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Original Article

The cost analysis of remifentanil and fentanyl for analgosedation in mechanically ventilated patients in intensive care: Post hoc analysis of an open-labelled pilot randomised controlled study

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ABSTRACT

Objective: To compare total hospital costs associated with remifentanil versus fentanyl for analgosedation in mechanically ventilated intensive care unit (ICU) patients, given increasing interest in remifentanil as a feasible alternative, but limited economic evidence.
Design: Cost analysis of a single-centre, prospective, randomised controlled trial (remi-fent1 RCT).
Setting: Nepean Hospital ICU, New South Wales, Australia.
Patients: Adult patients admitted between June 2020 and August 2021 requiring invasive mechanical ventilation (IMV) who were randomised to receive remifentanil or fentanyl as part of their analgosedation regimen.
Main outcome measures: The primary outcome was total hospital bed-day costs (Australian Dollars), estimated from a healthcare payer perspective using the Australian Independent Hospital Pricing Authority National Pricing Model for the financial year 2020–2021. Health-related quality of life (HRQoL) at 6 months was measured using the generic EuroQoL 5-dimension 5-level (EQ-5D-5L) instrument. Prespecified subgroup analyses examined age (arbitrary cut-off 65 years) and duration of IMV (arbitrary cut-off 72 h).
Results: A total of 210 patients were analysed (remifentanil n = 104; fentanyl n = 106). Opioid acquisition costs were comparable between groups. Total mean hospital bed-day costs were lower in the remifentanil group compared with the fentanyl ($48,301 [$38,644-$57,958] vs. $37,012 [95% confidence interval {CI}: $27,834-$46,191]; p = 0.006). The remifentanil group was associated with lower total hospital costs in older patients (≥65 years) and in those ventilated for ≤72 h. At 6 months, 110 patients were alive, with 7 lost to follow-up, (61/103 remifentanil [59.2%] vs. 59/100 fentanyl [59.0%]; p = 0.80). Among survivors, remifentanil continued to demonstrate lower overall hospital costs, but 6-month HRQoL remained similar between groups (EQ-5D-5L index 0.83 vs. 0.87; p = 0.24).
Conclusion: Remifentanil was associated with lower total hospital costs than fentanyl, without differences in survival or HRQoL at 6 months, suggesting that remifentanil may be a lower-cost alternative for analgosedation. However, the results are exploratory and require confirmation in larger, adequately powered multicentre phase-2 trials.

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Key take home messages

- The manuscript reports a post hoc cost analysis comparing remifentanil with fentanyl using data from a previously published pilot RCT (10.1016/j.ccrj.2023.10.012).
- Remifentanil was associated with significantly lower ICU and total hospital bed-day costs compared with fentanyl.
- No differences were observed in 6-month survival or HRQoL, indicating comparable long-term clinical outcomes.
- Cost benefits were most pronounced in older patients (≥65 years) and those requiring ≤72 h of mechanical ventilation.
- Opioid acquisition costs were similar, suggesting that the savings were driven by reduced ICU/hospital resource utilisation.
- Overall, these exploratory findings warrant validation in larger multicentre trials.

1. Introduction

In Australian intensive care units (ICUs), over 50,000 patients require resource-intensive treatments such as invasive mechanical ventilation (IMV) annually,[1] often receiving opioid and sedatives infusions to manage pain and anxiety.[1,2] Such treatments could increase the daily costs by an additional 20–26%.[3,4] Decreasing the duration of IMV may lead to clinical and economic benefits.[5] Fentanyl, a commonly used opioid,[6] may result in prolonged deep sedation, immune suppression, and hypotension when administered over an extended duration,[7–9] potentially delaying weaning from IMV.[10] In contrast, remifentanil is an ultra-short acting opioid,[7] with rapid, predictable onset and offset, organ-independent metabolism, a short context-sensitive half-life,[11] and no tissue accumulation.[7,11] Although not yet widely adopted for ICU analgosedation, a recent prospective, open-label, pilot randomised controlled trial (RCT) demonstrated that remifentanil had an equivalent or better safety profile than fentanyl, with trends suggesting earlier extubation, fewer delirium episodes, faster ICU discharge, and more ventilator-free days.[12] Despite its clinical advantages, the higher acquisition cost of remifentanil compared with fentanyl,[10] may present an economic disincentive to its widespread adoption. Additionally, there is limited evidence that remifentanil use leads to overall hospital cost savings sufficient to offset its higher acquisition cost, specifically in the Australian context. Existing studies report mixed findings, with no robust cost analyses conducted in the Australian context.

In this post-hoc study, we aimed to compare the cost analysis of remifentanil with fentanyl in adult ICU patients requiring IMV. Using an analytic 6-month timeframe, we compared the costs, mortality, and health-related quality-of-life outcomes associated with the alternative treatments.

2. Methodology

This is a substudy of a single-centre, open-label, prospective feasibility RCT (the remi-fent 1 study)[12] that was conducted between June 2020 and August 2021. The remi-fent 1 study received ethics approval from the Nepean Blue Mountains Ethics Committee (2020/ETH00311, 04/30/2020) and was registered with the Australia New Zealand Clinical Trials Registry (ID: ACTRN12620000719932). Written informed consent or consent to continue after enrolment was obtained for all patients in accordance with local legal and ethical requirements. All intubated adults (≥18 years) who were likely to need IMV beyond the next calendar day, requiring opioid analgesic continuous infusion to facilitate ventilation were included. Randomisation was performed in a 1:1 ratio using sealed envelopes with computer-generated block randomisation sequences. An independent data and safety monitoring committee provided oversight. For this substudy, we followed the patients for 6 months after enrolment (28 days, 3 months, and 6 months).

2.1. Variables

We used the data already collected for the Remi-Fent 1 study. Apart from the patient demographics and acute illness severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II and III, and Australian and New Zealand Risk of Death [ANZROD]), we collected further information on ICU organ supports (IMV, and need for tracheostomy), incidence of delirium, ICU, post-ICU, and hospital length of stay, and outcome at hospital discharge (dead or alive) and discharge destination (home, and nonhome discharge). Additional data included pertinent investigations (biochemical, radiological, microbiological, miscellaneous, and drug-screening) during the index hospitalisation, along with the information of the follow-up phone calls. We also collected the mortality at 6 months. Health-related quality of life (HRQoL) was assessed during the follow-up phone call by the research team. For survivors, HRQoL was assessed using the EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire in structured telephone interviews conducted within 2 weeks of the 6-month follow-up date by trained research coordinators in the ICU. The EQ-5D-5L is a validated assessment tool that collates responses to five domains of quality-of-life assessments, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, scored across five levels (no problems, slight problems, moderate problems, severe problems, extreme problems, or unable). A utility of zero is equivalent to death, and one indicates full life. As patients were mechanically ventilated at the time of recruitment, a utility value of zero was assumed at baseline. Patients who died at any point during the trial were assigned a utility value of zero. The EQ-5D-5L was valued using the Australian reference algorithm.[13]

2.2. Clinical outcomes

The clinical outcomes of mortality and HRQoL were assessed 6 months after enrolment.

2.3. Cost analysis

The healthcare resource-use outcomes included the duration of the index ICU and hospital admission. The healthcare costs included ICU, post-ICU, opioid, and micro-costing of all investigations during the indexe admission and the total overall hospital cost. The ICU costs were also calculated separately using a per bed-day cost, based on the Australian Independent Hospital Pricing Authority's National Pricing Model, multiplied by the length of ICU stay for the financial year 2020–2021 (Supplementary Table 1).[14] The primary cost analysis focused on hospital bed-day costs during the index admission, from ICU admission until hospital discharge or in-hospital death. Patients who died in the ICU incurred ICU costs until the date of death, but no post-ICU ward costs; thus, such that post-ICU costs for these patients were zero by definition. No costs beyond the initial index hospitalisation were included. HRQoL at 6 months, measured using the EQ-5D-5L and associated utility scores, were

treated as a secondary outcomes, providing contextual information on longer-term patient status rather than forming the basis of a full cost-utility model. This cost analysis is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist (Supplementary Table 2).

2.4. Remifentanil and fentanyl unit cost price

The costing analysis used the procurement cost of fentanyl during the study period. The total pharmacy cost for the remifentanil and fentanyl administered to patients in their respective groups was estimated based on the unit price of AU$2.40 for one ampoule (1 mg) for remifentanil and AU$2.25 for one ampoule (500 mcg) for fentanyl, respectively.[12]

2.5. Costing

The primary economic outcome was ICU cost, derived from ICU length of stay using standardised cost weights. ICU and hospital bed-days were used as inputs for cost estimation rather than independent outcomes. Total hospital cost, including post-ICU ward stay, was analysed as a secondary outcome. We used total hospital bed-day cost as a proxy for resource use. Survival and HRQoL at 6 months were reported as secondary clinical outcomes. Given the feasibility design and limited sample size, no formal incremental cost-effectiveness analysis (e.g. Incremental cost-effectiveness ratio (ICER)) was performed. Instead, costs and outcomes were compared descriptively.

2.6. Statistical analysis

We performed the data analysis using IBM SPSS Version 30 (Armonk, NY). All analyses were conducted according to the randomised allocation (intention-to-treat). We compared binary outcomes for treatment allocation using the X^2 test, and continuous data were reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) based on their distribution. We assessed the probability of survival using Kaplan–Meier survival analysis, using the log-rank test to compare groups, and reported results as hazard ratios (HRs) with 95% confidence intervals (95% CI). The patients were censored at 180 days. If the patients were not alive when contacted, the date of death was recorded as the previous check-in date (for example, if a patient had died at the 3-month call, the censor date was 28 days). The primary economic outcome was ICU cost, derived from ICU length of stay using standardised cost weights. Hospital costs were analysed as a secondary outcome. ICU and hospital bed-days were used as inputs for cost estimation rather than independent outcomes. These costs were reported as mean [SD], using the *t*-test to compare means and reported as mean differences. We then performed an exploratory cost analysis based on three prespecified subgroups that included age (arbitrary cut-off <65 versus ≥65 years), mechanical ventilation duration (<72 versus ≥72 h), and those who were alive at 180 days. We used a two-sided p-value of <0.05 to indicate statistical significance. As reported in the original Remi-Fent1 study,[12] missing data, arising from nonmandatory fields were considered likely not missing at random, and no imputation was performed. There were no missing data with regards to cost (for all participants) and EQ-5D-5L (for survivors at 6 months) data. As this was a single-centre feasibility RCT,[12] the study was not powered to detect small to moderate differences in economic or clinical outcomes, nor to support extensive adjusted regression modelling for costs or HRQoL. Consequently, the cost and HRQoL comparisons are primarily unadjusted and should be interpreted as exploratory.

3. Results

3.1. Baseline comparison

Of the 210 patients included in the cost analysis, 104 received remifentanil, and 106 received fentanyl (Fig. 1). Six patients died early within 24 h (3 each in the remifentanil and fentanyl groups). Mortality data at 6 months were available for all patients. The baseline characteristics were essentially comparable between the two groups and are summarised in Supplementary Table 3. The mean [SD] dose of the opioid infusion was 9.5 [2.7] mcg/kg/hour (0.2 [0.1] mcg/kg/min) in the remifentanil group and 5.2 [2.1] mcg/kg/hour in the fentanyl group.

3.2. Healthcare resource use and costs

There was no difference in the proportion of patients who received IMV on day 1, those who received IMV for >72 h, or those who underwent tracheostomy. However, the median [IQR] duration of IMV was shorter for patients in the remifentanil group (60 [39–210] hours versus 96 [52–192] hours; p = 0.011) with more ventilator-free days at day 28 (26.2 [23.6–27.4] versus 24.3 [20.8–25.7]; p = 0.005) than in the fentanyl group. The ICU, post-ICU and overall hospital lengths of stay were also shorter for patients in the remifentanil group. However, at 6 months, survival was 58.9% (61/104) in the remifentanil group and 55.7% (59/106) in the fentanyl group (p = 0.52). There were no statistically significant differences in ICU, hospital, or 6-month mortality between groups; however, the study was not powered to detect differences in mortality. The discharge dispositions for those who survived the indexed hospitalisation were also comparable between the two groups (Supplementary Table 4). Their time to survival at 6 months was comparable between the two groups (hazard ratio [HR] = 1.49; 95% CI: 0.96–2.31; p = 0.08; Fig. 2).

3.3. Cost analysis at hospital discharge

The opioid cost between the two groups was comparable. The remifentanil group had a lower mean [95% CI] ICU bed-day cost ($25,654.32 [$17,740,44-$33,568.19] versus $31,736.87 [$24,139.33-$39,334.40]; p = 0.005), post-ICU bed-day cost ($7459.08 [$5127.11-$9791.05] versus $12,448.68 [$8643.90-$16,253.45]; p = 0.012) and overall hospital bed-day cost ($37,012.42 [$27,834.16-$46,190.68] versus $48,301.25 [$38,644.47-$57,958.02]; p = 0.006) than the fentanyl group (Fig. 3; Table 1, Supplementary Table 5). The costs related to pathological, radiological drug-screen, microbiological, and miscellaneous investigations were comparable between the two groups (Supplementary Tables 6–10).

3.4. Health-related quality of life at 6 months

As a secondary outcome, HRQoL at 6 months was assessed among the 110 patients who were alive at follow-up. After excluding the 7 patients lost to follow-up, the survival was 59.2% (61/103) for the remifentanil group and 59.0% (59/100) for the fentanyl group (p = 0.80). The proportion of patients reporting problems across the five HRQoL domains was comparable at 6 months between the two groups. The mean [95% CI] EQ index was comparable between the two groups at 6 months (0.83 versus 0.87; p = 0.24; Table 2). Given the reduced sample and the

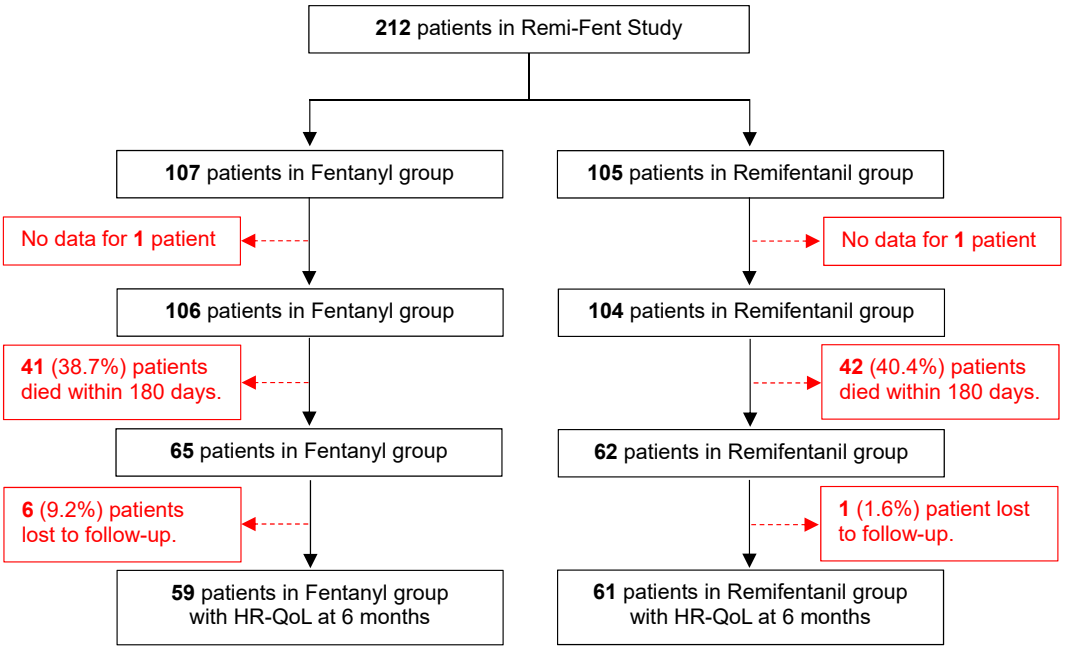

Fig. 1. Consort diagram for the remi-fent study cost analysis.

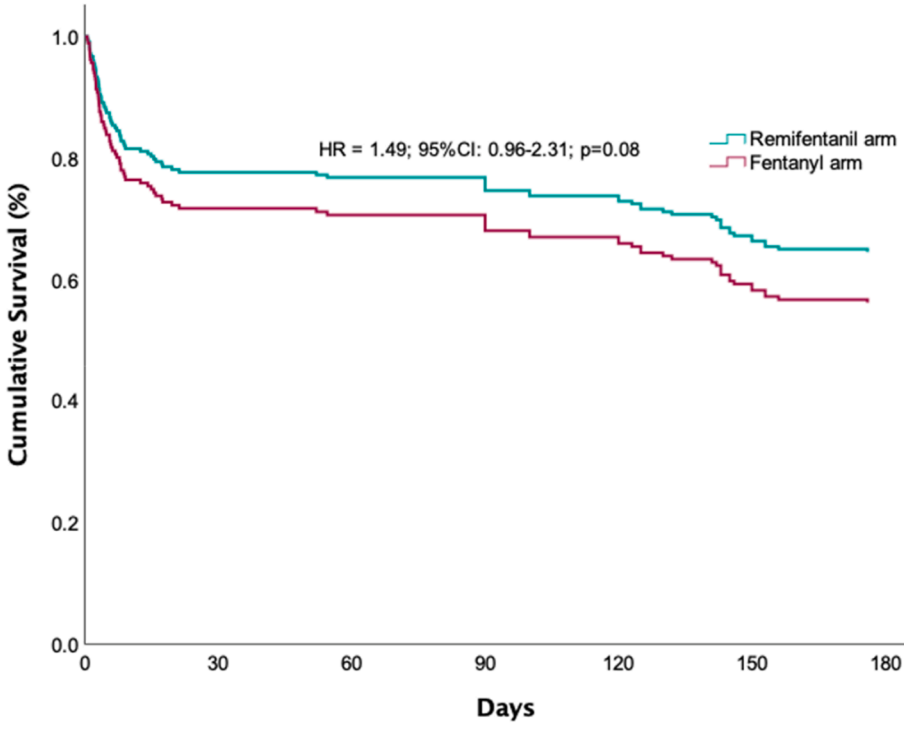

Fig. 2. Kaplan–Meier survival analysis, using the log-rank test to compare groups.

feasibility design, these HRQoL results are not powered to detect small differences between groups and should be interpreted cautiously.

3.5. Subgroup analyses

Exploratory subgroup analysis demonstrated lower observed costs in the remifentanil group among older patients and among those with shorter durations of mechanical ventilation. Based on age, there were lower post-ICU bed-day costs ($p = 0.006$), and therefore total hospital costs $39,236.26 [$22,828.93-$55,643.59] versus $52,426.90 [$35,330.86-$69,522.95]; $p = 0.036$) only for the older patients in the remifentanil group than the fentanyl group (Table 1). Based on the IMV duration, there were lower ICU bed-day costs ($p < 0.001$), and therefore total hospital costs $15,482.91 [$11,855.55-$19,110.27] versus $22,236.82 [$16,738.55-$27,735.09]; $p = 0.005$) only for those who received IMV for $\leq$72 h in the remifentanil group compared with the fentanyl group

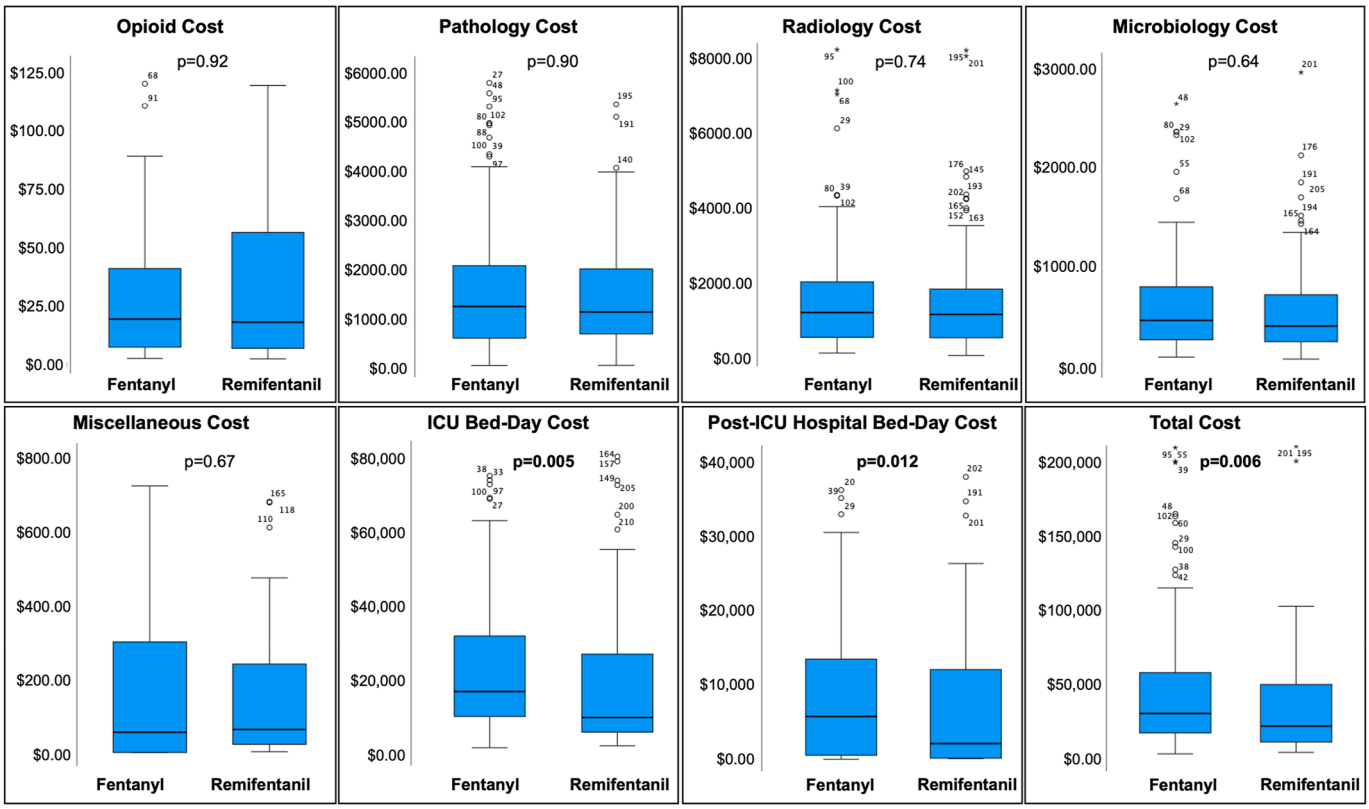

Fig. 3. Overall costing.

Table 1
Total cost difference between the two groups.

	Remifentanil group (mean [95% CI] cost) AUD	Fentanyl group (mean [95% CI] cost) AUD	Mean difference in cost	p-value
ICU bed-day cost	$25,654.32 [$17,740,44-$33,568.19]	$31,736.87 [$24,139.33-$39,334.40]	$6082.54	**0.005**
Post-ICU hospital bed-day cost	$7459.08 [$5127.11-$9791.05]	$12,448.68 [$8643.90-$16,253.45]	$4989.59	**0.012**
Total hospital cost	$37,012.42 [$27,834.16-$46,190.68]	$48,301.25 [$38,644.47-$57,958.02]	$11,293.53	**0.006**
Total hospital cost for patients <65 years	$34,953.31 [$25,348.75-$44,557.86]	$45,373.36 [$33,797.42-$56,949.31]	$10,420.05	0.07
Total hospital cost for patients ≥65 years	$39,236.26 [$22,828.93-$55,643.59]	$52,426.90 [$35,330.86-$69,522.95]	$13,190.64	**0.036**
Total hospital cost for IMV <72 h	$15,482.91 [$11,855.55-$19,110.27]	$22,236.82 [$16,738.55-$27,735.09]	$6753.91	**0.005**
Total hospital cost for IMV ≥72 h	$61,178.19 $44,307.63-$78,048.75]	$65,406.03 [$51,192.71-$79,619.35]	$4227.81	0.80
Total hospital cost for patients alive at 6 months	$35,521.38 [22,763.23-$48,279.54]	$53,153.58 [$40,478.64-$65,828.51]	$17,632.20	**0.002**

Bold p-value signifies statistical significance.
ICU, intensive care unit, IMV, invasive mechanical ventilation, AUD, Australian dollar.

(Table 1). For those who were alive at 6 months: the mean ICU bed-day, post-ICU bed-day, and overall hospital costs were lower in the remifentanil group, when compared with the fentanyl group $35,521.38 [22,763.23-$48,279.54] versus $53,153.58 [$40,478.64-$65,828.51]; p = 0.002; Table 1). There were no differences between the two groups in mean HRQoL in survivors, either by age or duration of IMV.

4. Discussion

4.1. Summary of key findings

In this post-hoc pilot cost analysis, remifentanil was associated with lower total hospital bed-day costs than fentanyl during the index admission, while there were no statistically significant differences in survival and HRQoL at 6 months appeared between the two groups. There was no overall difference in the costs related to biochemical, microbiological, and radiological investigations between the two groups. The reported HRQoL domains were similar between the two groups at 6 months; however, the cost analysis suggested that remifentanil is a more cost-effective alternative to fentanyl for analgosedation due to lower costs for equivalent outcomes. Finally, use of remifentanil was associated with a significant reduction in total hospital costs in older patients (≥65 years) and those receiving IMV for ≤72 h. These results should be viewed as suggestive rather than definitive, reflecting the limited sample size and absence of comprehensive adjusted regression analyses. The findings are best interpreted as hypothesis-generating and supportive of further evaluation in larger trials.

Table 2
EuroQoL 5-dimension 5-level (EQ-5D-5L) at 6 months follow-up.

	Remifentanil group	Fentanyl group	p-value
Mobility			0.15
- No/slight problems with walking about	46/61 (75.4%)	50/59 (84.7%)	
- Moderate/severe problems or unable to walk about	16/61 (24.6%)	9/59 (15.3%)	
Self-care			0.64
- No/slight problems with self-care	52/61 (85.2%)	52/59 (88.1%)	
- Moderate/severe problems or unable to wash or dress	9/61 (14.8%)	7/59 (11.9%)	
Usual activities			0.10
- No/slight problems doing usual activities	43/61 (70.5%)	49/59 (83.1%)	
- Moderate/severe problems or unable to do usual activities	18/61 (29.5%)	10/59 (16.9%)	
Pain/discomfort			0.47
- No/slight in pain or discomfort	43/61 (70.5%)	45/59 (76.3%)	
- Moderately/severely/ extremely pain or discomfort	18/61 (29.5%)	14/59 (23.7%)	
Anxiety and depression			0.18
- Not at all or slightly anxious or depressed	42/61 (68.9%)	47/59 (79.7%)	
- Moderately/severely/ extremely anxious or depressed	19/61 (31.1%)	12/59 (20.3%)	
EQ index, mean (95%-CI)	0.83 (0.77−0.89)	0.87 (0.83−0.91)	0.24

4.2. Comparison with previous literature

An initial economic modelling study from Germany found no difference in costs between remifentanil/propofol use and fentanyl/midazolam use.[15] In contrast, a Markov modelling study observed that remifentanil-based sedation was associated with reduced ICU costs compared with conventional analgesia and sedation.[16] We observed similar findings in our study, where we demonstrated an overall reduction in ICU bed-day and overall hospital costs in patients who received remifentanil. This was particularly observed in older patients and those who received IMV for <72 h. There is good evidence to suggest that older and frailer patients with critical illness were associated with considerably poorer health outcomes.[17] Therefore, the choice of sedative agents was critical and may enable better outcomes for ventilated older ICU patients.[18–20] Remifentanil, with its unique pharmacokinetics and pharmacodynamics,[7,11] makes it particularly suitable for this cohort of older patients needing shorter-term ventilation and offers certain advantages over fentanyl.

Cost-effectiveness analysis was not calculated in previously published studies.[15,16] The minimal difference in investigation costs during the indexed hospitalisation in both treatment arms suggests that the opioid choice did not affect the downstream costs in healthcare utilisation. Interestingly, there was no difference between the treatment groups in HRQoL of survivors at 6 months. This may be because remifentanil and other opioids are similar in most regards.[21] However, these results should be interpreted with caution for a few reasons as these outcome measures were assessed in small samples and were not statistically powered to assess certain health outcomes during the short duration of ICU stay and detect differences in mortality outcomes.

Importantly, our findings indicate that remifentanil was associated with lower costs of the initial hospital admission than fentanyl and showed minimal difference in mortality and quality-of-life outcomes for survivors at six months.

4.3. Study implications

First, our findings suggest that, in this pilot setting, remifentanil may offer more favourable short-term ICU and hospital costing compared with fentanyl as a primary agent for analgosedation in ICU patients. However, these exploratory results require confirmation in adequately powered multicentre phase-2 trials and prespecified economic analyses. Second, use of remifentanil was associated with a meaningful reduction in hospital costs, particularly among older patients and those requiring shorter durations of IMV. Although these cost savings may not necessarily translate into clinically significant improvements for patients, these findings offer useful insight for policymakers by providing an economic rationale to guide decisions on ICU resource allocation and utilisation from a healthcare system perspective. This is particularly relevant given the increasing pressure on ICU resources, especially during crises like the COVID-19 pandemic. Future trials should incorporate prospective collection of postdischarge healthcare utilisation and costs to determine whether reductions in ICU or index hospital costs are offset or reinforced by longer-term resource use. They should also prespecify regression-based cost-utility analyses that adjust for important baseline and clinical covariates.

4.4. Strengths

Our study has several strengths. This was the first Australian RCT to compare the costs associated with remifentanil and fentanyl in critically ill patients requiring IMV. Second, detailed microcosting of biochemical and radiological investigations contributing to the total hospital costs was performed. Third, inclusion of all randomised patients ensured that the cost analysis reflects real-world ICU practice. Finally, we conducted robust statistical analyses and explored cost differences across relevant subgroups.

4.5. Limitations

This study has several important limitations. First, it was conducted at a single centre, which limits the generalisability of our findings to other ICU settings. Second, as a feasibility study, it was not adequately powered to detect clinically meaningful outcomes, raising the possibility of overestimating the treatment effect. Third, the cost estimates were based on New South Wales ICU and hospital cost weights, which are lower than those generated from the Independent Hospital Pricing Authority's national average[14] and the opioid unit costs in our study were more similar ($2.40 versus $2.25 per ampoule)[12] than those previously reported.[22] While this may not have affected the relative cost differences between remifentanil and fentanyl, it could have implications for broader service planning and budgeting. Fourth, the cost data only included the hospital costs of the main episode of care, and data on additional service use after discharge were not available. The analysis was conducted from a hospital perspective, excluding other potential direct and indirect costs, such as outpatient visits, emergency department presentations, pharmaceutical expenses, and productivity losses for both patients and caregivers. Besides, this approach does not capture postdischarge or long-term healthcare costs and therefore represents a partial economic perspective. The study also employed a relatively short 6-month

time horizon, meaning that posthospital events, such as readmission or further healthcare utilisation beyond this follow-up point, were not captured. This limited follow-up may have affected both the total cost estimates and quality-of-life outcomes. However, the critically ill cohort of patients in this study may have further reduced the overall sample size of patients who survived at one year and potentially compromised the findings and their interpretation. Sixth, the absence of baseline EQ-5D-5L data restricted the ability to assess changes in quality-of-life utility value comparisons. Seventh, we also acknowledge that costs incurred months after discharge are unlikely to be directly attributable to the initial cost strategy; accordingly. In addition, given the feasibility design and relatively smaller sample size, weighted ICU length of stay for organ supports, adjusted regression analyses for costs and HRQoL were not feasible; therefore, economic comparisons are largely unadjusted, subject to residual confounding, and should be interpreted as exploratory rather than definitive.

5. Conclusion

Remifentanil was associated with lower ICU and hospital costs in this pilot study, without statistically significant differences in survival or HRQoL. Further evaluation through cost analysis is warranted in adequately powered multicentre phase-2 trials before these findings can inform clinical practice or policy.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential conflict of interests: Ashwin Subramaniam is the Associate Editor of the Critical Care and Resuscitation Journal. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No financial support, including any institutional departmental funds, was used for the study.

Ethics approval and consent to participate

All experimental protocols were approved by the Nepean Blue Mountains Ethics Committee (2020/ETH00311, 04/30/2020) and was registered with the Australia New Zealand Clinical Trials Registry (ID: ACTRN12620000719932), with a waiver of the need for informed consent.

All methods were carried out following the relevant guidelines and regulations of the Declaration of Helsinki.

Availability of data and materials

The data generated and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2026.100189.

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