to 5 or 10 mg/mL by the Hospital Pharmacy at Akershus University Hospital. The PCA dose was calculated based on the total opioid use in the previous 24 hours, using morphine equivalence tables[20] and adjusted for the patient's response to prior parenteral rescue doses if available. PCA concentrations (5 or 10 mg/mL) were selected for initial infusion rates of 0.2–0.8 mL/hour.

PCA pumps were connected subcutaneously via an upper arm Neria infusion set and intravenously (peripheral/central venous catheter). Initial bolus doses were at least equal to the hourly infusion rate, but never lower than 2.5 mg. Bolus doses were administered by a nurse on patient request. Doses were titrated stepwise for optimal analgesia with minimal side effects.

Randomisation

Randomisation (1:1 allocation) was computer-generated in blocks of six to eight patients by the Department of Surgical Research at Akershus University Hospital. Allocation sequences were stored, with only the pharmacy having access. Patients were individually unblinded at 48 hours or on withdrawal.

Statistics

Analyses followed the intention-to-treat principle, with per-protocol sensitivity analysis. Safety analyses included all participants who received at least one dose of the study drug.

Sample size calculation ($\alpha=0.05$, power=90%) was based on detecting a 12-hour clinically meaningful difference in time to stable infusion rate (assumed SD=12 hours). This required 23 patients per group; 30 per group were included to account for 25% dropout. The statistical analysis plan was registered on ClinicalTrials.gov on 19 December 2023.

Descriptive statistics included means with SDs or medians with quartiles for continuous variables, and frequencies for categorical variables. The primary outcome was analysed using an independent samples t-test, with Mann-Whitney U test and Tobit regression as sensitivity analyses due to potential skewness and right-censoring. Time to bolus effect was assessed by a Cox proportional hazards model, accounting for potential within-patient correlations using robust variance. The proportional hazards assumption was assessed using Schoenfeld residuals and, if violated, a Cox model with a time-dependent covariate was considered. As a sensitivity analysis, the Cox model with gamma-distributed frailty was estimated. Boluses <60 min apart were excluded to avoid overlap in analgesic effect.

Bolus effectiveness (NRS reduction ≥2) across 12-hour intervals was analysed using generalised linear mixed model with random effects for patients and fixed effects for time period, study arm and the interaction between these two. Similar analysis was performed for the proportion of partially effective boluses (NRS reduction <2, but no repeat bolus within 60 min). Results were presented as average predicted probability (in percentage) within each arm and the mean between-group difference in probability with the corresponding 95% CIs and p values.

Continuous outcomes, including pain scores, opioid consumption, sedation level, vital parameters, ESAS symptoms, opioid side effect scores, were analysed using linear mixed models with random effects for patients. The models included fixed effects for time, treatment arm and their interaction. Between-group differences at individual time points were tested post hoc. Exploratory analyses of total 48-hour morphine consumption included linear regression models, with covariates for albumin, eGFR, pain score, administration route and interactions. EORTC QLQ-C30 subscales were analysed using paired t-tests, PGIC by Mann-Whitney U test and complications by χ^2 test or Fisher's exact test.

Survival at 4-week follow-up was analysed using the log-rank test.

No imputation for missing data was performed as there were no missing values for the primary outcome, and linear mixed models and generalised linear mixed models include all available data, yielding unbiased estimates under the assumption of missing completely at random. This assumption was considered reasonable due to the low and balanced dropout rate. Missing data on bolus time to effect were also similarly distributed between groups.

All statistical tests were two-sided, with $p<0.05$ considered statistically significant. The results were reported as means with corresponding 95% CIs. Analyses were performed using Stata V.18.

RESULTS

Participant flow and baseline characteristics

60 patients were included in the study, with 31 allocated to the SC arm and 29 to the intravenous arm (figure 1). Over the 48-hour study period, 10 (16.7%) patients withdrew, evenly distributed between the two treatment arms. Seven withdrew due to disease deterioration, and three due to additional pain medication needs. Baseline characteristics were similar between groups (table 1). Initial morphine dosing, based on prior opioid use, yielded a mean infusion rate of 2.4 mg per hour (95% CI: 2.2 to 2.7) and a mean bolus dose of 4.6 mg (95% CI: 4.0 to 5.1), with no between-group differences (table 2).

After 48 hours, all patients were unblinded and 32 continued with the study infusion route. 15 patients switched from SC to intravenous morphine, primarily

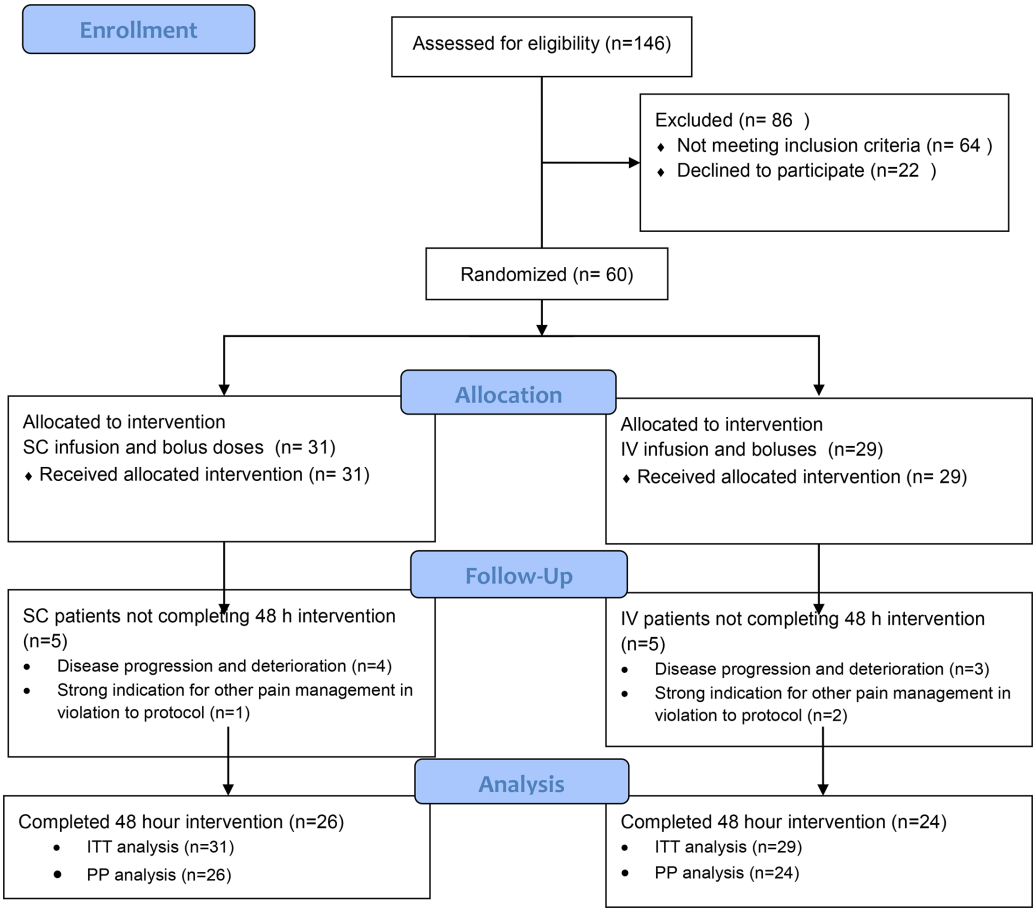

Figure 1 Consolidated Standards of Reporting Trials flow diagram of participant enrolment, randomisation, allocation, follow-up and analysis. IV, intravenous; ITT, intention-to-treat; PP, per-protocol; SC, subcutaneous.

due to existing central access (n=6) or to enhance opioid effect (n=5). Two switched due to SC occlusion, one due to SC site pain and one due to side effects prompting rotation to oxycodone. Three intravenous patients switched: one to oral opioids and two to oxycodone.

Primary outcome

The mean (95% CI) time from the start of continuous infusion until the final dose adjustment was 20.4 hours (15.2 to 25.6) in the SC group and 16.3 hours (10.5 to 22.2) in the intravenous group, with a mean difference of 4.1 hours (−3.6 to 11.7; p=0.293) (figure 2). Mann-Whitney U test and Tobit regression yielded consistent results.

Secondary outcome

A total of 288 bolus doses, given at least 60 min apart, resulted in clinically significant pain relief (NRS reduction ≥2). Time to effect was documented for 80% of these bolus doses. Median (Q1, Q3) time to effect was 20 (15, 23) min for SC and 15 (10, 20) min for intravenous (figure 3). The proportional hazards assumption was met. The hazard for effective bolus was not significantly different between the arms (HR=1.08, 95% CI: 0.61 to 1.88, p=0.795). A frailty model confirmed the absence of significant between-group differences despite within-patient variance.

Exploratory outcomes

Across the 60 patients, 604 bolus doses were administered (mean 10.1 per patient, 95% CI: 8.5 to 11.6, range 0–25), with no between-group differences. NRS scores were registered before 597 boluses (98.8%) and both before and after 570 (94.4%). Bolus use declined significantly over time, with mean 6.3 (95% CI: 5.3 to 7.3) boluses in the first 24 hours and 4.3 (95% CI: 3.5 to 5.2) boluses at 24–48 hours (mean difference: 2.0, 95% CI: 1.1 to 2.9; p<0.001) with no interaction between time and administration route.

Predicted probabilities for effective boluses (NRS reduction ≥2) ranged from 56% to 76% across time intervals (table 3). No significant interaction between time and administration route was found. When including partly effective boluses (NRS<2, no repeat bolus within 60 min), the predicted probability of success increased to 76–96%. The only statistically significant difference occurred at 24–36 hours, where the intravenous group had a higher proportion of fully or partly effective boluses (intravenous: 94.5%, SC: 82.4%; p=0.027).

Table 1 Patient baseline characteristics

Variable	SC (n=31)	IV (n=29)
Demographics		
Age (mean±SD)	64.7±10.3	67.4±9.1
BMI (mean±SD)	23.6±5.1	24.2±6.3
Female (n (%))	17 (55)	14 (48)
Karnofsky score (median (Q1, Q3))	60 (40, 70)	50 (50, 60)
Biochemistry, n		
Haemoglobin (g/L)	111±17	109±22
C-reactive protein (mg/L)	79±83.3	68.3±64.4
INR	1.1±0.2	1.1±0.2
eGFR (mL/min/1.73 m²)	84.3±19.7	84.1±20.6
Bilirubin (µmol/L)	13.5±19.0	27.3±74.6
Albumin (g/L)	35.6±7.9	35±7.8
Principal diagnosis, n		
Digestive cancers	16	14
Lung cancers	4	2
Gynaecological cancers	2	4
Urinary tract cancers	3	3
Breast cancer	3	2
Prostate and male genital cancers	1	1
Head and neck cancers	0	2
Metastatic/unspecified cancers	0	1
Haematological cancers	1	0
Melanoma and skin cancers	1	0
Metastatic situation, n		
Lung	16	18
Bone	14	12
Liver	13	13
Peritoneal carcinomatosis	5	6
CNS	3	1
Ongoing anticancer treatment, n		
Chemotherapy	8	6
Radiotherapy	3	4
Immunotherapy	2	2
Comorbidity, n		
Circulatory system diseases	11	9
Endocrine and metabolic diseases	5	10
Neoplasms	7	7
Respiratory system diseases	6	7
Medication, n (%)		
Opioids	31 (100)	29 (100)
Non-opioid analgesics	18 (58)	14 (48)
Sedatives/anxiolytics	11 (35)	9 (31)
Corticosteroids	9 (29)	9 (31)
Antiepileptics	4 (13)	11 (38)

BMI, body mass index; CNS, central nervous system; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; IV, intravenous; SC, subcutaneous.

Pain scores (mean±SD) decreased significantly over time in both groups (p<0.001): SC from 3.9±2.3 to 2.1±1.8, intravenous from 3.3±2.0 to 2.3±2.1. No significant difference between groups was observed.

Opioid consumption (mean±SD) over 48 hours was 209±121 mg (SC) and 215±117 mg (intravenous). No significant predictors were identified in linear regression including age, albumin, haemoglobin, body mass index, baseline pain, sex, eGFR and route.

Infusion rates (mean±SD) increased by 0.9±1.1 mg/hour, from 2.4±1.0 mg/hour to 3.4±1.7 mg/hour and bolus doses by 2.1±2.3 mg, from 4.6±2.2 mg to 6.6±3.4 mg (both p<0.001), with no between-group differences.

No significant group differences were observed in opioid-related side effects (table 4). Constipation decreased in both groups. No trends or differences were found for other ESAS symptoms including shortness of breath, anxiety, depression, appetite and well-being (table 5).

EORTC QLQ-C30 scores at baseline indicated high role and social functioning, but low scores in emotional, cognitive and global quality of life (see online supplemental file 1). Symptom burden was high, especially fatigue, pain, appetite loss and constipation. After 48 hours, insomnia scores improved in both groups. Other changes were below clinical relevance thresholds, with no between-group differences.

At 48 hours, 81% (39/48) rated their condition as 'better' or 'much better' on the PGIC (SC: 88%, intravenous: 74%). Six patients (13%) reported 'unchanged' (SC: 12%, intravenous: 13%). Three patients (all intravenous) reported their condition as 'worse'.

Safety and adverse events

Vital signs remained stable, with no significant between-group differences (see online supplemental file 2). Mean daytime respiratory rate was 15 (95% CI: 14.6 to 15.5), dropping at night to 13 in both groups (SC: 95% CI: 12.9 to 13.9; intravenous: 95% CI: 12.5 to 13.5), with a mean difference of −1.28 (95% CI: −1.68 to –0.89, p<0.001). The intravenous group had slightly lower rates overall (−1.04, 95% CI: −2.05 to –0.02, p=0.045). There was no significant change from start to end of the 48-hour intervention.

20 patients switched from SC to intravenous during follow-up, most due to pre-existing venous access. Other reasons included occlusion (n=2), local reaction (n=2) and attempts to improve bolus dose effectiveness (n=4). A total of 40 participants had a central venous access device during or after the intervention, including 16 peripherally inserted central catheters, 10 venous access ports and 14 midline catheters. Complications related to intravenous central lines included thrombosis with infection (n=1), bleeding (n=1), self-discontinuation (n=1), leakage (n=1) and occlusion (n=2).

Serious adverse events occurred in two patients. One developed venous catheter thrombosis and sepsis 10 days post-study, requiring hospitalisation and resolving with anticoagulants and antibiotics.

Table 2 Mean (SD) opioid infusion rates (mg/hour) and bolus doses (mg) at 0 and 48 hours

Variable	SC	SC Min - Max	IV	IV Min - Max	P value
Starting infusion dose (mg/h)	2.5±1.0	1.0 to 5.0	2.5±1.0	0.5 to 4.0	0.888
Starting bolus dose (mg/dose)	4.6±2.4	2.0 to 10.0	4.6±2.4	2.0 to 10.0	0.618
Infusion dose at 48 hours (mg/h)	3.3±1.7	0.5 to 9.0	3.3±1.7	0.5 to 6.0	0.740
Bolus dose at 48 hours (mg/dose)	6.7±3.5	2.0 to 15.0	6.7±3.5	2.5 to 15.0	0.779
Change in infusion dose (mg/h)	0.8±1.1	−1.0 to 4.0	0.8±1.1	−1.0 to 3.0	0.447
Change in bolus dose (mg/dose)	2.0±2.3	−2.0 to 7.5	2.0±2.3	−2.0 to 10.0	0.933

P values calculated using independent samples t-test.
IV, intravenous; Max, maximum; mg/dose, milligrams per dose; mg/h, milligrams per hour; Min, minimum; SC, subcutaneous.

Another experienced recurrent delirium 40 hours into the intervention, leading to study exclusion. The event was considered unrelated to the intervention, as opioid doses had been reduced from the patient's prior tolerance levels. Delirium resolved with antipsychotic treatment.

At 4-week follow-up, 23 of the 50 patients who completed the intervention were alive. Survival did not differ significantly between groups (log-rank p=0.69).

DISCUSSION

This randomised controlled trial demonstrated that opioid rotation to SC or intravenous morphine via PCA was comparably effective and safe for patients with cancer transitioning from oral or transdermal opioids. Across multiple clinically relevant outcomes—including time to stable infusion rate, time to effect of bolus doses, bolus effectiveness, opioid consumption, pain and symptom scores, side effects and quality of life—no statistically or clinically meaningful differences were observed between the two administration routes over 48 hours. These findings suggest the choice of parenteral route can be guided by practical considerations without compromising analgesia or safety.

The mean time to final infusion rate was reached within the first 24 hours in both groups, suggesting that titration can typically be completed within this time frame, regardless of administration route. In previous studies, titration was typically completed prior to continuous infusion, limiting direct comparisons.[21–23] Our study was powered to detect a 12-hour difference in time to final infusion rate, considered clinically meaningful, as it could affect length of hospitalisation. However, the observed difference of approximately 4 hours was neither statistically nor clinically significant.

For time to effect from individual bolus doses, neither statistically nor clinically meaningful difference between SC and intravenous was observed. This contrasts with pharmacokinetic studies showing a 10–15 min longer time to maximum concentration for SC morphine in palliative care patients[24] and healthy individuals.[25] However, this pharmacokinetic difference did not translate into a detectable delay in perceived pain relief in our study. The ESMO guideline strongly recommends intravenous titration in acute situations with severe cancer pain, where rapid onset is considered critical.[2] This is based on studies using more aggressive intravenous than SC protocols, assuming faster effect with intravenous, for example, morphine every 5–10 min intravenous versus 30 min SC.[26 27] Our findings suggest that when bolus dosing protocols are identical, SC titration does not result in slower onset of pain relief compared with intravenous,

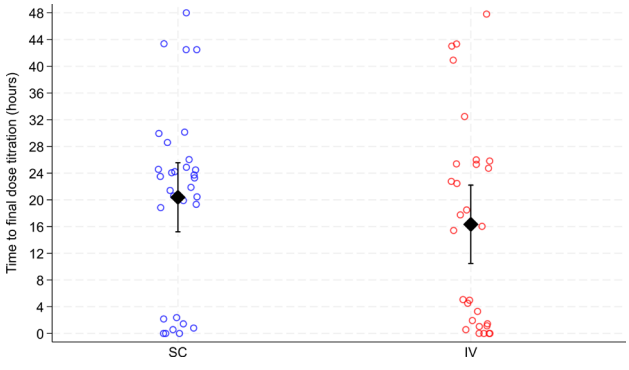

Figure 2 Distribution of individual patient values for time to final infusion rate. Each circle represents one patient. Group means (SC and IV) are shown as black diamonds with 95% CI. Mean difference: 4.1 hours (–3.6 to 11.7; p=0.293). IV, intravenous; SC, subcutaneous.

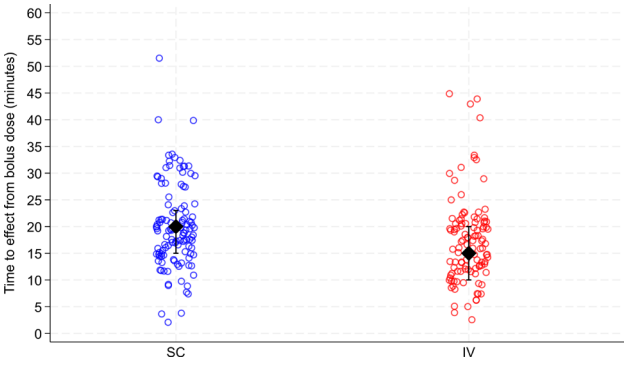

Figure 3 Distribution of individual bolus dose times to effect. Each circle represents a recorded observation (Numerical Rating Scale reduction ≥2) following a bolus dose, grouped by administration route. Black diamonds indicate the median time to effect with interquartile ranges (Q1, Q3). Median (Q1, Q3): 20 (15, 23) min for SC and 15 (10, 20) min for IV (HR=1.08, 95% CI: 0.61 to 1.88, p=0.795). IV, intravenous; SC, subcutaneous.

Table 3 Model-estimated percentage of effective, partly effective and ineffective bolus doses across time intervals for SC and IV administration (mean % with 95% CI)

Bolus type	SC % mean (95% CI)	IV % mean (95% CI)	Mean SC-IV difference (95% CI)	P value
Bolus count period 0–12 hours	31 patients, 94 boluses	29 patients, 119 boluses		
Effective (NRS reduction ≥2)	65.0 (50.9 to 79.1)	57.9 (45.8 to 70.2)	−7.1 (−25.6 to 11.5)	0.456
Partly effective (NRS reduction <2, no repeat bolus)	11.9 (4.3 to 19.6)	18.0 (9.2 to 26.7)	6.0 (−4.6 to 16.7)	0.267
Ineffective (NRS reduction <2, repeat bolus provided)	20.9 (10.0 to 31.9)	21.6 (13.3 to 29.9)	0.7 (−0.13 to 0.14)	0.921
Bolus count period 12–24 hours	31 patients, 79 boluses	28 patients, 78 boluses		
Effective (NRS reduction ≥2)	65.6 (51.8 to 79.3)	70.9 (58.0 to 83.8)	5.3 (−13.6 to 24.3)	0.580
Partly effective (NRS reduction <2, no repeat bolus)	23.1 (11.2 to 35.0)	13.4 (4.2 to 22.5)	−9.7 (−24.8 to 5.3)	0.206
Ineffective (NRS reduction <2, repeat bolus provided)	10.1 (3.0 to 17.3)	14.2 (5.4 to 23.1)	4.1 (−6.8 to 15.0)	0.459
Bolus count period 24–36 hours	29 patients, 78 boluses	24 patients, 60 boluses		
Effective (NRS reduction ≥2)	56.2 (39.4 to 72.9)	65.6 (52.9 to 78.2)	9.4 (−11.2 to 30.0)	0.371
Partly effective (NRS reduction <2, no repeat bolus)	23.3 (10.8 to 35.8)	30.1 (16.5 to 43.6)	6.7 (−11.0 to 24.5)	0.456
Ineffective (NRS reduction <2, repeat bolus provided)	17.6 (8.0 to 27.3)	5.5 (0.8 to 10.1)	−12.2 (−22.9 to −1.4)	0.027
Bolus count period 36–48 hours	28 patients, 52 boluses	24 patients, 44 boluses		
Effective (NRS reduction ≥2)	70.1 (55.2 to 85.0)	75.7 (59.3 to 92.1)	5.6 (−16.6 to 27.8)	0.620
Partly effective (NRS reduction <2, no repeat bolus)	13.2 (2.2 to 24.2)	13.2 (0.9 to 25.5)	0.02 (−16.6 to 0.17)	0.998
Ineffective (NRS reduction <2, repeat bolus provided)	15.5 (4.4 to 26.6)	10.1 (0.8 to 19.4)	−5.4 (−19.2 to 8.4)	0.444

Bolus categories were defined as follows: effective=NRS reduction ≥2 following the bolus. Partly effective=NRS reduction <2 with no repeat bolus administered. Ineffective=NRS reduction <2 with a repeat bolus provided. n=number of boluses administered within each time period.
IV, intravenous; NRS, Numerical Rating Scale; SC, subcutaneous.

challenging the assumption of clinically relevant advantage of intravenous in this setting. The lack of difference on the group level does not rule out the possibility that individual patients with poor peripheral circulation, severe cachexia or peripheral oedema might benefit from intravenous administration.

In both groups, bolus frequency declined over time, suggesting improved analgesia with infusion titration. Still, a mean of 4.3 boluses during 24–48 hours exceeds trial reports, considering near-zero bolus use optimal.[21 22] However, this level of bolus use aligns with patterns observed in retrospective studies of intravenous PCA[28] and both intravenous and SC PCA in palliative care settings,[29] and supports the notion that flexible bolus use may better accommodate diurnal variation in opioid need.[30]

The proportion of bolus doses resulting in clinically meaningful pain relief (NRS reduction ≥2) was comparable between groups across all time intervals. The only statistically significant difference was observed in the 24–36 hours window, where intravenous showed higher efficacy when including partly effective boluses, although the clinical relevance of this isolated finding is limited. The clinical relevance of an NRS reduction ≥2 depends on baseline pain severity; the same absolute reduction may represent moderate or substantial relative improvement, with floor effects further limiting interpretability at low baseline scores.[31] Moreover, this definition captures changes in intensity, but may not fully reflect the subjective experience of pain relief.

Table 4 Mean (SD) opioid side effect score in SC and IV groups at 0, 24 and 48 hours

	SC			IV				
Side effect	SC 0 hour	SC 24 hours	SC 48 hours	IV 0 hour	IV 24 hours	IV 48 hours	P (48 hours vs 0 hour)	P (IV interaction)
Nausea	0.9±1.5	1.3±1.6	1.0±1.6	1.1±1.8	1.2±2.4	0.8±1.6	0.684	0.443
Vomiting	0.4±0.9	0.4±1.1	0.5±1.2	0.9±2.2	0.9±2.0	0.5±2.1	0.554	0.113
Constipation	3.7±3.6	2.6±3.1	1.6±2.3	2.9±3.2	2.2±3.0	0.9±1.7	0.022	0.830
Drowsiness	4.7±2.2	4.4±2.6	3.9±2.9	4.8±2.7	4.7±2.6	4.7±2.7	0.144	0.405
Confusion	0.6±1.2	0.7±1.9	0.9±2.0	1.6±2.4	1.2±2.4	0.8±1.7	0.252	0.137
Disorientation	0.4±0.8	0.2±0.5	0.4±1.1	0.7±1.5	0.5±1.6	0.2±0.4	0.976	0.204
Hallucinations	0.9±1.7	0.4±1.1	0.6±1.5	0.5±1.3	0.2±0.5	0.3±1.0	0.551	0.927
Seeing shadows	1.2±2.3	0.6±1.2	0.6±1.3	1.1±2.1	0.9±1.9	0.4±0.9	0.141	0.860
Vivid dreams	1.2±2.3	1.3±2.5	0.6±1.6	0.9±1.9	1.1±1.9	1.2±2.4	0.097	0.094
Muscle twitching	1.1±1.6	1.0±1.6	1.4±1.9	1.5±2.0	1.1±1.7	1.2±2.0	0.622	0.660

IV, intravenous; SC, subcutaneous.

Table 5 Mean (SD) ESAS score in SC and IV groups at 0, 24 and 48 hours. Pain was the only symptom that changed significantly over time (p<0.001), with no group time interaction (p=0.51)

	SC			IV		
Symptom	SC 0 hour	SC 24 hours	SC 48 hours	IV 0 hour	IV 24 hours	IV 48 hours
Pain	3.9±2.3	2.8±1.8	2.1±1.8	3.3±2.0	2.8±2.3	2.3±2.1
Tiredness	4.9±2.8	3.9±2.8	4.9±3.1	4.6±1.9	4.7±2.6	4.5±2.8
Drowsiness	4.2±2.6	3.3±2.8	4.1±2.6	4.7±2.6	4.6±2.6	3.9±2.8
Nausea	1.1±1.8	1.0±1.3	1.0±2.2	1.1±1.6	0.6±1.6	0.8±1.4
Appetite	3.9±3.2	3.6±3.5	4.8±3.5	4.2±3.5	4.3±3.7	3.4±3.9
Shortness of breath	2.6±2.9	2.5±2.6	2.0±2.4	2.6±2.3	2.2±2.8	2.0±2.9
Depression	2.0±2.7	1.6±2.4	2.6±2.9	2.9±2.5	2.5±2.5	2.4±3.1
Anxiety	1.2±1.6	1.9±2.7	2.2±3.1	2.2±2.3	1.8±2.6	2.5±3.1
Well-being	3.4±2.5	3.2±2.1	3.7±1.9	4.6±2.4	3.9±2.1	3.9±2.2

ESAS, Edmonton Symptom Assessment Scale; IV, intravenous; SC, subcutaneous.

At 48 hours, the bolus-to-infusion dose per hour ratio had stabilised to approximately 2:1 in both groups, corresponding to a bolus dose of around 1:12 of the 24-hour infusion dose. This likely reflects both patient needs and clinical convention. The fixed 20 min lockout time for PCA boluses appeared adequate in both groups, considering the observed time to effect.

Symptom burden was high, particularly for fatigue, pain and appetite loss and aligned more closely to a German palliative care population[32] than to EORTC metastatic cancer reference values or the Norwegian general population.[16 17] Insomnia improved in both groups, possibly reflecting better symptom control or opioid-induced sedation, although daytime sedation (measured by RASS-PAL) did not increase. The 7-day EORTC QLQ-C30 recall limits the sensitivity to changes over the 48-hour period.

Opioid-related side effects, vital signs and sedation scores were comparable between groups, with constipation significantly reduced in both groups, likely due to proactive bowel care during admission. Infusion-related complications were rare but included one case of PICC-associated thrombosis and infection in the intravenous group, highlighting caution against unnecessary central access despite low complication rates in palliative care.[7 8] Post-intervention, some SC patients switched to intravenous, driven by clinical practice.

Pain scores at the start of PCA infusion were moderate, likely due to rescue opioids given between study decision and PCA initiation. While this reflects standard practice, more intense baseline pain could have influenced clinical outcomes.

The dose range and volumes used were within levels generally well absorbed subcutaneously. However, in situations with higher infusion volumes, poor peripheral perfusion, limited subcutaneous tissue or peripheral oedema, SC absorption may be less predictable. Our study excluded such patients, and while no statistically or clinically meaningful differences were observed, intravenous administration may be preferred where SC delivery is compromised.

Despite these limitations, the study has several important strengths. It is the first randomised controlled trial directly comparing SC and intravenous infusion and bolus dosing in palliative care patients. The double-blind, double-dummy design ensured balanced treatment conditions and minimised bias. Inclusion criteria and outcomes were aligned with routine practice in palliative care units. The sample size was sufficient to detect clinically meaningful differences in the primary outcome, and dropouts were few and balanced between arms.

In conclusion, the present study did not demonstrate a clinically or statistically significant difference between SC and intravenous morphine administered via PCA in palliative care patients with cancer. Future research should investigate whether intravenous administration offers advantages in patients with severe cachexia, oedema or in the imminently dying, where SC absorption may be impaired.

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