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ORIGINAL RESEARCH ARTICLE

Clinical and Economic Evaluation of the Impact of Midazolam on Morphine Therapy for Pain Relief in Critically Ill Ventilated Infants with Respiratory Distress Syndrome

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Abstract

Background The impact of midazolam on the overall performance of morphine therapy for pain in ventilated neonates with respiratory distress syndrome (RDS) has never been investigated.

Objective This study is a clinical and economic analysis of morphine monotherapy versus morphine plus midazolam in ventilated infants with RDS.

Methods A decision-analytic model from the hospital perspective was developed to follow the consequences of the use of the study drugs. Clinical and resource utilization data were extracted based on a retrospective cohort study of 104 neonates with RDS receiving morphine alone versus in combination with midazolam at the main neonatal intensive care unit (NICU) in Qatar, from 2014 to 2019. Primary outcome measures were the analgesia success rate, via the Premature Infant Pain Profile scale, and overall costs of therapies. Multivariate statistical analyses confirmed no significant variations in baseline characteristics between study groups.

Results With 0.05 significance and 80% power, morphine had a higher rate of successful analgesia (65.4 vs. 34.6%; risk ratio 1.91; 95% confidence interval 1.11–3.28; $p = 0.019$). Overall costs were also in favor of morphine compared with its combination with midazolam, with cost savings of 40,959 Qatari Riyal ($US11,222), year 2019/20 values. The Monte Carlo analyses confirmed the economic advantage of morphine alone in 100% of cases and demonstrated that it is not sensitive to uncertainties in study model inputs.

Conclusions Morphine monotherapy enabled enhanced pain relief over its combination with midazolam in the NICU, at a reduced overall cost. Morphine alone, therefore, seems to be a dominant analgesia strategy.

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Key Points

The study explores the impact of the addition of midazolam to morphine for the management of pain in infants receiving respiratory ventilation because of respiratory distress syndrome.

The overall pain relief achieved with morphine alone exceeded that achieved with midazolam plus morphine. This was mostly due to a greater need for increased doses and alternatives with the midazolam combination.

The decline in the overall success with the combination, compared with morphine alone, was also associated with an increase in the overall therapy cost.

1 Introduction

Between 7 and 50% of infants in the neonatal intensive care unit (NICU) setting are diagnosed with respiratory distress syndrome (RDS). In premature infants, approximately 92% of those born at 24–25 weeks' gestation are diagnosed with RDS [1, 2]. At the main tertiary referral NICU in Qatar, RDS is the second most common reason for admission [3].

In neonates with RDS, pain (a risk factor for agitation) is a frequent adverse effect of the mechanical ventilation (MV) procedure [4, 5]. Keeping in mind that neonates do feel and react to pain [6], pain management is necessary to improve the patient experience of ventilation [7]. Opioids are the mainstay pharmacological treatment with MV in NICU, with morphine being the most commonly used [4, 7, 8], added to a globally increasing consumption rate over the years (20% in 2014–2018) [2]. As an example, in Europe and the USA, morphine constituted 26.4 and 54.6%, respectively, of all analgesics used [9]. A similar trend has been observed in the NICU of the Women's Wellness and Research Center (WWRC) in Qatar, where morphine analgesia is used with MV in RDS [3]. To emphasize, as with opioids in general, morphine is not recommended for routine preemptive use with MV, particularly in preterm neonates, and should only be used when needed [5, 10], *vide infra*. However, in the Qatari NICU, when morphine is deemed to be the treatment of choice, some clinicians have used it in combination with the sedative midazolam. This is based on the assumption of enhanced pain relief given a potential synergic effect between opioids and benzodiazepines [11] and because midazolam reduces anxiety and motor activity, improving tolerance of the endotracheal tube, which may help control the MV and make it less painful [12]. However, the decision to add midazolam is not consistent or evidence based, and is based on personal observations and experiences with patients. In a clinical trial, Anand et al. [13] found that midazolam performed poorly relative to morphine as monotherapy for facilitating MV in neonates; however, a later study by the same author indicated that both are used concurrently in practice and that evaluations of the outcomes of this in practice are lacking [14]. No literature evidence on the clinical or economic value of morphine as monotherapy versus its combination with midazolam in neonates exists.

The current research sought to evaluate the cost effectiveness of adding midazolam to morphine for pain relief in neonatal MV with RDS in the NICU.

2 Methods

2.1 Design

A retrospective cohort-based cost-effectiveness analysis (CEA) model was used.

2.2 Model Structure

A decision-analytic model was constructed to follow the use and consequences of study drugs before potential titration. The model included seven potential patient management pathways based on whether the initial analgesia was a success and on the reasons behind failure. Figure 1 illustrates the follow-up structure of the model.

2.3 Cohort Study Setting

This study was conducted in the NICU of WWRC at the Hamad Medical Corporation (HMC) in Qatar. HMC is the primary provider of public healthcare in the country [15]. This NICU facility has a capacity of 112 beds.

2.4 Outcome Measures

Primary outcome measures were as follows:

- Successful analgesia rate: identified using the Premature Infant Pain Profile (PIPP) scale, which is a reliable and common measure used globally to identify the status of pain in infants [16]. The PIPP scale is validated for this purpose in both preterm and term infants [16–19]. In HMC, this is documented by nurses into Cerner. Here, success is an objectively measured outcome, whereby, in the WWRC NICU, nurses calculate the overall PIPP score by evaluating seven indicators for each infant. A score of 0–6 indicates no or mild pain, and a score of ≥7 indicates moderate/severe pain. Pharmacological inter-

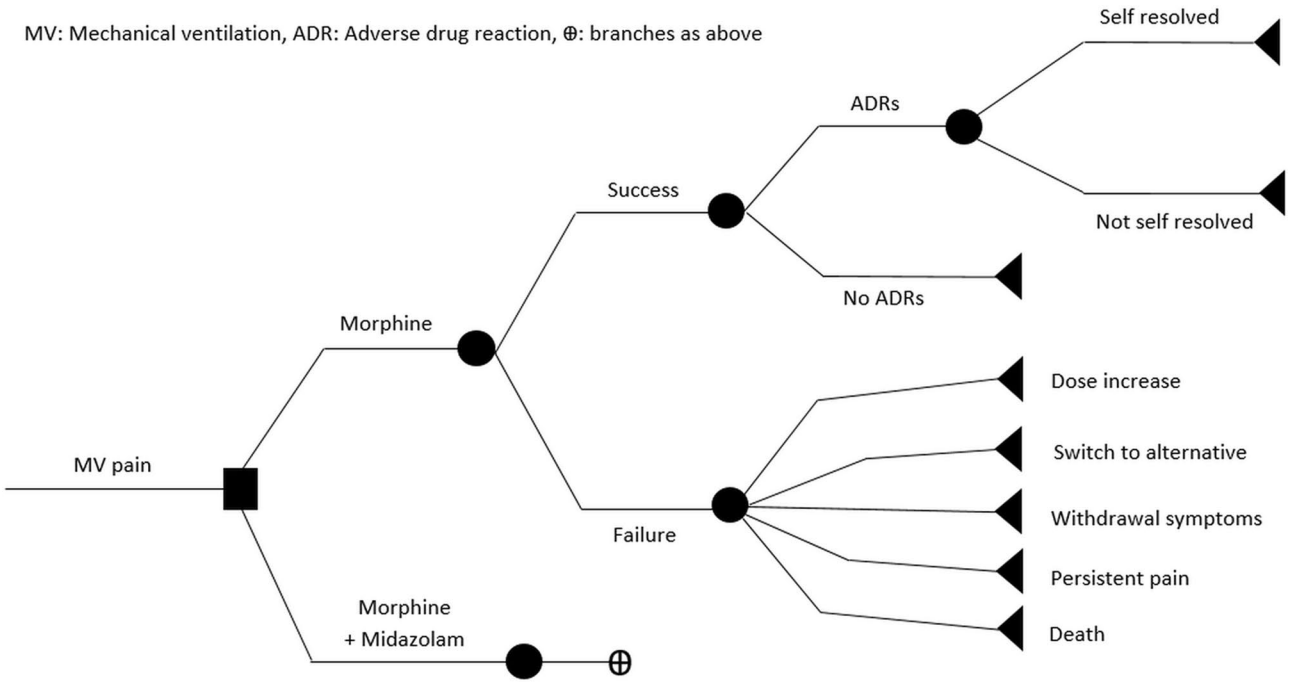

Fig. 1 Decision-analytic model tree of study drugs. *ADR* adverse drug reaction, *MV* mechanical ventilation. The circle symbol with a '+' within it indicates branches as above

ventions are deemed necessary when pain is moderate/severe. In the study setting, pharmacological interventions could also be initiated with mild pain to avoid further anticipated pain and agitation. See appendix 1 in the electronic supplementary material (ESM) for a detailed description of the PIPP score.

- Total direct medical costs of pain management based on the economic value estimates of the resource utilization.

Secondary measures were the need for increased medication doses; the need for alternative therapy; durations of therapies, ventilation, and NICU stay; withdrawal symptoms associated with therapies; persistent pain; adverse drug reactions (ADRs); and mortality.

2.5 Outcome Measure Definitions

Analgesia success was reflected by a neonate's final overall PIPP score reduced to, or maintained at (with mild pain), < 7 after receiving the initial analgesia dose and before any possible dose increase and regardless of ADRs. ADR events took place after receiving either study drug. The main events of interest were desaturation, urinary retention, edema, decreased gastrointestinal motility, respiratory depression, hypotension, and seizure [3, 18, 19]. A final PIPP score that was not maintained at or reduced to < 7 following the initial analgesia doses was considered analgesia failure. Consequences of analgesia failure were as follows:

- Increased dose: In the WWRC NICU, morphine is titrated at a dose of 1–5 μg/kg.
- Switching to an alternative, from either study drug to fentanyl monotherapy.
- Development of withdrawal symptoms: defined as seizure, agitation, irritability, and tachycardia emerging following day 5 of the study drugs [20], with a final PIPP score of > 7 where the initial score was < 7.
- Mortality: defined as all-cause death during the first 28 days of the infant's life [21].
- Persistent pain: final PIPP score remained >7 after receiving first-line study drugs and any alternative measures.

2.6 Ethics Approval

All ethics approvals were granted by the Medical Research Center of HMC (MRC0272/2016).

2.7 Patient Data

Clinical and resource utilization data of neonates were extracted from the patient medical records based on the Cerner database of neonates in HMC, from 2014 to 2019.

Inclusion criteria were as follows:

- Preterm and full-term neonates with RDS on MV who received first-line morphine as monotherapy or in combi-

nation with midazolam after intubation. Based on international standard dosing guidelines for first-line neonatal analgesia and sedation [22, 23], morphine was given at 100–200 µg/kg loading dose and 15–30 µg/kg/h continuous infusion, whereas the morphine plus midazolam combination was given at 100–200 µg/kg loading dose and 15–30 µg/kg/h continuous infusion of morphine, plus 100–200 µg/kg and then 10–60 µg/kg/h continuous infusion of midazolam.

- As part of standard care at WWRC, a bolus dose of fentanyl (1–2 µg/kg) is given to all NICU neonates to relieve the pain of the intubation procedure.

The following exclusion criteria were applied:

- Neonates with pulmonary hypertension, pulmonary hemorrhage, congenital anomalies, birth defects, or hypoxic-ischemic encephalopathy.
- Neonates who did not receive ventilation or analgesic/sedative therapies.
- Neonates who did not receive analgesics or sedatives for other underlying conditions.
- Neonates who did not receive other analgesics/sedatives.

2.8 Sample Size

No studies have evaluated morphine monotherapy versus its combination with midazolam, so no background information was available on which of the two alternatives would perform better. The anticipated analgesia success rate with morphine was 68%, based on recent evidence generated at the study setting [3], where the definition of successful analgesia was identical to that in the current study. With this, and based on an anticipated 40% difference (either way) by neonatologists at the Qatari NICU, 51 neonates were required in each drug group, at $\alpha = 0.05$ and power of 80% (clinical calculator, ClinCalc.com). Pre-determining a single direction of an outcome resulted in a smaller sample size. The detailed sample size calculation is as follows:

N1={1.96*$\sqrt{}$(0.544*0.456*(1+1/1))+0.84*$\sqrt{}$(0.68*0.32+(0.408*0.592/1))}2/0.2722. N1=51. N2=K*N1=51

In total, 52 medical records were requested for inclusion into each study group, based on the descending order of the neonatal admission numbers in the records. Any excluded patient record was replaced with another order for a record until the sample size was achieved.

2.9 Statistical Analyses

We used SPSS version 24.0 (IBM Corp.; Armonk, NY, USA) to measure the baseline demographics. Categorical data were tested via Chi-squared and Fisher's exact tests, whereas continuous data were tested using Student's t-test and the Mann–Whitney test. A multivariate statistical analysis of covariance model was used to evaluate the robustness of the statistical differences between drug outcomes, based on differences in patient variables at baseline between study groups. These variables are initial PIPP scores, birth weight, gestational age, intrauterine growth restriction, necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus, patients with patent ductus arteriosus who received pharmacological or surgical treatments, sepsis, bronchopulmonary dysplasia, chorioamnionitis, antenatal steroid, postnatal steroid, premature rupture of membrane, maternal preeclampsia, perinatal asphyxia, multiple pregnancy, 1-minute APGAR, 5-minute APGAR, surfactant, doses of surfactant, patients who received caffeine treatment, and total parenteral nutrition (TPN). Categorical variables were presented via numerical and percentage/probability measures, and continuous variables were presented as means and standard deviations. All tests were at the $\alpha = 0.05$ level.

2.10 Perspective of Economic Model

The pharmacoeconomic analysis was performed from the hospital perspective of the WWRC. The costs of direct medical resources were the only costs included.

2.11 Model Cost Inputs and Calculations

The medical resources included in the economic model, for which direct medical costs were calculated, were (1) morphine, midazolam, and fentanyl; (2) ADR management, including oxygen therapy for desaturation, catheter for urinary retention, caffeine citrate for apnea, dobutamine for bradycardia, phenobarbital for joint stiffness or spasms, naloxone for respiratory depression, furosemide for edema; (3) MV; (4) diagnostics and monitoring tests in NICU; and (5) NICU stay. See appendix 2 in the ESM for details of direct medical costs of included model resources.

The values of cost variables were adjusted to year 2019/20 Qatari Riyal (QAR) [24]. Given the acute nature of the disease and the therapy, no discounting of costs was performed. Medication prices were HMC wholesale prices.

2.11.1 Sensitivity Analysis

Base-case values of input data, being retrospectively based, can be associated with uncertainty. To investigate the robustness of outcomes against the uncertainty, and to enhance the generalizability of conclusions over a range of model inputs, one-way and probabilistic sensitivity analyses were conducted. All uncertainty analyses were conducted using the Monte Carlo simulation by @Risk-7.5® (Palisade Corporation, NY, USA).

2.11.1.1 One-Way Sensitivity Analysis An uncertainty of ±10% was assigned to the model's price input values, e.g., medications, laboratory tests. An uncertainty of ±3% was used for study durations (i.e., MV, NICU). The sensitivity analysis was run using a uniform type of Monte Carlo value distribution.

2.11.1.2 Probabilistic Sensitivity Analysis To account for inherent uncertainties in key inputs, the base case of the model was re-analyzed according to a multivariate simulation of input data. Uncertainty of ±3%, with 10,000 iterations of modeling, was assigned to all the probabilities in the model, and the probability of an economic advantage of a study drug was calculated. A triangular value distribution was used.

3 Results

3.1 Baseline Characteristics of the Study Infants

The baseline characteristics between the study groups ($n = 52$, each) did not differ significantly ($p > 0.05$), except in the use of vecuronium ($p = 0.004$; Table 1).

3.2 Clinical Outcomes

Base-case model analysis indicated a significantly enhanced rate of successful analgesia in the morphine monotherapy group: 65.4% ($n = 34$) versus 34.6% ($n = 18$), risk ratio 1.91; 95% confidence interval (CI) 1.11–3.28; $p = 0.019$. As already indicated, this success rate is that of the initial administration of study drugs, not including dose titration. Failure because of increased dose and need for alternatives was only observed in patients receiving the combination medication. Failure cases because of withdrawal symptoms and persistent pain were similar between the study groups: two versus three, and no versus one patient, respectively, with morphine alone versus its combination. Five more deaths were reported with morphine than with the combination (15 vs. 10 patients, respectively). All successful pain relief involved ADRs, primarily desaturation, with rates of both being higher with morphine monotherapy (34 vs. 18 and 26 vs. 11 events, respectively). Table 2 shows the probabilities of patient outcomes, including ADRs.

Of the eight patients with failure due to increased dose in the combination group, two had an increased morphine dose above the standard therapeutic range, five had an increased midazolam dose beyond the standard therapeutic range, and one had an increased dose of morphine and midazolam within the standard range. While the average morphine dose was generally higher with morphine monotherapy, doses among both study groups are considered equivalent: all below 50% of the lower end of standard dose range. In patients with successful analgesia, the average loading and maintenance doses were as follows: 148.9 ± 31.7 and 25.2 ± 8.2 μg/kg with morphine monotherapy, 110.3 ± 8.6 and 19.7 ± 4.3 μg/kg and 116.2 ± 17.5 and 13.2 ± 2.5 μg/kg with morphine and midazolam combination. Table 3 shows the details of the comparative doses of morphine and midazolam.

Vital signs were similar between study groups following administration of the study drugs, with overlapping ranges of measures. In neonates where analgesia was successful, the durations of therapy, MV, and NICU stay were all longer with the morphine plus midazolam combination relative to morphine alone, but the difference was not statistically significant. While also not statistically different, the duration on morphine was longest in patients with failure because of withdrawal symptoms. For the combination study group, durations were longest in patients with failures due to increased dose and the switch to alternative therapies, and the difference was not statistically significant. Table 4 provides details of the durations of medications, MV, and NICU stay.

Multivariate statistical analysis showed that the statistical difference in analgesia success between study groups did not statistically vary after accounting for different variables. The variables were gestational age ($p = 0.09$), birth weight ($p = 0.19$), initial PIPP scores ($p = 0.54$), intrauterine growth restriction ($p = 0.4$), necrotizing enterocolitis ($p = 0.82$), intraventricular hemorrhage ($p = 0.64$), patent ductus arteriosus ($p = 0.19$), patients with patent ductus arteriosus who received pharmacological or surgical treatments ($p = 0.78$), sepsis ($p = 0.25$), bronchopulmonary dysplasia ($p = 0.39$), chorioamnionitis ($p = 0.4$), antenatal steroid ($p = 0.83$), postnatal steroid ($p = 0.51$), premature rupture of membrane ($p = 0.12$), maternal preeclampsia ($p = 0.71$), perinatal asphyxia ($p = 0.86$), multiple pregnancy ($p = 0.07$), 1-minute APGAR ($p = 0.41$), 5-minute APGAR ($p = 0.73$), surfactant ($p = 0.19$), doses of surfactant ($p = 0.32$), patients who received caffeine treatment ($p = 0.16$), and TPN ($p = 0.31$).

3.3 Cost of Therapy

The base-case analysis demonstrated that using morphine monotherapy comes with a cost saving of QAR40,361 ($US11,058) compared with the use of the combination with midazolam. Table 2 shows the detailed costs of outcomes.

The main contributing resource categories to the overall cost of therapies for morphine alone were hospitalization (46%), monitoring and diagnostic tests and procedures (32%), and MV (19%) and for morphine plus midazolam were hospitalization (52%), monitoring and diagnostic tests (31%), and MV (17%). The contribution of initial analgesia

Table 1 Main baseline patient demographics

Characteristic	Morphine monotherapy ($n = 52$)	Morphine plus midazolam ($n = 52$)	p-Value
Sex			
Male	41 (78.9)	37 (71.1)	0.77
Female	11 (21.1)	15 (28.9)	
Gestational age (weeks)			
Pre-term (< 37)	39 (75)	37 (71.1)	1
Full-term (≥ 37)	13 (25)	15 (28.9)	
Pre-term (< 37)	28.2 ± 4.5	26.5 ± 2.9	0.36
Full-term (≥ 37)	38.6 ± 1.1	39.3 ± 1.1	
Additional test for pre-term (< 37)	30.4 ± 5.9	30.1 ± 6.3	0.99
Age when intubation was started (days)	1.7 ± 0.9	1 ± 0.2	0.16
Age when sedation was started (days)	3.03 ± 2.9	2.4 ± 2.3	0.13
Birth weight (g)			
≥ 2500	16 (30.8)	13 (25)	0.41
< 2500 and ≥ 1500	5 (9.6)	5 (9.6)	
< 1500 and ≥ 1000	11 (21.1)	5 (9.6)	
< 1000	20 (38.5)	29 (55.8)	
≥ 2500	3350 ± 650.9	3222.5 ± 511.5	0.14
< 2500 and ≥ 1500	1877.5 ± 85.8	1788 ± 52.3	
< 1500 and ≥ 1000	1212.9 ± 178.9	1190 ± 193.1	
< 1000	747.5 ± 134.4	766.6 ± 148.8	
Additional test for birth weight <1500	1764.7 ± 1190	1522.5 ± 1083.5	0.28
Small for gestational age			
Yes	0 (0)	0 (0)	NA
No	52 (100)	52 (100)	
Intrauterine growth restriction			
Yes	5 (9.6)	5 (9.6)	1
No	47 (90.4)	47 (90.4)	
Postnatal age at time of diagnosis (days)	1.2 ± 0.7	1 ± 0.2	0.75
Ethnicity			
Arab	45 (86.5)	43 (82.7)	0.8
Non-Arab	7 (13.5)	9 (17.3)	
Type of delivery			
Vaginal	22 (42.3)	26 (50)	0.8
Cesarean	30 (57.7)	26 (50)	
Multiple pregnancy			
Single	36 (69.23)	41 (78.85)	0.57
Multiple	16 (30.77)	11 (21.15)	
Received vecuronium			
Yes	9 (17.3)	30 (57.7)	0.004
No	43 (82.7)	22 (42.3)	
Initial PIPP scores			
0–6	47 (90.4)	49 (94.2)	1
7–12	5 (09.6)	3 (05.8)	
> 12	0 (0)	0 (0)	
0–6	3.4 ± 1.5	3.5 ± 1.8	0.24
7–12	7.3 ± 0.9	9 ± 1.4	
> 12	NA	NA	

Table 1 (continued)

Characteristic	Morphine monotherapy ($n = 52$)	Morphine plus midazolam ($n = 52$)	p-Value
Necrotizing enterocolitis			
Yes	4 (7.69)	9 (17.31)	0.42
No	48 (92.31)	43 (85.69)	
Necrotizing enterocolitis in < 1500 and ≥ 1000 birth weight neonates			
Yes	0 (0)	1 (0.2)	0.3
No	11 (100)	4 (0.8)	
Necrotizing enterocolitis in < 1500 and < 1000 birth weight neonates			
Yes	7 (22.58)	12 (35.29)	0.67
No	24 (77.42)	22 (64.71)	
Intraventricular hemorrhage			
Yes	10 (19.23)	13 (25)	0.76
No	42 (80.77)	39 (75)	
Intraventricular hemorrhage in < 1500 and ≥ 1000 birth weight neonates			
Yes	0 (0)	2 (0.4)	0.07
No	11 (100)	3 (0.6)	
Intraventricular hemorrhage in < 1500 and < 1000 birth weight neonates			
Yes	13 (41.94)	7 (20.59)	0.49
No	18 (58.06)	27 (79.41)	
Patent ductus arteriosus			
Yes	23 (44.23)	25 (48.08)	1
No	29 (55.77)	27 (51.92)	
Patients with patent ductus arteriosus who received treatment pharmacological or surgical therapy			
Yes	18 (34.62)	15 (28.85)	0.79
No	34 (65.38)	37 (71.15)	
Sepsis			
Yes	33 (63.46)	43 (82.69)	0.53
No	19 (36.54)	9 (17.31)	
Bronchopulmonary dysplasia			
Yes	4 (7.69)	4 (7.69)	1
No	48 (92.31)	48 (92.31)	
Chorioamnionitis			
Yes	4 (7.69)	5 (9.62)	1
No	48 (92.31)	47 (90.38)	
One-minute APGAR score			
Critically low (0–3)	31 (59.62)	20 (38.46)	0.11
Fairly low (4–6)	12 (23.08)	25 (48.08)	
Generally normal (7–10)	9 (17.3)	7 (13.46)	
Five- minute APGAR score			
Critically low (0–3)	20 (38.46)	12 (23.08)	0.25
Fairly low (4–6)	12 (23.08)	9 (17.31)	
Generally normal (7–10)	20 (38.46)	31 (59.61)	
Surfactant			
Yes	30 (57.69)	36 (69.23)	0.44
No	22 (42.31)	16 (30.77)	
Number of doses of surfactant			
0	23 (44.23)	15 (28.85)	0.58
1	12 (23.08)	12 (23.08)	
2	10 (19.23)	13 (24.99)	
3	7 (13.46)	12 (23.08)	

Table 1 (continued)

Characteristic	Morphine monotherapy ($n = 52$)	Morphine plus midazolam ($n = 52$)	p-Value
Caffeine treatment			
None	23 (44.23)	20 (38.46)	0.78
Loading only	18 (34.62)	9 (17.31)	
Loading followed by maintenance	11 (21.15)	23 (44.23)	
Total parenteral nutrition			
Yes	44 (84.62)	46 (88.46)	0.71
No	8 (15.38)	6 (11.54)	
Duration of total parenteral nutrition	14.9 ± 19.8	40.3 ± 42.8	0.07
Duration of total parenteral nutrition among infants < 1500 g	15.7 ± 20.7	41.6 ± 42.9	0.06
Antenatal steroid			
Yes	26 (50)	26 (50)	1
No	26 (50)	26 (50)	
Postnatal steroid			
Yes	12 (23.08)	28 (53.85)	0.07
No	40 (76.92)	24 (46.15)	
Premature rupture of membrane			
Yes	13 (25)	10 (19.23)	0.76
No	39 (75)	42 (80.77)	
Maternal preeclampsia			
Yes	2 (3.85)	0 (0)	1
No	50 (96.15)	52 (100)	
Perinatal asphyxia			
Yes	13 (25)	5 (9.62)	0.18
No	39 (75)	47 (90.38)	
Yes	0 (0)	0 (0)	NA
No	52 (100)	52 (100)	

Data are presented as mean ± standard deviation or *N* (%) unless otherwise indicated

NA not applicable, *PIPP* Premature Infant Pain Profile

and medications for ADRs was negligible (< 0.1%) for both study drugs. Appendix 3 in the ESM provides details of direct medical cost components of the drug therapies, as per outcomes, and appendix 4 shows the relative direct medical costs of resource categories for the total therapy costs, with hospitalization, laboratory tests, and MV contributing the most to therapy costs, all in favor of monotherapy.

3.4 Sensitivity Analysis

Appendix 5 in the ESM provides the values of variables and their uncertainty ranges in the one-way sensitivity analyses. The model was not sensitive to uncertainties in the model's variables.

Appendix 6 in the ESM shows the model probability inputs and their uncertainty distributions in the probabilistic sensitivity analysis. Based on the Monto Carlo simulation, an incremental cost-effectiveness probability analysis illustrated that the dominance status of morphine over its combination persisted in 100% of simulated patient cases, with 0% probability for the incremental cost-effectiveness ratio becoming positive. The average cost saving associated with morphine alone was QAR40,959 ($US11,222), within the range QAR38,905–43,029 (95% CI 40,885–41,033) ($US10,659–11,789; 95% CI 11,201–11,242). Figure 2 presents a cost-saving probability curve.

A tornado analysis of therapy consequences as per influence on the economic outcome of the model was conducted (appendix 7 in the ESM). The difference in the failure probability between the study groups contributed the most to cost savings with morphine. The uncertainty in the probability of analgesia success affected the outcome of the morphine group the most, followed by the probability of failure due to death, whereas uncertainty in the probability of failure due to increased dose is what affected the morphine plus

Table 2 The probabilities and costs of study therapies

Therapy outcome	Morphine monotherapy			Morphine plus midazolam		
	Probability	Cost per patient	Proportional cost	Probability	Cost per patient	Proportional cost
Analgesia success with ADRs[a]	0.654	62,275.67 (17,062)	40,728.29 (11,186.02)	0.346	92,523.76 (25,349)	32,013.22 (8771)
Analgesia success without ADRs	0	NA	NA	0	NA	NA
Analgesia failure						
Analgesia failure due to increased dose	0	NA	NA	0.25	131,831.4 (36,118)	32,957.85 (9030)
Analgesia failure due to need for alternatives	0	NA	NA	0.153	118,471.31 (32,458)	18,126.11 (4966)
Analgesia failure due to withdrawal symptoms	0.058	43,027.93 (11,788.47)	2,495.62 (685.42)	0.038	15,263.16 (4181.69)	580 (159.30)
Analgesia failure due to death	0.288	24,586.67 (6,736.08)	7080.96 (1,944.79)	0.192	34,582.19 (9474)	6639.78 (1819)
Analgesia failure due to persistent pain	0	NA	NA	0.019	18,374.21 (5034.03)	349.11 (95.88)
Total cost per patient	50,304.87 (13,816.23) 95% CI 50,280–50,329 (13,775–13,789)[b]			90,666.07 (24,840) 95% CI 90,620–90,712 (24,827–24,852)[b]		

Costs are presented as Qatari Riyal ($US)

ADR adverse drug reaction, *CI* confidence interval, *NA* not applicable

[a]ADRs with monotherapy were desaturation ($n = 26$); desaturation and mechanical ventilation adjustment ($n = 2$); desaturation and urinary retention ($n = 3$); desaturation, urinary retention, and mechanical ventilation adjustment ($n = 1$); desaturation and joint stiffness ($n = 1$); and desaturation and edema ($n = 1$), for a total of 34 events. ADRs with the combination were desaturation ($n = 11$); desaturation and mechanical ventilation adjustment ($n = 2$); desaturation and urinary retention ($n = 1$); desaturation, edema, and mechanical ventilation adjustment ($n = 2$); and desaturation and edema ($n = 2$), for a total of 18 events

[b]Based on multivariate sensitivity model analyses

Table 3 Doses of study drugs

Study clinical outcome	Morphine		Morphine plus midazolam			
	Average loading dose (mcg/kg)	Average maintenance dose (mcg/kg/h)	Morphine		Midazolam	
			Average loading dose (mcg/kg)	Average maintenance dose (mcg/kg/h)	Average loading dose (mcg/kg)	Average maintenance dose (mcg/kg/h)
Analgesia success	148.9	25.2	110.3	19.7	116.2	13.2
Analgesia failure						
Increased dose	NA	NA	110.4	35.6	119.3	43.5
Therapy switch to alternatives	NA	NA	Initial therapy: Loading morphine (111), maintenance morphine (15.6), loading midazolam (110.4), maintenance midazolam (11.3) Alternative therapy: Loading alternative fentanyl (3), maintenance alternative fentanyl (5)			
Withdrawal symptoms	163.7	26.6	133.1	18.5	104.7	10.9
Death	119.3	21.8	114.9	15.5	119.3	13.6
Persistent pain	NA	NA	119.6	20.4	117.6	10.5

NA not applicable

Table 4 Durations of analgesia, mechanical ventilation, and neonatal intensive care unit stay

Study clinical outcome	Morphine monotherapy	Morphine plus midazolam	Morphine monotherapy	Morphine plus midazolam	Morphine monotherapy	Morphine plus midazolam
	Duration of therapy (h)		Duration of MV (h)		Duration of NICU stay (day)	
Analgesia success	144	254	168	296	47	75
p-Value	0.07		0.07		0.35	
Analgesia failure						
Increased dose	NA	732	NA	848	NA	97
p-Value	–		–		–	
Therapy switch to alternatives	NA	792	NA	504	NA	128
p-Value	–		–		–	
Withdrawal symptoms	288	268	600	274	27	12
p-Value	0.67		1		1	
Death	192	276	360	432	16	34
p-Value	0.1		0.67		0.14	
Persistent pain	NA	320	NA	344	NA	15
p-Value	–		–		–	

MV mechanical ventilation, *NA* not applicable, *NICU* neonatal intensive care unit

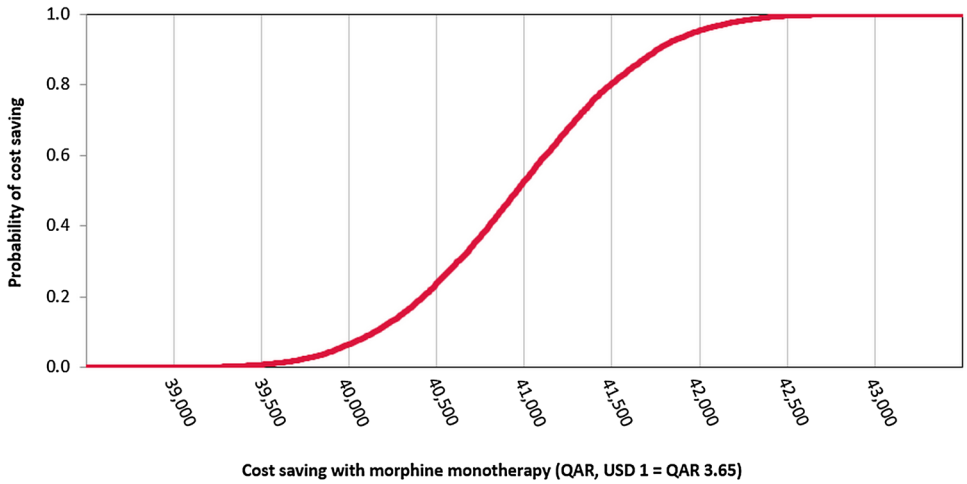

Fig. 2 Cost-saving probability curve with morphine monotherapy. *QAR* Qatari Riyal

midazolam outcome the most, followed by the success probability.

4 Discussion

Pain is stressful and potentially has long-term developmental and cognitive consequences in infants [10, 25, 26]. MV interacts negatively with pain and agitation, causing unsynchronized breathing and suboptimal ventilation. This adds to the clinical instability, including alterations in heart and respiratory rates, intracranial and blood pressures, and oxygen saturation, in addition to the development of complications, e.g., intraventricular hemorrhage [13]. Neonatal pain, therefore, needs to be routinely assessed for supportive treatment, including to reduce agitation [4, 27]. At the WWRC NICU, the PIPP score is routinely assessed for all neonates.

At the WWRC study site, a local guideline of administration of morphine for pain relief for ventilated infants during the NICU stay was formed by neonatologists and pharmacists to achieve a common consensus among neonatologists based on the available evidence in the literature. The guideline allows clinicians to adjust doses based on the patient's response, where the dosing starts with a loading dose of 100–200 mcg/kg/dose over 1 h followed by continuous infusion of 10–30 mcg/kg/h. This dosing is similarly applied for both preterm and term neonates. Strategies such as daily sedation interruption are not common practice in the local NICU at HMC. Daily interruption of sedation instead of continuous infusion or protocolized sedation of sedatives has

been shown to be an effective approach in the adult population for reducing drug bioaccumulation, allowing patients to be more awake, enhancing neurological assessment, facilitating assessment of effects of discontinuation of medications, and resulting in significant reductions in the duration of MV and ICU and hospital stay [28–31]. However, in critically ill children and neonates, the effectiveness and safety of daily sedation interruption are not as proven. Data in the literature are sparce and conflicting. For example, Gupta et al. [32] found that the length of MV and duration of ICU stay were significantly lower with interrupted sedation group than with continuous infusion, with no significant differences in adverse event rates. Vet et al. [33] found a lack of improvement with daily sedation interruption and unexpected mortality compared with protocol sedation.

This is the first clinical and economic evaluation study of morphine alone versus its combination with midazolam in critically ill infants undergoing MV due to a respiratory indication, including RDS. Morphine alone was associated with both greater analgesia success (by 47.1%), with an average cost saving of QAR40,959 ($US11,222) per patient.

Clinically, our results do not indicate that adding midazolam to morphine reduces the analgesic effect of morphine. Rather, they indicate a greater need for increased doses and alternative therapies with the midazolam combination, reducing the overall success rate with morphine alone, which is consistent with results from analgesia-based sedation studies in adults comparing analgesia alone and analgesia and sedation [34–37]. Just as in the current study, analgesia plus sedation therapies were associated with poorer patient outcomes, mostly as a result of prolonged MV and ICU stays. While general differences in durations in favor of morphine alone in this study were not statistically significant, this does not imply no observed clinical consequences. This is because the study was not powered to conduct a statistical assessment of the duration outcome and because no standards exist for calculating the clinical impact of important changes in outcomes [38]. This is particularly true also for the economic impact, where the lack of statistical significance behind the difference in durations does not translate into a lack of economic impact from that difference.

Indeed, apart from patients with withdrawal symptoms, the durations of MV and NICU stay consistently showed a longer trend in patients receiving the midazolam combination. This is in agreement with growing evidence about midazolam being potentially associated with longer ICU and MV durations, which may be because midazolam has active metabolites that can accumulate, leading to prolonged effects [4, 39]. This mostly explains the increased extent of failures because of a need for increased morphine doses and because of switching to alternative therapies in patients receiving the combination, where a particularly prolonged overall period of therapy was observed.

The similar incidence of withdrawal symptoms between the study groups could potentially be because the duration of therapy was only slightly different in patients with withdrawal symptoms. Similarly, the addition of midazolam did not seem to worsen the rate of persistent pain compared with morphine alone. Mortality events were more common in the monotherapy group relative to the combination group. However, the association between morphine and mortality has been controversial in the literature. One local study reported that mortality increased with opioids, but several meta-analyses found mortality was not associated with the use of opioids [5, 6, 10, 40, 41]. To note, death in those studies, similar to our current study, was all-cause death, which further undermines the direct association between morphine and increased mortality [42, 43]. Also, in studies where morphine was administered using equal therapy durations to comparators, Anand et al. [18] and Quinn et al. [44] have shown that comparative mortality was found to be equivalent.

While the average morphine dose was generally higher in the morphine monotherapy group, doses among both study groups were considered equivalent as they were all below 50% of the lower end of the standard dose range, and will not have had a differential influence on outcomes.

Considering the economic data reported in this study, morphine monotherapy is superior to its combination with midazolam, with a dominance (higher effect and lower cost) that was maintained in 100% of patient cases in the multivariate Monte Carlo simulation.

The outcome that had the highest contribution (proportional/weighted cost) in overall cost of morphine alone was success. The morphine combination was associated with a higher cost of success with the combination per patient (Table 2), mostly due to increased hospitalization and MV with the combination (Table 4). However, the proportional cost of this outcome was lower than with morphine alone, which is due to a lower probability of success with the combination. Failure due to increased doses was the outcome that contributed most to the combination cost, due to the higher probability of this outcome when it also involved increased hospitalization and MV durations (Tables 2 and 4). The mortality proportional cost was lower with the combination and, hence, more mortality cases with morphine alone was not a contributor to the overall cost saving with morphine. The resource category that constituted most of the overall costs was hospitalization, for both study drugs, which is anticipated in a setting such as the NICU, where resources and particularly hospitalization are relatively costly.

All patients with successful pain relief reported ADRs that needed further management, more with morphine as monotherapy than with the combination, with the primary difference being in desaturation events. However, this does not have major economic consequences on the study

outcomes, given that desaturation was managed with oxygen therapy and did not offset the higher cost associated with the additional use of midazolam for longer durations.

The reliance on pharmacological interventions for neonatal analgesia and sedation is being increasingly debated, primarily because of safety and efficacy concerns with these interventions [40, 45]. However, based on the available evidence, pharmacological interventions are still generally indicated for pain and stress in NICU settings during MV. Opioids are commonly used for the management of moderate and severe pain with MV in the NICU [40, 45]. Of all the opioids, morphine is the most effective, including at the WWRC [3, 10]. However, morphine has several safety disadvantages, especially in neonates, including tachyphylaxis, hypotension, extended MV, and time to enteral feeding [10]. In addition, the literature suggests that opioids, including morphine, are associated with no positive effect on survival, ventilation time, long- and short-term neurological consequences, bronchopulmonary dysplasia, necrotizing enterocolitis, or hospital stay [10]. Morphine's effectiveness and safety profile are not fully established, particularly in preterm neonates, and remains under active investigation. The literature indicated the scarcity of scientific evidence about the optimal regimens for opioids [34] but suggested a general overestimation of anticipated adverse effects [34]. However, for now, morphine is an effective and commonly used therapy when pain relief with MV is deemed necessary, but it has shown an increasing trend globally [2]. Morphine produces analgesia and sedation effects, has a broad therapeutic range, and weakens the physiological response in neonates. It improves ventilator synchrony in ventilated neonates [10].

Midazolam, a benzodiazepine, is another therapy with a long history in the NICU for preterm and term neonates. However, unlike morphine, its ability to provide pain relief is controversial [6]. The safety profile of midazolam is also of concern, as it includes respiratory depression, hypotension, dependence, and tolerance [5, 6]. Nevertheless, midazolam provides sedation, antianxiety, hypnosis, anticonvulsant, and muscle relaxation effects [6]. While midazolam is limited by a relative lack of studies in support of its use in infants, its use is very common with MV [45]. It is associated with a rapid onset and short duration with single doses [4].

One study compared morphine plus midazolam with morphine alone in neonates with respiratory conditions [46]. The clinical trial reported the combination as safe and marginally more effective than the morphine alone. However, this trial assessed the sedation scores of therapies, not pain relief. The study was also not RDS specific and included a variety of overlapping indications for MV that are not all respiratory based, including RDS, apnea, sepsis, pneumonia, shock, and persistent pulmonary hypertension, which limits generalizability. For example, infants with persistent pulmonary hypertension do not respond to conventional ventilation and require high-frequency ventilation in addition to inhaled nitric oxide with different doses of analgesia. Importantly, morphine administration was only based on the maintenance infusion, without a loading dose, and was administered at a dose below the international range of standard morphine dose used in this study, underestimating the performance of morphine alone. In addition, this trial was limited in sample size and was not adequately powered, including 33 patients in total.

Our results, while indicating that morphine alone is associated with enhanced success against pain, do not imply that morphine should be universally used in all patients with RDS on MV. As already indicated, morphine is not recommended for routine use with MV, particularly in preterm infants, and should only be used when needed [5, 10]. Even when analgesia is deemed necessary, other options should be available for consideration as pharmacotherapeutic decisions are multifactorial and medications are multicriteria in nature. For example, fentanyl is favored over morphine in neonates with pre-existing hypotension [5, 45]. Another option is dexmedetomidine, which provides potent analgesic and sedative effects; however, its routine use is not recommended and is limited by a lack of clinical experience of its use in neonates [47–49]. Acetaminophen and non-steroidal anti-inflammatory drugs are increasingly considered as suitable for use with MV in neonates. With appropriate doses, they are both effective and relatively safe compared with opioids. However, data on their effectiveness with MV in neonates are limited [14, 45, 50]. Apart from the different pharmacological alternatives, non-pharmacologic therapies also continue to form a groundwork for pain and agitation relief in neonates, not only in helping eliminate pain and reducing the need for analgesics but also in reducing the number of painful events [51]. Nevertheless, non-pharmacological practices are currently under-utilized and under-investigated and, in some cases, have been found to be inconvenient and difficult to apply and appear to be less effective at limiting pain and agitation [5, 52, 53].

At WWRC, vecuronium can be administered with analgesics or sedatives prior to intubation to paralyze critically ill neonates. While more patients in the combination regimen of our study received vecuronium, the cost-effectiveness outcome in the study was in favor of morphine monotherapy. Adjusting for the impact on vecuronium only further adds to the advantage of the morphine monotherapy.

Importantly, a multivariate statistical analysis showed that potential confounding effects due to observable differences in the main baseline characteristics between study groups, which were not significant, did not affect the statistical difference in pain relief.

As already indicated in Sect. 2.7, fentanyl is used for pain with intubation before analgesia as a standard NICU

practice at the study setting because of its rapid onset of action. However, fentanyl will not influence the comparative performance of the study drugs because all neonates who undergo MV will receive fentanyl equally. Similarly, and regardless of underlying medical condition and pain therapy received, TPN is mostly administered as an essential source of nutrition in neonatal management. As such, and because administration of TPN and its duration were not significantly different between the study groups, in addition to the infeasibility of the retrospective micro-costing of TPN as its content considerably varies between infants, the cost of TPN is not included in the current analysis.

Patients were followed until NICU discharge, and the micro-costing approach of unitized resources in patient management was used. Within the context of a cohort study, the allocation bias in this study was eliminated via systematic patient selection, descendingly based on patient admission numbers. In addition, patient inclusion was based on a pre-ordered de-identified patient list and not on direct access to patient histories in the Cerner database. Moreover, given the sensitive nature of the neonatal setting, no clinical data were missing from the records that could have threatened quality.

The effect estimate in the calculation of sample size was estimated by expert opinion and not based on prior results. While this is a valid method to use in calculating sample size [54–56], it is acknowledged as a limitation in this study. Another limitation is that we did not assess long-term neurological outcomes of therapies in neonates. Furthermore, pain relief was tangibly measured via a standardized tool; however, it is an intrinsic limitation in this type of retrospective research that historical data collection can be associated with bias, which cannot be prevented. Nevertheless, the study outcome was insensitive to the potential uncertainty in the model's probability, including the rate of success. A further limitation is the possibility of unidentified confounders that cannot be considered in the analysis, such as genetic variations among individuals. Nor was the severity of illness evaluated as a baseline characteristic for neonates, mainly because documentation was lacking in medical records, including data for retrospective assessment, i.e., arterial oxygen partial pressure to fractional inspired oxygen ratio and presence of multiple seizures [57]. Nevertheless, with the similarities in all reported baseline characteristics between study groups, a mostly similar severity of illness between groups can be assumed.

With the lack of available high-caliber CEAs of NICU analgesia [58], the importance of the results in the study extends beyond the current setting. This is particularly important given the study's use of a valid standardized pain assessment, utilization of internationally recommended drug regimens, specific RDS indication of interest, and the sensitivity analyses conducted.

5 Conclusion

Neonatal MV pain assessment and treatment are essential components of neonatal intensive care. Since only a few randomized trials have been conducted in this regard, cohort studies for judging hypotheses and clinical trials are needed. The study is the first to investigate the clinical and economic consequences of adding midazolam to morphine in critically ill infants on MV due to a respiratory indication in the NICU. Morphine alone was associated with a significant improvement in overall analgesia performance compared with its combination with midazolam, by over 47%, and was associated with cost savings of over 44%. The dominance of the morphine monotherapy approach persisted in 100% of patient cases. Considering the study's perspective and limitations, the results contradict the assumption that the addition of midazolam can potentially enhance the overall analgesia performance of morphine with MV in RDS.

Declarations

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Author contributions Al-Badriyeh D conceived and designed the study. All authors contributed to data collection and analysis, result interpretation, and revising the manuscript. Abushanab D wrote the first manuscript draft. All authors read and approved the final manuscript.

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