Clinical and Economic Analysis of Morphine Versus Fentanyl in Managing Ventilated Neonates With Respiratory Distress Syndrome in the Intensive Care Setting

Dina Abushanab, MSc(Pharm)[1]; Omar Alsoukhni, PharmD[1]; Fouad AbouNahia, MD[2]; and Daoud Al-Badriyeh, PhD[3]

[1]Pharmacy Department, Hamad Medical Corporation, Doha, Qatar; [2]Neonatal Intensive Care Unit Department, Hamad Medical Corporation, Doha, Qatar; and [3]College of Pharmacy, Qatar University, Doha, Qatar

ABSTRACT

Purpose: Morphine and fentanyl opioids are common analgesic agents for consideration in the neonatal intensive care unit (NICU) for neonates with respiratory distress syndrome (RDS) and undergoing mechanical ventilation (MV). The aim of this study was to evaluate the clinical and economic impact of morphine versus fentanyl in neonates with RDS undergoing MV.

Methods: Retrospective cost-effectiveness analysis of critically ill neonates with RDS receiving standard doses of morphine versus fentanyl at Women's Wellness and Research Center, Qatar. Clinical data of neonates were extracted from medical records of patients from 2014 to 2016. A decision analytic model based on the hospital's perspective was constructed to follow possible consequences of the initial dosing of analgesia, before potential titration. Primary end points were successful pain relief rate based on the Premature Infant Pain Profile scale and overall direct medical cost of therapy. Study population of 126 neonates was used to achieve results with 80% power and 0.05 significance. Sensitivity analysis was conducted to enhance robustness of conclusions against input uncertainties and to increase generalizability of results.

Findings: Morphine achieved a success of 68% versus 43% with fentanyl (risk ratio = 1.72; 95% CI, 1.16–2.56; $P = 0.0075$). Morphine was associated with a minimal incremental cost-effectiveness ratio of USD 135 per additional case of successful pain relief over fentanyl. Higher morphine cost was reported in 2% of cases. Sensitivity analysis found model insensitivity to input uncertainties except NICU stay and cost of MV.

Implications: This is the first cost-effectiveness evaluation of morphine versus fentanyl in the NICU. Morphine significantly improved the relieve of pain over fentanyl. It had 98% probability of dominance over fentanyl. Results in this study support the use of morphine over fentanyl as first-line monotherapy with MV in NICU settings. (*Clin Ther.* 2019;41:714–727) © 2019 Published by Elsevier Inc.

Keywords: analgesia, cost-effectiveness, decision analytic model, intensive care unit, neonates, Premature Infant Pain Profile.

INTRODUCTION

Approximately, 30% to 40% of neonatal admissions to hospitals are because of respiratory distress syndrome (RDS).[1] At the neonatal intensive care unit (NICU), Women's Wellness and Research Center (WWRC), Qatar (the major tertiary neonatal referral unit in the country, at Hamad Medical Corporation [HMC]), RDS is the second reason, after prematurity, for NICU admissions (n = 629; 30%) (unpublished data, extracted from the local statistical Vermont Oxford database, NICU, WWRC, HMC).

The use of opioids as analgesic and sedative agents is common in neonates with RDS and undergoing mechanical ventilation (MV) because it facilitates the

Accepted for publication February 11, 2019
https://doi.org/10.1016/j.clinthera.2019.02.009
0149-2918/$ - see front matter

stressful procedure of MV, enhances ventilator–patient synchrony, and provides relieve of pain; also there is a major risk factor for agitation with MV.[2–4] Globally, in 2004 to 2008, consumption of morphine and fentanyl increased by 19.8% and 31.1%, respectively.[5] Morphine and fentanyl opioids are the analgesic agents for consideration in Qatari NICU of HMC. The local use of these, nevertheless, is not based on comparative evidence when different analgesic agents are used by different clinicians based on personal experiences. Recently, however, most clinicians have increasingly resolved to use morphine over fentanyl because of its therapeutic advantages[6]; its lower potential to cause withdrawal symptoms and tolerance, which reduces dependence and addiction. Nonetheless, others prefer fentanyl because of its rapid action compared with morphine.[7] Indeed, there is no literature evidence about the comparative success of the drugs as monotherapies, including studies that are based on initial dosing before potential titration. In addition, pharmacoeconomic evaluations of these agents have only been conducted in adult ICUs.[8–14] No published studies have evaluated the economic impact of fentanyl versus morphine with respect to neonates with pain.

This research aimed to perform a cost-effectiveness analysis (CEA) of morphine versus fentanyl in neonates with RDS undergoing MV in the NICU setting.

PATIENTS AND METHODS

Study Design

This is a comparative retrospective cost-effectiveness cohort study.

Setting

The setting was the NICU in WWRC at HMC, the public and main health care provider in Qatar, including 8 major specialized hospitals.[15]

Ethics Approval

Ethics approval (MRC0272/2016) was obtained from the Medical Research Center at HMC.

Population

Patient data were obtained through the Cerner electronic medical history database in HMC, in the period 2014 to 2016.

Inclusion Criteria

Neonates who underwent MV because of RDS and who received morphine or fentanyl as a first-line analgesic after intubation were included. In the NICU of WWRC, it is standard care for all patients that a bolus dose of fentanyl (1–2 μg/kg) is given to control pain with the intubation procedure.

According to first-line analgesia and sedation at standard doses, according to international guidelines,[16] the two study groups were fentanyl (0.5–3 μg/kg loading dose, followed by 1–5 μg/kg per hour continuous infusion) and morphine (100–200 μg/kg loading dose, followed by 15–30 μg/kg per hour continuous infusion).

Exclusion Criteria

Excluded neonates were those with congenital anomalies, pulmonary hypertension, and hypoxic-ischemic encephalopathy; non-ventilated or non-analgesia neonates; neonates who received analgesia for other indications; or neonates who received other analgesic or sedative agents such as midazolam as a combination with the study agents.

Outcome Measures

Primary Measures

The first primary measure was rate of successful analgesia with the study drugs, based on the Premature Infant Pain Profile (PIPP) scale as documented by the nurses. The PIPP scale is one of the most validated and reliable measures used in literature to reflect clinical and pain status.[17] The pain relief success is an objective outcome in the NICU of WWRC as nurses follow 7 measures to calculate the overall PIPP score for each infant (see Appendix A in the online version at doi:10.1016/j.clinthera.2019.02.009). A PIPP score of 0 to 6 indicates no or mild pain, and a PIPP score >7 indicates moderate to severe pain, when the pharmacologic intervention is initiated. With mild pain, the pharmacologic intervention is also initiated to avoid expected pain and associated agitation due to MV.

The second primary measure is resource utilization, including an estimation of the overall direct medical costs of managing pain.

Secondary Measures

Secondary measures were the need for alternative analgesic, adverse drug reactions (ADRs), the need

for increased medication doses, the durations of MV, alternative analgesia medication, NICU stay, the withdrawal symptoms, the mortality, and persistent pain.

Definitions of the Outcome Measures

A successful analgesia was defined as a neonate's final PIPP score that is maintained at 7 or reduced to <7 after receiving the initial dosing of any of the analgesic agents and before any potential increase in dose. Success was with or without ADRs. ADRs were defined as patient events that occur after receiving either morphine or fentanyl. Events of relevance and interest were desaturation, urinary retention, decreased gastrointestinal motility, respiratory depression, hypotension, and seizure.[18–20]

The analgesia failure was defined as a neonate's final PIPP score that is not maintained or reduce to <7 after receiving the initial administration of any of the analgesic agents. Here, the therapy consequences were first to increase the dose. In the NICU of WWRC, morphine doses are titrated by 1 to 2 μg/kg and fentanyl doses are titrated by 1 to 5 μg/kg. Second is to switch to an alternative. This was to switch morphine to fentanyl or vice versa should first-line analgesia fail. No other options were considered for alternatives in this setting. The third consequence was to experience withdrawal symptoms. When symptoms such as seizure, agitation, irritability, and tachycardia developed after the fifth day of receiving analgesia,[21] with the final PIPP score >7 when the initial PIPP score was <7. Another consequence was death, defined as death that arose while receiving analgesia during the first 28 days of life.[22] The last consequence was persistent pain. This is when the patient did not respond to first-line analgesic agents and any alternative measures provided as reflected by a neonate's elevated final PIPP score.

Model Structure

A decision analytic model was constructed to follow the analgesia therapies of neonates and their consequences. The model included 7 possible treatment pathways, depending on whether the initial analgesia was successful and on the causes and results of failures. The model tree is illustrated in Figure 1.

Sample Size

From literature results for morphine versus fentanyl[18] and an estimated 70% success rate with morphine by specialists at the Qatari NICU, a sample size of 60 patients needed to be included in each study arm (n = 120) to measure an anticipated pain relief rate difference of at least 35%, with $\alpha = 0.05$ and power = 80% (clinical calculator, ClinCalc.com). Detailed sample size calculation is as follows:

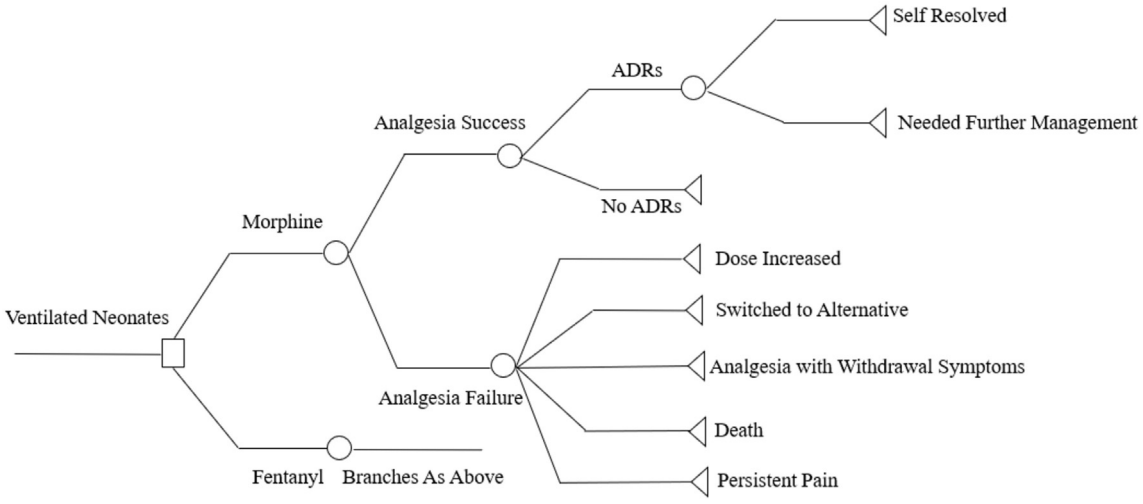

Figure 1. Decision tree model of morphine monotherapy versus fentanyl monotherapy. ADR = adverse drug reaction.

$N1 = \{1.96 \times \sqrt{(0.52 \times 0.48 \times (1+1/1))} + 0.84 \times \sqrt{(0.7 \times 0.3 + (0.35 \times 0.65/1))}\}^2/0.35^2 = 31$. $N2 = K \times N1 = 31$. The required number of patient medical records was ordered for study inclusion according to the ascending order of the records' hospital admission numbers in the Cerner database. A list of 63 patients in each group was generated before final selection based on inclusion/exclusion criteria. Every time an ordered patient was excluded, a replacement patient was ordered, based on the successive ascending hospital numbers in the Cerner database until sample size was achieved.

Statistical Analysis

SPSS version 22.0 (IBM Corp, Armonk, NY) was used to measure the baseline demographic characteristics. The χ^2 and Fisher's exact tests were used to test categorical data between the 2 study groups. For continuous data, the Student's *t* test and Mann–Whitney test were used to compare both groups. A multivariate ANCOVA model was used to assess the statistical differences between study therapy groups, considering changes from baseline values of PIPP scores, birth weight, and gestational age. Numerical and percentage measures were used to describe the categorical variables, and the mean SD measures were used to describe the continuous variables.

Perspective

The economic modeling adopted the WWRC hospital perspective, with only the direct medical costs of neonatal management considered.

Model Cost Inputs and Calculations

Medical costs that are considered in the study include (1) total acquisition cost of morphine and fentanyl; (2) management of ADRs caused by study's analgesic agents (ie, oxygen therapy for desaturation, catheter for urinary retention, caffeine citrate for apnea, furosemide for edema, dobutamine for bradycardia, phenobarbital for joint stiffness or spasms, naloxone for respiratory depression); (3) MV equipment; (4) diagnostic, laboratory, and monitoring tests during the NICU stay (see Appendix B in the online version at doi:10.1016/j.clinthera.2019.02.009); and (5) NICU stay per day.

All calculated costs are in Qatari Riyal (QAR) and adjusted for the financial year 2016 to 2017.[23] The overall cost of therapy comprised the primary costs of initial analgesic agents and secondary costs associated with patient management, including failure. Medication costs were based on drug wholesale prices by HMC, including Ministry of Public Health resources.[24] The model's cost inputs are summarized in Appendix B.

Sensitivity Analysis

One-way Sensitivity Analysis

Uncertainty of ±3% was used for the duration of MV and NICU stay, ±5% was tested for the doses of analgesic agents, and a ±10% range was used with estimated price inputs. With a uniform type of distribution, the sensitivity analysis was run using Monte Carlo with the @Risk-7.5 analysis tool (Palisade Corporation, Ithaca, NY). Variables and their uncertainty ranges are listed in Appendix C (in the online version at doi:10.1016/j.clinthera.2019.02.009).

Probabilistic Sensitivity Analysis

Uncertainty analysis was performed to determine the probability of a therapy's economic advantage by means of the Monte Carlo simulation. A triangular type of distribution and uncertainty of ±3%, based on 10,000 model simulations, was used for all model probabilities. Model probabilities and their uncertainty distributions are shown in Appendix D (in the online version at doi:10.1016/j.clinthera.2019.02.009).

RESULTS

Demographic Characteristics of Study Participants

All baseline demographic characteristics were not significantly different, with $P < 0.05$ between both groups (n = 63, each) (Table I).

Clinical Outcomes

At the base case of analysis, the number of neonates with successful pain relief was significantly higher in the morphine group (43 [68%] versus 27 [43%]; risk ratio = 1.72; 95% CI, 1.16–2.56; $P = 0.0075$). The reported ADRs with success and their costs are found in Appendix E (in the online version at doi:10.1016/j.clinthera.2019.02.009). Probability of pain relief success and other patient outcomes are presented in Table II.

Regarding neonates with analgesia failure due to receiving an increased dose, 12 patients on fentanyl

Table I. Main baseline patient demographic characteristics.

Characteristic	Morphine Group (n= 63)	Fentanyl Group (n= 63)	*P*
Sex, no. (%)			0.59
Male	34 (53.97)	38 (60.32)	
Female	29 (46.03)	25 (39.68)	
Gestational age, mean (SD), wk			0.09
Preterm (<37 wk)	28.77 (4.42)	30.49 (3.83)	
Full term (≥37 wk)	38.88 (1.13)	39.60 (1.26)	
Gestational age, no. (%)			0.34
Preterm (<37 wk)	55 (87.30)	50 (79.37)	
Full term (≥37 wk)	8 (12.70)	13 (20.63)	
Preterm gestational age (<37 wk), mean (SD), wk	28.58 (5.26)	30.10 (3.58)	0.18
Birth weight, mean (SD), g			0.07
≥2500	3069.71 (368.55)	3208 (362.47)	
<2500 and ≥1500	1832.50 (329.49)	1886.33 (280.40)	
<1500 and ≥1000	1175.88 (160.35)	1342.14 (202.61)	
<1000	694.17 (139.12)	782.14 (140.89)	
Birth weight, no. (%)			0.15
≥2500 g	19 (30.16)	21 (33.33)	
<2500 and ≥1500 g	8 (12.70)	17 (26.98)	
<1500 and ≥1000 g	17 (26.98)	12 (19.05)	
<1000 g	19 (30.16)	13 (20.64)	
Very and extremely low birth weight (<1500 g), mean (SD), g	920.97 (284.55)	998 (282.90)	0.22
Nationality, no. (%)			0.32
Qatari	19 (30.16)	26 (41.27)	
Arab	25 (39.68)	25 (39.68)	
Non-Arab	19 (30.16)	12 (19.05)	
Type of delivery, no. (%)			0.2
Vaginal	28 (44.44)	20 (31.75)	
Cesarean	35 (55.56)	43 (68.25)	
Received vecuronium, no. (%)			1
Yes	11 (17.46)	11 (17.46)	
No	52 (82.54)	52 (82.54)	
Initial PIPP scores, mean (SD)			0.32
0–6	3.16 (1.47)	3.17 (1.91)	
7–12	8.60 (1.36)	7.91 (1.51)	
>12	–	16 (0.0)	
Initial PIPP scores, no. (%)			0.09
0–6	57 (90.48)	53 (84.13)	
7–12	6 (09.52)	9 (14.29)	
>12	0 (0.0)	1 (01.58)	

PIPP = Premature Infant Pain Profile.

Table II. Outcome probabilities and weighted costs of morphine monotherapy and fentanyl monotherapy.

Therapy Outcome	Morphine			Fentanyl		
	Probability	Cost per Patient, QAR (USD)	Proportional Cost, QAR (USD)	Probability	Cost per Patient, QAR (USD)	Proportional Cost, QAR (USD)
Analgesia success with ADRs	0.68	56,477.59 (15,473)	38,404.76 (10,522)	0.43	84,170.60 (23,060)	36,193.36 (9916)
Analgesia success without ADRs	0	NA	NA	0	NA	NA
Analgesia failure						
Analgesia failure due to increased dose	0.06	49,990.06 (13,696)	3,173.97 (870)	0.43	25,304.46 (6933)	10,844.77 (2971)
Analgesia failure due to need for alternatives (fentanyl or morphine)	0.05	85,375.86 (23,391)	4,065.52 (1114)	0.1	31,137.43 (8531)	2965.47 (812)
Analgesia failure due to withdrawal symptoms	0.02	13,126.36 (3596)	208.35 (57)	0	NA	NA
Analgesia failure due to death	0.17	25,941.17 (7107)	4529.41 (1241)	0.02	14,690.98 (4025)	233.19 (64)
Analgesia failure due to persistent pain	0.02	16,059.43 (4400)	254.91 (70)	0.03	8681.53 (2379)	275.60 (76)
Total cost per patient	50,636.93 (13,873)			50,512.39 (13,839)		

ADR = adverse drug reaction; NA = not applicable; QAR = Qatari Riyal.

had increased doses that went above the standard therapeutic range and 15 patients received the increased doses within the standard range. In the morphine group, the patients (n = 4) were given increased doses to above the normal range.

Vital signs did not vary between the study groups after drug administration, with overlapping ranges of measures.

A multivariate ANCOVA model found that the statistical difference between morphine and fentanyl did not statistically change after accounting for baseline differences of values of PIPP scores, birth weight, and gestational age ($P = 1$).

Comparative durations of analgesia, MV, and NICU period can be found in Appendix F (in the online version at doi:10.1016/j.clinthera.2019.02.009).

Comparative doses of morphine and fentanyl are summarized in Appendix G (in the online version at doi:10.1016/j.clinthera.2019.02.009). In patients with successful pain relief, mean (SD) loading and maintenance doses were 111 (7) μg/kg and 16 (4) μg/kg for morphine and 3 (0.8) μg/kg and 3.5 (1.5) μg/kg for fentanyl, respectively.

Cost of Analgesia

At the base case, with being minimally more costly (QAR 50,637 [USD 13,909] versus QAR 50,512 [USD 13,874], morphine achieved successful pain relief in 68% of patients versus 43% with fentanyl (Table II). This is an incremental cost-effectiveness ratio (ICER) of QAR 490.36 (USD 135) per additional case of pain relief success with morphine over fentanyl. The detailed cost of resource use in the overall therapy can be found in Appendix H (in the online version at doi:10.1016/j.clinthera.2019.02.009).

Sensitivity Analysis

One-way Sensitivity Analysis

The model was insensitive to changes in most of the model's variables. The result was sensitive to the MV cost and NICU stay; that is, threshold analysis found that when the cost of MV decreased from QAR 430.15 (USD 118) to 404.35 (USD 114), or when the NICU stay with fentanyl decreased in the successful analgesia or increased dose pathways from 45 and 27 days to 44.65 and 26 days, respectively, or when NICU stay of successful morphine patients decreased from 47 days to a threshold value of 46.6 days, the overall cost saving shifted in favor of morphine.

Probabilistic Sensitivity Analysis

Of importance, morphine had a 98% probability of having an economic advantage over fentanyl. An ICER probability curve is presented in Figure 2. A tornado diagram that ranks different clinical therapy outcomes per their impact on the model outcome was generated (see Appendix I in the online version at doi:10.1016/j.clinthera.2019.02.009). Here, the isolated model outcome that had the most impact on the ICER outcome of the study was analgesia with increased doses (fentanyl), whereas analgesia success (fentanyl) had the lowest influence, with none affecting the dominant status of morphine.

DISCUSSION

Preterm infants spend long periods of time receiving care at the NICU and undergoing a variety of painful procedures, such as MV, which may cause alternation in the development and cognition in later childhood.[25] Neonatal pain must be assessed and treated; therefore, in the NICU of WWRC, all neonates are routinely assessed for pain with the PIPP scale. This is also relevant to reducing the agitation in the NICU, which is because of the strong evidence of correlation between it and pain in neonates.[4,26]

It is not universally accepted that neonates require analgesic or sedative agents during MV, when some favor using the nonpharmacologic interventions in infants. These, however, are probably inconvenient and less likely to relieve pain and agitation.[27] Other techniques may reduce the need for analgesic and sedative agents and lower the risk of brain injury such as making changes in the mode of ventilation. Practitioners, nevertheless, were reported to potentially find this difficult, which can result in complications such as hypoxia.[28]

With morphine and fentanyl being the most common, opioids are currently the most effective therapy for the reduction of the neonatal pain score with MV in the NICU, including the moderate to severe pain.[29] They produce both analgesia and sedation, have a wide therapeutic window, and also weaken the physiologic stress responses of neonates.[29] Morphine and fentanyl, however, are associated with considerable safety profile concerns with significant impact on clinical outcomes. The disadvantages of morphine include tachyphylaxis, hypotension, and the prolongation of MV and time to full enteral feedings

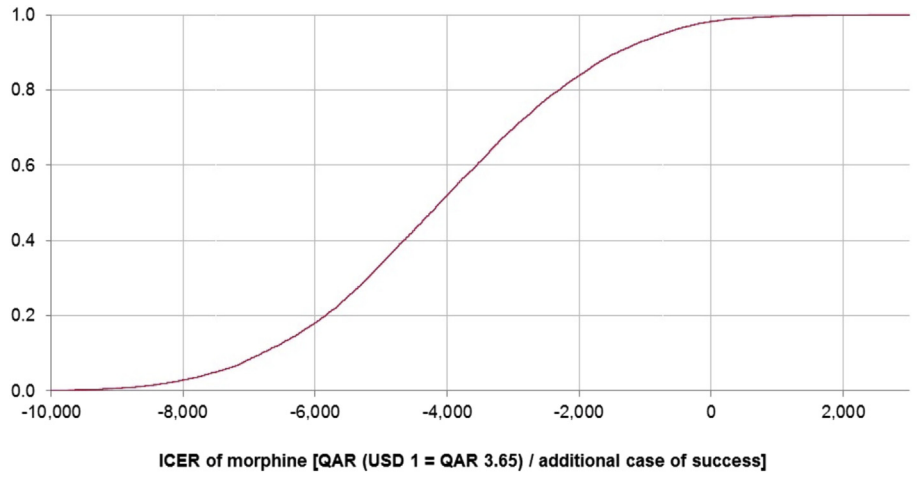

Figure 2. Incremental cost-effectiveness ratio (ICER) probability curve, with morphine. QAR = Qatari Riyal.

in neonates. Disadvantages of fentanyl, however, include fast tachyphylaxis and tolerance, increased requirement for ventilation, and chest wall rigidity.[27] They were found to be associated with no difference in mortality, time on assisted ventilation, long- and short-term neurologic sequelae, bronchopulmonary dysplasia, necrotizing enterocolitis, or length of hospital stay.[29] Opioids, therefore, are not recommended for routing preemptive use with neonatal MV and should only be used selectively based on clinical judgment and evaluation of pain indicators. Although nonopioids, as a result, are increasingly considered for use in neonatal pain management,[30] these remain to be considerably limited. Benzodiazepines provide little pain relief effect and are also associated with significant safety profile concerns, including respiratory depression, hypotension, myoclonic jerking, and excessive sedation.[31] They are even controversial in preterm neonates because of concerning incidence of brain injury.[19] Dexmedetomidine is a more promising alternative to opioids, but with the potential benefit only sufficiently found in adults so far. Although this may imply potential benefit in neonates, extensive multidisciplinary research must still be completed before dexmedetomidine is considered for widespread use in preterm neonates.[32–34] For now, and based on available data, opioids remain to be considered not only the most-effective but also the most commonly used in cases when pain relief with MV is necessary. In fact, as already discussed, the use of morphine and fentanyl seems to have been globally increasing recently.[5]

This study is the first pharmacoeconomics evaluation of the analgesic agents fentanyl versus morphine in the management of neonates with RDS undergoing MV in the NICU setting. All patients were followed until NICU discharge.

Morphine improved pain relief levels over fentanyl with relatively enhanced analgesia success (36.76%) in favor of morphine, corresponding to a minimal ICER of QAR 490.36 (USD 135) with morphine per additional case of pain relief success. Morphine dominated fentanyl in 98% of cases.

In the NICU at WWRC, vecuronium is potentially administered in addition to analgesic agents to paralyze critically ill neonates; hence, it can potentially influence the analgesia effect of the study drugs. The effect of vecuronium, however, is counterbalanced because the use of agent did not differ between the comparator groups in this study. With a similar trend, all other patient demographic characteristics were also not different between the study groups at baseline. Of note, the list of the neonatal characteristics assessed at baseline is relevant and comprehensive of known potential confounding factors, which can particularly be seen compared with relevant studies in the

literature.[18–20,35–40] Here, however, although no statistical differences were reported between treatment groups, one may not want to overlook observable difference in the baseline PIPP score, age, and weight of included neonates. Hence, a multivariate analysis of covariance model was used to ensure that such observed differences do not influence the measured statistical difference between morphine and fentanyl.

The PIPP score was used to reflect the analgesia status of the patient as the main clinical end point in this study. The PIPP scale has been previously validated and used to reflect the preterm and term neonates' need for pain relief.[17–19,41] Successful analgesia was a PIPP maintained at a score of 7 or reduced to a score <7. As discussed in Patients and Methods, neonates with mild pain did receive pharmacologic intervention to avoid anticipated pain and associated agitation due to MV.

The only study that directly compared morphine and fentanyl as monotherapies was a 1999 randomized controlled trial (RCT) conducted by Saarenmaa et al,[18] which reported no significant differences between the drugs except in the β-endorphin level in favor of fentanyl. RCTs may not be generalizable to local practices; moreover, morphine and fentanyl were evaluated in neonates with different overlapping disorders, including RDS, infection, and persistent pulmonary hypertension. This study was not purely conducted in neonates with RDS; hence, generalizability is limited. Patients with persistent pulmonary hypertension, for example, do not respond to conventional ventilation and require high-frequency ventilation in addition to inhaled nitric oxide with different doses of analgesia.[42] Moreover, the fentanyl loading dose in the RCT was >3-fold the currently recommended dose of fentanyl (10.5 μg/kg versus 0.5–3 μg/kg),[16] which could have easily overestimated the comparative performance of fentanyl compared with the local setting of the study.

The association between mortality and morphine is controversial. Although a local study reported increased mortality with opioids, several meta-analyses and studies reported no increase in mortality with opioids.[3,27,29–31] This is added to because mortality in these studies, just like in the present study, is an all-cause mortality. The mortality, hence, is multifactorial and might be caused by a variety of overlapping factors such as prematurity and RDS.[43,44] Referring to the RCT by Anand et al,[19] however, the mortality rate was found to be comparable based on similar durations of analgesia between study groups.[9] In Quinn et al,[45] mortality among study groups, although not clearly defined, did not differ when followed, based on equal groups' durations of therapy. Hence, the increased mortality with morphine in this study can be attributed to the large difference in the duration of analgesia observed (12 days with morphine over fentanyl). Of relevance, one may suggest that the reduced cost of morphine in 98% of cases is due to the higher mortality rate with morphine, suggesting that the death of a neonate translates to a reduced use of resources. This, however, cannot be the case in this study because the mortality outcome pathway with morphine was associated with longer durations of analgesia, MV, and NICU compared with fentanyl, adding more to the cost of morphine than the cost of fentanyl.

Although not examined in any of the previous neonatal studies, withdrawal symptoms from an opioid are considered one of the most important factors that cause brain noradrenaline abnormalities and lead to opioid dependence.[46] In our study, this was observed in patients receiving morphine, but other associated causes cannot be ruled out, such as infections or that the observed average duration of analgesia was longer in the morphine group (Appendix F).

In this study, one may question whether the outcomes were measured using equivalent doses of drugs. In the success arm, and in all arms, however, the average doses of drug were higher relative to respective standard dose ranges with fentanyl than with morphine (Appendix G). Adjusting doses to equivalency is only anticipated to increase the dose and the effect of morphine further. Similarly, any lack of equivalency between the drug doses does not explain the higher prevalence of ADRs with morphine. The justification of the higher ADRs with morphine is mostly the longer duration of analgesia, MV, and NICU stay in the morphine group.

All the patients with successful pain relief had at least 1 ADR that needed further management. Here, at baseline, the highest drug cost was observed when the patient had success associated with ADRs, higher with fentanyl than with morphine (Table II). Nevertheless, morphine was associated with more of

the success associated with ADRs than fentanyl and, consequently, a higher overall cost of therapy.

Despite the higher probability of switching fentanyl to the less-expensive morphine than the converse in the morphine group, the costs of the initial therapies were high enough to minimize the influence of alternative therapies on the comparative overall cost of therapies, with morphine dominating fentanyl.

The economic outcomes were insensitive to the one-way uncertainties associated with input variables except the cost of MV, NICU stay during analgesia success, and NICU stay while receiving increased doses in the fentanyl group. This is useful for identifying situations in which morphine is better than fentanyl or vice versa. In this context, threshold analysis was performed to enhance the clinical interpretability of such sensitivity and to help understand how the direction of cost saving varies with variations in the value of inputs, especially among institutions.

The cohort design of the study is appropriate for measuring the effectiveness as per real-life practices. This, in addition to following patients until NICU discharge, is important and represents more realistic NICU costs, better enhancing the relevance of evidence to practice. Allocation bias is not a concern in this study because patient selection, as already discussed earlier, was systematic, ascendingly based on successive hospital admission numbers, in addition to that the inclusion/exclusion of patients was based on an ordered blinded pool of patients and not directly based on the Cerner database of patients. Furthermore, because of the sensitive nature of the population, no clinical data were missing in records that could have jeopardized the quality of results.

This study is not without limitations. One limitation relates to the standard NICU use of fentanyl to control pain with intubation before analgesia due its rapid onset of effect.[7] The potential influence of fentanyl on subsequent analgesia cannot be excluded. This, however, cannot be prevented and is of no consequence to the comparative value of the study analgesic agents because it is standard care that all neonates undergoing MV receive the fentanyl to control pain during intubation. A second limitation is that the effect size used in the sample size calculations was based on expert opinion. Although this is a valid approach used in sample size calculations,[47–49] it is possibly less certain than data obtained from published studies. To note, however, there is no generalizable sources of effect size to refer to in this study, in addition to that the estimated effect sizes in this study were highly consistent with the actually reported effect estimates of the study drugs, and that the post hoc examination of the 95% CI associated with the reported risk ratio of the success indicates significance. Another limitation is that because only neonates with RDS were observed, the applicability of the study findings to patients with other conditions, such as meconium aspiration syndrome, is unknown. In addition, because of time constraints, long-term outcomes, including cognitive and language functions, were not examined. Although analgesia success was objectively measured based on a standardized scale, one cannot ignore the possibility of bias in historical data. This, however, cannot be prevented and is an inherent limitation of retrospective research. Important, nonetheless, is that the probabilistic sensitivity analysis confirmed the robustness of study outcomes against the potential variability in model probabilities, including the analgesia success. In addition, despite adjustments for all known confounders, there is a possibility that unknown confounders (eg, genetic factors) were not accounted for in this analysis, which might have influenced effect estimates of study drugs.

The results are important for stakeholders and policy makers, especially given an anticipated increase in ICU expenditures over the coming years[50] and the limited number of high-quality CEA studies of analgesia in ICU patients.[51] Of importance, the sensitivity analyses, the validated pain assessment, and the use of internationally recommended dose regimens strengthen the study's findings to extend beyond informing clinicians in the local setting. Within this context, it is important to emphasize that, although morphine seems to be mostly dominant over fentanyl for pain relief, this does not imply that morphine should universally be the opioid of choice for pain in all neonates with MV for RDS. After all, the purpose of the present study was only to provide decision makers with an additional dimension of information for consideration in the selection among alternatives. From the study's decision analytic model and limitations, the findings that morphine has been associated with enhanced pain relief over fentanyl, at a lower cost, will certainly reduce uncertainty among practitioners in common practice and will provide an

overall guidance for the future use of the medications. Nevertheless, the cost-effectiveness research is inherently limited by being only able to compare the cost of therapy against a single medication criterion at a time, usually the main indication. In real life, however, medications are multicriteria in nature, with alternatives performing differently in terms of important different criteria, such as ADRs. For morphine and fentanyl, therefore, in the clinical decision making at the level of neonates as individuals, it is vital and only appropriate that clinicians also balance the adverse effects of morphine and fentanyl when choosing between them, weighing their risk against benefit, and taking into consideration the underlying neonatal condition and the availability of supportive alternatives.[3] For example, fentanyl is preferred over morphine in hypotensive neonates, although morphine is favored over fentanyl with chest wall rigidity.[32,52,53] Fentanyl also has less impact on gastrointestinal motility compared with morphine and is therefore preferred in the extremely premature when morphine is potentially associated with prolongation of time to full enteral feedings.[18,54] For example, tachyphylaxis is more rapidly developed with fentanyl than with morphine,[27] which is an issue in patients with seizures because of the development of withdrawal symptoms. In addition, although fentanyl mostly produces similar respiratory depression as morphine at equivalent doses, fentanyl potentially causes adverse pulmonary impact independent of respiratory depression.[39] Another example is that in cases of well-controlled settings in which resources are available to rapidly and adequately manage associated side effects, such as bradycardia and chest wall rigidity, fentanyl is preferred as a rapidly acting opioid for analgesia.[31]

Follow-up studies are recommended to evaluate the effect of morphine on long-term neurologic outcomes in neonates and to measure relevant associations of interest in analgesic agent use, such as analgesia-related mortality with the duration of analgesia, and the gestational age and birth weight with analgesia use in neonatal patients.

CONCLUSIONS

This is the first CEA to evaluate the economic and clinical outcomes of morphine and fentanyl as standalone analgesic agents in neonates undergoing MV because of RDS. The control of pain in neonates with RDS was statistically significantly higher with morphine. In 98% of cases, morphine was dominant over fentanyl, that is, it achieved higher effectiveness and lower cost. Considering local practices and budget limits, the results suggest the appropriateness of the recent general trend of favoring morphine over fentanyl as monotherapies with MV in NICU settings of HMC. The clinical decision making, however, is complex and multifactorial and goes beyond the pain relief to also consider the safety profile concerns of morphine and fentanyl against anticipated benefit.

CONFLICTS OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

We acknowledge the receipt of study funding by Office of Academic Research, Qatar University, Qatar. This work was supported by Qatar University grant QUUG-CPHeCPH-15/16−8. We also appreciate the support of the neonatal intensive care unit team at the Women's Wellness and Research Center, Hamad Medical Corporataion, Qatar, for the provision of local statistics data via the Vermont Oxford database at the unit.

D. Al-Badriyeh conceived and designed the study, participated in data collection and analysis, interpreted the results, and revised the manuscript. D. Abushanab contributed to the study design, performed data collection and analysis, interpreted results, and wrote the first manuscript draft. O. Alsoukhni participated in study design and result interpretation. F. AbouNahia contributed to the interpretation of results. All authors read and approved the final manuscript.

REFERENCES

1. Saboute M, Kashaki M, Bordbar A, Khalessi N, Farahani Z. The incidence of respiratory distress syndrome among preterm infants admitted to neonatal intensive care unit: a retrospective study. *Open J Pediatr*. 2015;5:285−289. https://doi.org/10.4236/ojped.2015.54043.

2. Aranda JV, Carlo W, Hummel P, et al. Analgesia and sedation during mechanical ventilation in neonates. *Clin Ther*. 2005;27:877–899. https://doi.org/10.1016/j.clinthera.2005.06.019.
3. Hall RW, Boyle E, Young T. Do ventilated neonates require pain management? *Semin Perinatol*. 2007;31:289–297. https://doi.org/10.1053/j.semperi.2007.07.002.
4. Bennett S, Hurford WE. When should sedation or neuromuscular blockade be used during mechanical ventilation? *Respir Care*. 2011;56:168–176. https://doi.org/10.4187/respcare.01095.
5. Silbermann M. Current trends in opioid consumption globally and in Middle Eastern countries. *J Pediatr Hematol Oncol*. 2011;33:S1–S5. https://doi.org/10.1097/MPH.0b013e3182121872.
6. Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. *Br J Pharmacol*. 2011;164:1322–1334. https://doi.org/10.1111/j.1476-5381.2011.01335.x.
7. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology*. 1987;66:433–435.
8. Al MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based analgo-sedation vs. conventional analgesia and sedation for patients on mechanical ventilation in The Netherlands. *Crit Care*. 2010;14:R195. https://doi.org/10.1186/cc9313.
9. Zhou Y, Jin X, Kang Y, et al. Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: a prospective, randomized study. *Crit Care*. 2014;18:R122. https://doi.org/10.1186/cc13922.
10. Carrasco G, Molina R, Costa J, Soler JM, Cabré L. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost-benefit analysis. *Chest*. 1993;103:557–564. https://doi.org/10.1378/chest.103.2.557.
11. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, et al. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. *Crit Care Med*. 1997;25:33–40. https://doi.org/10.1097/00003246-199701000-00009.
12. Swart EL, van Schijndel RJ, van Loenen AC, Thijs LG. Continuous infusion of lorazepam versus medazolam in patients in the intensive care unit: sedation with lorazepam is easier to manage and is more cost-effective. *Crit Care Med*. 1999;27:1461–1465. https://doi.org/10.1097/00003246-199908000-00009.
13. Barrientos-Vega R, Sanchez-Soria MM, Morales-Garcia C, Cuena-Boy R, Castellano-Hernández M. Pharmacoeconomic assessment of propofol 2% used for prolonged sedation. *Crit Care Med*. 2001;29:317–322. https://doi.org/10.1097/00003246-200102000-00018.
14. Cox CE, Reed SD, Govert JA, et al. Economic evaluation of propofol and lorazepam for critically ill patients undergoing mechanical ventilation. *Crit Care Med*. 2008;36:706–714. https://doi.org/10.1097/CCM.0B013E3181544248.
15. Hamad Medical Corporation [homepage on the internet]. Doha: About Us 2018 [Cited 2018 September 20]. Available from: https://microsites.harveynash.com/hmc/about-us/.
16. *Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online*. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2018.
17. Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. *Clin J Pain*. 1996;12:13–22. https://doi.org/10.1097/00002508-199603000-00004.
18. Saarenmaa E, Huttunen P, Leppaluoto J, Meretoja O, Fellman V. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomized trial. *J Pediatr*. 1999;134:144–150. https://doi.org/10.1016/S0022-3476(99)70407-5.
19. Anand KJ, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med*. 1999;153:331–338. https://doi.org/10.1001/archpedi.153.4.331.
20. Simons SH, van Dijk M, van Lingen RA, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA*. 2003;290:2419–2427. https://doi.org/10.1001/jama.290.18.2419.
21. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hershenson MB. Tolerance and dependance in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology*. 1990;73:1136–1140. https://doi.org/10.1097/00000542-199012000-00011.
22. World Health Organization. Infant [homepage on the internet]: Newborn 2017 [Cited 2017 February 1]. Available from: http://www.who.int/topics/infant_newborn/en/.
23. Qatar Central Bank [homepage on the internet]. Doha: Main Economic Indicators 2017 [Cited 2017 February 14]. Available from: http://www.qcb.gov.qa/English/Publications/Statistics/Pages/EconomicIndicatros.aspx.
24. Ministry of Public Health [homepage on the internet]. Doha: [Cited 2017 February 24]. Available from: https://www.moph.gov.qa/home-en.
25. Badr LK, Abdallah B, Hawari M, et al. Determinants of premature

infant pain responses to heel sticks. *Pediatr Nurs*. 2010;36:129–136.
26. Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol*. 2008;28:55–60. https://doi.org/10.1038/sj.jp.7211861.
27. McPherson C. Sedation and analgesia in mechanically ventilated preterm neonates: continue standard of care or experiment? *J Pediatr Pharmacol Ther*. 2012;17:351–364. https://doi.org/10.5863/1551-6776-17.4.351.
28. Mora Carpio AL, Mora JI. Positive End-Expiratory Pressure (PEEP) [Updated 2018 Oct 27]. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2018 Jan [Internet], Available from: https://www.ncbi.nlm.nih.gov/books/NBK441904/ [last accessed October 1, 2018].
29. Bellù R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2010;95:F241–F251. https://doi.org/10.1136/adc.2008.150318.
30. Shah PS, Dunn M, Lee SK, Allen AC, Singhal N. Early opioid infusion and neonatal outcomes in preterm neonates ≤28 weeks' gestation. *Am J Perinatol*. 2011;28:361–366. https://doi.org/10.1055/s-0030-1270112.
31. Hall RW, Anand KJ. Pain management in newborns. *Clin Perinatol*. 2014;41:895–924. https://doi.org/10.1016/j.clp.2014.08.010.
32. O'Mara K, Gal P, Wimmer J, et al. Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature neonates. *J Pediatr Pharmacol Ther*. 2012;17:252–262. https://doi.org/10.5863/1551-6776-17.3.252.
33. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007;298:2644–2653. https://doi.org/10.1001/jama.298.22.2644.
34. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology*. 2009;111:1075–1084. https://doi.org/10.1097/ALN.0b013e3181b6a783.
35. Anadkat JS, Kuzniewicz MW, Chaudhari BP, Cole FS, Hamvas A. Increased risk for respiratory distress among white, male, late preterm and term infants. *J Perinatol*. 2012;32:780–785. https://doi.org/10.1038/jp.2011.191.
36. Sun H, Xu F, Xiong H, et al. Characteristics of respiratory distress syndrome in infants of different gestational ages. *Lung*. 2013;191:425–433. https://doi.org/10.1007/s00408-013-9475-3.
37. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ*. 2008;336:85–87. https://doi.org/10.1136/bmj.39405.539282.BE.
38. Condò V, Cipriani S, Colnaghi M, et al. Neonatal respiratory distress syndrome: are risk factors the same in preterm and term infants? *J Matern Fetal Neonatal Med*. 2016;30:1267–1272. https://doi.org/10.1080/14767058.2016.1210597.
39. Orsini AJ, Leef KH, Costarino A, Dettorre MD, Stefano JL. Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. *J Pediatr*. 1996;129:140–145.
40. Guinsburg R, Kopelman BI, Anand KJ, et al. Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. *J Pediatr*. 1998;132:954–959.
41. de Melo GM, Lélis AL, de Moura AF, Cardoso MV, da Silva VM. Pain assessment scales in newborns: integrative review [in Portuguese]. *Rev Paul Pediatr*. 2014;32:395–402. https://doi.org/10.1016/j.rpped.2014.04.007.
42. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr*. 1997;131:55–62.
43. Glass HC, Costarino AT, Stayer SA, et al. Outcomes for extremely premature infants. *Anesth Analg*. 2015;120:1337–1351. https://doi.org/10.1213/ANE.0000000000000705.
44. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. 10, mortality and acute complications in preterm infants. In: Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention*. Washington (DC): National Academies Press (US); 2007. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11385/ [last accessed December 17, 2018].
45. Quinn MW, Otoo F, Rushforth JA, et al. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. *Early Hum Dev*. 1992;30:241–248. https://doi.org/10.1016/0378-3782(92)90073-P.
46. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect*. 2002;1:13–20. https://doi.org/10.1151/spp021113.
47. Brasher PM, Brant RF. Sample size calculations in randomized trials: common pitfalls. *Can J Anaesth*. 2007;54:103–106. https://doi.org/10.1007/BF03022005.

48. Gupta KK, Attri JP, Singh A, Kaur H, Kaur G. Basic concepts for sample size calculation: critical step for any clinical trials!. *Saudi J Anaesth*. 2016;10:328–331. https://doi.org/10.4103/1658-354X.174918.
49. Biau DJ, Kernéis S, Porcher R. Statistics in brief: the importance of sample size in the planning and interpretation of medical research. *Clin Orthop Relat Res*. 2008;466:2282–2288. https://doi.org/10.1007/s11999-008-0346-9.
50. Angus DC, Kelley MA, Schmitz RJ, et al. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284:2762–2770. https://doi.org/10.1001/jama.284.21.2762.
51. Talmor D, Shapiro N, Greenberg D, Stone PW, Neumann PJ. When is critical care medicine cost-effective? A systematic review of the cost-effectiveness literature. *Crit Care Med*. 2006;34:2738–2747. https://doi.org/10.1097/01.CCM.0000241159.18620.AB.
52. Anand KJ, Hall RW, Desai N, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004;363:1673–1682. https://doi.org/10.1016/S0140-6736(04)16251-X.
53. Fahnenstich H, Steffan J, Kau N, Bartmann P. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med*. 2000;28:836–839. https://doi.org/10.1097/00003246-200003000-00037.
54. Menon G, Boyle EM, Bergqvist LL, et al. Morphine analgesia and gastrointestinal morbidity in preterm infants: secondary results from the NEOPAIN trial. *Arch Dis Child Fetal Neonatal Ed*. 2008;93:F362–F367. https://doi.org/10.1136/adc.2007.119297.

Address correspondence to: Daoud Al-Badriyeh, PhD, Associate Professor of Pharmacoeconomics and Outcomes Research, College of Pharmacy, Qatar University, Doha, 2713, Qatar. E-mail: daoud.a@qu.edu.qa

APPENDIX. SUPPLEMENTARY DATA

The following are the supplementary data to this article:

Appendix A. Premature infant pain profile assessment tool for neonates

Indicators	0	1	2	3	Score
Gestational age	≥ 36 weeks	32–35 weeks	28–31 weeks	< 28 weeks	
Behavioral state	Active, awake, eyes open, facial movements	Quiet, awake, eyes open, no facial movements	Active, awake, eyes closed, Facial movements	Quiet, asleep, eyes closed, no facial movements	
Heart rate maximum (bpm)	0-4/min increase	5-14/min increase	15-24/min increase	≥25/min increase	
O2 saturation	92–100%	89–91%	85–88%	84% or less	
Brow bulge	None	Minimum	Moderate	Maximum	
Eye squeeze	None	Minimum	Moderate	Maximum	
Nasolabial furrow	None	Minimum	Moderate	Maximum	

Appendix B. Resource costs based on the neonatal intensive care at Hamad Medical Corporation

Item/Name of test	Unit	Unit cost (QAR)*
Morphine	15 mg/ml IV vial	1.97
Fentanyl	50 mcg/ml IV vial	6
Naloxone	0.4 mg/ml IV vial	2.75
Furosemide	10 mg/ml IV vial	0.6
Dobutamine	1 mg/ml IV vial	6.81
Phenobarbital	30 mg/ml IV vial	6.32
Complete blood count	1 test during NICU	30
Calcium	1 test during NICU	10
Bilirubin	1 test during NICU	10
Protein	1 test during NICU	10
Albumin	1 test during NICU	10
Alkaline phosphatase	1 test during NICU	10
Alanine aminotransferase	1 test during NICU	10
Aspartate aminotransferase	1 test during NICU	10
Glucose-6-phosphate dehydrogenase screen	1 test during NICU	20
Glucose	1 test during NICU	10
C-reactive protein	1 test during NICU	30
17 Hydroxyprogesterone, dried blood spot (DBS)	1 test during NICU	40
Amino acid and acy serum creatinine (Scr) DBS	1 test during NICU	360
Biotinidase DBS	1 test during NICU	30
Galactose-1-phosphate uridyltransferase	1 test during NICU	30
Thyroid stem hormone	1 test during NICU	40
Homocystine Scr	1 test during NICU	70

Appendix B. (*Continued*)

Item/Name of test	Unit	Unit cost (QAR)*
MRSA screening	1 test during NICU	130
Urine culture	1 test during NICU	50
PH	1 test during NICU	30
PO_2	1 test during NICU	10
Partial pressure of carbon dioxide (PCO_2)	1 test during NICU	10
Bicarbonate (HCO_3)	1 test during NICU	10
Base excess	1 test during NICU	10
Cytomegalovirus antibodies (CMV Ab) IgG	1 test during NICU	110
CMV Ab IgM	1 test during NICU	110
Herpes simplex type I IgG	1 test during NICU	30
Herpes simplex type I IgM	1 test during NICU	30
Herpes simplex type II IgG	1 test during NICU	30
Herpes simplex type II IgM	1 test during NICU	30
Rubella Ab IgG	1 test during NICU	110
Rubella Ab IgM	1 test during NICU	90
Toxoplasma Ab IgG	1 test during NICU	120
Toxoplasma Ab IgM	1 test during NICU	120
Urea	1 test during NICU	7.27
Creatinine	1 test during NICU	7.27
Sodium	1 test during NICU	10.91
Potassium	1 test during NICU	10.91
Chloride	1 test during NICU	10.91
Bicarbonate	1 test during NICU	8.48
Magnesium	1 test during NICU	9.7
Blood culture	1 test during NICU	125.18
Cerebrospinal fluid (CSF) culture	1 test during NICU	105.92
CSF analysis	1 test during NICU	120.37
Urinalysis tests	1 test during NICU	72.22
X-radiation (x-ray)	1 test during NICU	26.36
Computerized tomography scan (CT scan)	1 test during NICU	158.14
Ultrasound scan (US)	1 test during NICU	84.34
Magnetic resonance imaging (MRI)	1 test during NICU	263.57
Barium enema	1 test during NICU	71.69
Electrocardiogram-EKG	1 test during NICU	26.36
Water soluble contrast enema	1 test during NICU	15.81
Peripherally inserted central catheter (PICC line) insertion	1 test during NICU	21.08
Echocardiogram	1 test during NICU	115.97
Lumbar puncture	1 test during NICU	57.98
Oxygen therapy	1 test during NICU	211.54
NICU stay	Stay per day	527.14
Mechanical ventilator	1 machine	430.15

*USD 1 = QAR 3.65.

Appendix C. Variation ranges of input variables in the sensitivity analysis

Variable	Base case	Variation range (Uniform distribution)	
		Low	High
Cost of urea	7.27 QAR*	6.54	8
Cost of creatinine	7.27 QAR	6.54	8
Cost of sodium	10.91 QAR	9.82	12
Cost of potassium	10.91 QAR	9.82	12
Cost of chloride	10.91 QAR	9.82	11.9
Cost of bicarbonate	8.48 QAR	8.06	8.9
Cost of magnesium	9.7 QAR	8.73	10.67
Cost of blood culture	125.18 QAR	112.67	137.09
Cost of CSF culture	105.92 QAR	95.34	116.5
Cost of CSF analysis	120.37 QAR	95.32	116.52
Cost of urinalysis tests	72.22 QAR	65	79.44
Cost of x-ray	26.36 QAR	23.72	29
Cost of CT-scan	158.14 QAR	142.33	173.95
Cost of US-scan	84.34 QAR	75.91	92.77
Cost of MRI	263.57 QAR	237.31	289.83
Cost of barium enema	71.69 QAR	64.52	78.86
Cost of electrocardiogram-EKG	26.36 QAR	23.72	29
Cost of water soluble contrast enema	15.81 QAR	14.23	17.39
Cost of peripherally inserted central catheter (PICC line) insertion	21.08 QAR	18.98	23.2
Cost of echocardiogram	115.97 QAR	104.25	127.57
Cost of lumbar puncture	57.98 QAR	52.19	63.79
Cost of oxygen therapy	211.54 QAR	190.39	232.69
Cost of NICU stay	527.14 QAR	474.43	579.85
Cost of MV	430.15 QAR	387.14	473.17
Fentanyl monotherapy			
MV duration during analgesia success	6 days	5.82	6.18
MV duration during analgesia failure-high dose	4 days	3.88	4.12
MV duration during analgesia failure-alternative	9.27 days	8.99	9.55
MV duration during analgesia failure-death	6 days	5.82	6.18
MV duration during analgesia failure-persistent pain	1 day	0.97	1.03
NICU duration during analgesia success	45 days	43.65	46.35
NICU duration during analgesia failure-high dose	27 days	26.19	27.81
NICU duration during analgesia failure-alternative	33 days	32.01	33.99
NICU duration during analgesia failure-death	11 days	10.67	11.33
NICU duration during analgesia failure-persistent pain	9 days	8.73	9.27
Loading dose of fentanyl during analgesia success	2.11 mcg/kg	2	2.22

Appendix C. (*Continued*)

Variable	Base case	Variation range (Uniform distribution)	
		Low	High
Loading dose of fentanyl during analgesia failure-high dose	5.32 mcg/kg	5.05	5.59
Loading dose of fentanyl during analgesia failure-alternative	3 mcg/kg	2.85	3.15
Loading dose of morphine during analgesia failure-alternative	100 mcg/kg	95	105
Loading dose of fentanyl during analgesia failure-death	1 mcg/kg	0.95	1.05
Maintenance dose of fentanyl during analgesia success	4.57 mcg/kg	4.34	4.8
Maintenance dose of fentanyl during analgesia failure-high dose	4.3 mcg/kg	4.09	4.52
Maintenance dose of fentanyl during analgesia failure-alternative	3.33 mcg/kg	3.17	3.5
Maintenance dose of morphine during analgesia failure-alternative	13.33 mcg/kg	12.66	14
Morphine monotherapy			
MV duration during analgesia success	6 days	5.82	6.18
MV duration during analgesia failure-high dose	27 days	26.19	27.81
MV duration during analgesia failure-alternative	66 days	64.02	67.98
MV duration during analgesia failure-withdrawal symptoms	1 day	0.97	1.03
MV duration during analgesia failure-death	16 days	15.52	16.48
MV duration during analgesia failure-persistent pain	1 day	0.97	1.03
NICU duration during analgesia success	47 days	45.9	48.41
NICU duration during analgesia failure-high dose	54 days	52.38	55.62
NICU duration during analgesia failure-alternative	83 days	80.51	85.49
NICU duration during analgesia failure-withdrawal symptoms	15 days	14.55	15.45
NICU duration during analgesia failure-death	20 days	19.4	20.6
NICU duration during analgesia failure-persistent pain	16 days	15.52	16.48
Loading dose of morphine during analgesia success	125 mcg/kg	118.75	131.25
Loading dose of morphine during analgesia failure-high dose	292.5 mcg/kg	277.88	307.13
Loading dose of morphine during analgesia failure-alternative	120 mcg/kg	114	126
Loading dose of fentanyl during analgesia failure-alternative	3.73 mcg/kg	3.54	3.92
Loading dose of morphine during analgesia failure-death	127.5 mcg/kg	121.13	133.89
Maintenance dose of morphine during analgesia success	12.27 mcg/kg	11.66	12.88
Maintenance dose of morphine during analgesia failure-high dose	15 mcg/kg	14.25	15.75
Maintenance dose of morphine during analgesia failure-alternative	10 mcg/kg	9.5	10.5
Maintenance dose of fentanyl during analgesia failure-alternative	10 mcg/kg	9.5	10.5
Maintenance dose of morphine during analgesia failure-withdrawal symptoms	15 mcg/kg	14.25	15.75
Maintenance dose of morphine during analgesia failure-death	11.67 mcg/kg	11.09	12.25
Maintenance dose of morphine during analgesia failure-persistent pain	5 mcg/kg	4.25	5.75

*USD 1 = QAR 3.65.

Appendix D. Model probabilities and uncertainty distributions used in the Monte Carlo simulation

Input variables	Uncertainty distribution	
	Morphine monotherapy	Fentanyl monotherapy
Analgesia success	Triangle distribution, 66.20%-68.25%—70.30%	Triangle distribution, 41.57%-42.86%—44.15%
With ADRs	Triangle distribution, 97%-100%—103%	Triangle distribution, 97%-100%—103%
Self-resolved ADRs	Triangle distribution, 0%-0%—0%	Triangle distribution, 0%-0%—0%
ADRs needed further management	Triangle distribution, 97%-100%—103%	Triangle distribution, 97%-100%—103%
Without ADRs	Triangle distribution, 0%-0%—0%	Triangle distribution, 0%-0%—0%
Analgesia failure	Triangle distribution, 30.80%-31.75%—32.70%	Triangle distribution, 55.43%-57.14%—58.85%
Increased dose	Triangle distribution, 19.40%-20%—20.60%	Triangle distribution, 72.75%-75%—77.25%
Therapy switch to alternatives	Triangle distribution, 14.55%-15%—15.45%	Triangle distribution, 16.17%-16.67%—17.17%
Withdrawal symptoms	Triangle distribution, 4.85%-5%—5.15%	Triangle distribution, 0%-0%—0%
Death	Triangle distribution, 53.35%-55%—56.65%	Triangle distribution, 16.17%-16.67%—17.17%
Persistent pain	Triangle distribution, 4.85%-5%—5.15%	Triangle distribution, 5.39%-5.56%—5.73%

Appendix E. Adverse drug reactions, and their costs, associated with analgesia success

The adverse drug reactions associated with analgesia success	Morphine		Fentanyl	
	Total number of patients	Cost per patient QAR (USD)	Total number of patients	Cost per patient QAR (USD)
Desaturation	23	38,440.2 (10,532)	21	36,207.6 (9,920)
Desaturation and urinary retention	1	38,450.2 (10,534)	2	36,217.6 (9,923)
Desaturation, urinary retention, MV adjustment and edema	1	38,485.2 (10,544)	0	N/A
Desaturation and MV adjustment	7	38,440.2 (10,532)	0	N/A
Desaturation, MV adjustment, and urinary retention	1	38,450.2 (10,534)	1	36,217.6 (9,923)
Desaturation, MV adjustment, and edema	3	38,263.6 (10,483)	0	N/A
Desaturation and edema	6	38,263.6 (10,483)	0	N/A
Desaturation and respiratory depression	1	38,441.6 (10,532)	0	N/A

Appendix E. (*Continued*)

The adverse drug reactions associated with analgesia success	Morphine		Fentanyl	
	Total number of patients	Cost per patient QAR (USD)	Total number of patients	Cost per patient QAR (USD)
Desaturation, MV adjustment, and joint stiffness	0	N/A	1	36,216.0 (9,922)
MV adjustment	0	N/A	2	35,996.1 (9,862)

*N/A: Not applicable.

Appendix F. Duration of analgesia, MV, and NICU stay

Study clinical outcome	Morphine			Fentanyl		
	Duration of analgesia (hour)	Duration of MV (hour)	Duration of NICU stay (day)	Duration of analgesia (hour)	Duration of MV (hour)	Duration of NICU stay (day)
Analgesia success	120	144	47	90	144	45
Analgesia failure						
Increased dose	48	648	54	38	96	27
Therapy switch to alternatives	960	1584	83	72	216	33
Withdrawal symptoms	24	24	1	N/A	N/A	N/A
Death	312	384	20	24	216	11
Persistent pain	144	24	16	1	24	9

*N/A: Not applicable.

Appendix G. Doses of study therapy groups

Study clinical outcome	Morphine		Fentanyl	
	Average loading dose (mcg/kg)	Average maintenance dose (mcg/kg/hour)	Average loading dose (mcg/kg)	Average maintenance dose (mcg/kg/hour)
Analgesia success	111	16	3	3.5
Analgesia failure				
Increased dose	292.5	15	5.5	4.5
Therapy switch to alternatives	Initial therapy: 120 Alternative to fentanyl: 3	Initial therapy: 15 Alternative to fentanyl: 4	Initial therapy: 3 Alternative to morphine 100	Initial therapy 3 Alternative to morphine 15
Withdrawal symptoms	110	15	3	5
Death	127.5	15	1	5
Persistent pain	120	16	2.5	3

Appendix H. Cost components of the overall therapy

Cost component	Cost (QAR)*	Cost (QAR)
	Morphine	Fentanyl
Analgesia success with ADRs		
Initial analgesia	19.7	12.0
MV	2,580.9	2,580.9
NICU stay	24,775.7	23,721.4
Hematological tests	240.0	180.0
Chemistry tests	1,759.1	2,736.4
Metabolic tests	1,140.0	1,140.0
Microbiology tests	1,644.4	1,233.3
Blood gases tests	2,940.0	2,310.0
Virology tests	1,560.0	780.0
Diagnostic tests	1,568.8	1,302.0
Oxygen therapy	211.5	211.5
Catheter	10.0	10.0
Medications to treat ADRs	36.5	8.3
Analgesia failure due to increased dose		
Initial analgesia	41.4	18.0
MV	11,614.0	1,720.6
NICU stay	28,465.7	14,232.9
Hematological tests	210.0	N/A
Chemistry tests	2,345.5	2,540.9
Metabolic tests	1,140.0	1,140.0
Microbiology tests	822.2	1,233.3
Blood gases tests	2,310.0	1,750.0
Virology tests	1,560.0	780.0
Urinalysis tests	N/A**	216.7
Diagnostic tests	1,481.3	1,672.1
Analgesia failure due to receiving alternative		
Initial analgesia	17.7	12.0
Alternative analgesia	4.8	102.0
MV	28,389.8	3,871.3
NICU stay	43,752.9	17,395.7
Hematological tests	510.0	180.0
Chemistry tests	3,713.6	3,127.3
Metabolic tests	1,710.0	1,140.0
Microbiology tests	2,466.7	1,233.3
Blood gases tests	2,800.0	3,220.0
Urinalysis tests	N/A	72.2
Diagnostic tests	2,003.1	869.8
Analgesia failure due to withdrawal symptoms		
Initial analgesia	2.0	N/A
MV	430.2	N/A
NICU stay	7,907.2	N/A
Hematological tests	120.0	N/A
Chemistry tests	586.4	N/A
Metabolic tests	570.0	N/A
Microbiology tests	1,644.4	N/A
Blood gases tests	770.0	N/A
Virology tests	780.0	N/A
Diagnostic tests	316.3	N/A
Analgesia failure due to death		
Initial analgesia	19.7	6.0
MV	6,882.4	2,580.9
NICU stay	10,542.9	5,798.6
Hematological tests	210.0	60.0
Chemistry tests	1,563.6	1,954.6
Metabolic tests	1,140.0	570.0
Microbiology tests	1,233.3	411.1
Blood gases tests	2,030.0	2,730.0
Virology tests	780.0	N/A
Diagnostic tests	1,539.3	579.9
Analgesia failure due to persistent pain		
Initial analgesia	2	6.0
MV	430.2	430.2
NICU stay	8,434.3	4,744.3
Hematological tests	120.0	60.0
Chemistry tests	1,172.7	781.8
Metabolic tests	570.0	1,140.0
Microbiology tests	822.2	822.2
Blood gases tests	4,060.0	560.0
Diagnostic tests	448.1	137.1

*USD 1 = QAR 3.65, **N/A: Not applicable.

Appendix I. Tornado diagram of the variables as per their influence on the outcome.