KALAM INSTITUTE OF HEALTH TECHNOLOGY

Health Technology Assessment in India (HTAIn)

Health Technology Assessment of Low-Cost Portable Ventilator

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Study Title: Health Technology Assessment of Low-Cost Portable Ventilator

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List of Abbreviations

NIV	Non-invasive ventilation
IMV	Invasive mechanical ventilator
COPD	Chronic obstructive pulmonary disease
ARF	Acute respiratory failure
VAP	Ventilator associated pneumonia
CRDs	Chronic respiratory diseases
ICU	Intensive care unit
LCPV	Low-cost portable ventilators
GBS	Guillain barre syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO	Population, Intervention, comparator, and outcome
ETI	Endotracheal intubation
CPAP	Continuous positive airway pressure
NIMV	Noninvasive mechanical ventilation
MV	Mechanical ventilation
PSV	Positive support ventilator
QOL	Quality of life
ALS	Amyotrophic lateral sclerosis
QALY	Quality adjusted life years
ICER	Incremental Cost Effectiveness Ratio

Contents

Executive Summary

India has a disproportionately high burden of chronic respiratory and neuro muscular diseases. The contribution of chronic respiratory diseases in total Disability Adjusted Life Years in India increased from 4.5% in 1990 to 6.4% in 2016. The increasing contribution of these diseases to the overall disease burden across India and the high rate of health loss especially less-developed states, highlights the need for focused policy interventions to address this significant cause of disease burden in India

The Systematic Review on mechanical invasive ventilator and Low-cost portable ventilator on Chronic obstructive pulmonary disease (COPD), Pneumonia, Severe bronchial asthma, Acute respiratory failure (ARF), Neuromuscular diseases, Head trauma, Respiratory failure Guillain barre syndrome (GBS) concludes that mortality due to respiratory and neuromuscular diseases can be prevented with the use of an effective portable ventilator.

We have done a Health Technology Assessment for a new low-cost portable ventilator (LCPV. It has two components—a tablet size ventilator, a valve that attaches to patient's wind pipe and drives the air in and an android phone. This ventilator requires an external oxygen supply and it can also work with the air present around us.

In order to assess the clinical effectiveness of the ventilator, we didn't find any clinical trials. We took data for fifty patients from a retrospective cohort study and compared the cross-sectional variation of partial pressure of carbon dioxide (PaCO2) between a historical control and the new ventilator. We found no statistically significant variation between the two.

Lastly, in order to measure the cost-saving per Quality Adjusted Life Years (QALYs), assuming non-inferiority, we calculated the cost-savings if this ventilator in used for domiciliary purpose for the new intervention is cost-effective at Rs 4845/- per QALY gained, while the standard of care is cost-effective at Rs 4859/- per QALY gained. The difference in Incremental Cost Effectiveness Ratio between the other non-invasive ventilator and the new ventilator turns out to be approximately Rs 14 per QALY gained per patient.

Taking the Willingness to pay threshold as GDP per capita per month and assuming non-inferiority in terms of clinical effectiveness, the new ventilator turns out to be cost-effective. This device can be used for palliative care of COPD patients. This new LCPV also can be lifesaving in Epidemics like the current COVID 19 and other disaster scenarios

Chapter 1: Systematic Review on Mechanical Invasive Ventilator Verses Low-Cost Portable Ventilator

Introduction

A medical ventilator can be a lifesaving and they are used when a person can't breathe properly on all alone. Ventilators can be of two types Invasive and Noninvasive. Patients with respiratory muscle weakness have a low tidal volume (TV) and a high respiratory rate. This rapid shallow breathing is not due to abnormalities in gas exchange but is more likely to be due to severe muscle weakness and/or impaired afferent and efferent connections of the motor neurons by the underlying neuromuscular diseases and other respiratory disorders. Ventilation (invasive & non-invasive) is widely used in patients with respiratory disorders (Chronic obstructive pulmonary disease (COPD), Pneumonia, Severe bronchial asthma, Acute respiratory failure (ARF), Head trauma).

Invasive mechanical ventilator (IMV) is a device that was placed inside the trachea through the mouth, such as an endotracheal tube or the skin, such as a tracheostomy tube, whereas noninvasive ventilator (NIV) uses the breathing support administered through a face mask or nasal mask, where air was usually added with oxygen, and it was given through the mask under positive pressure. Mechanical ventilation is used to treat 30–40% of patients admitted to critical care [1, 2]. The duration of patient under invasive ventilation is mostly associated with increased mortality rate.

LCPV has become a commonly used alternative to invasive ventilation [2]. LCPV implemented as an alternative to intubation should be provided in an intensive care or high-dependency unit. It can be safely administered in an adequately staffed and monitored ward [3]. Both the invasive and non-invasive (NIV) modes are available in the LCPV, and based on the Cochrane review guidelines 2014 on the use of non-invasive weaning, which included 16 randomized studies and concluded that NIV weaning was superior to invasive weaning with significantly reduced mortality, weaning failures, ventilator associated pneumonia (VAP), intensive care and hospital length of stay and total duration of mechanical ventilation [4].

Disease profile

The Economic and Social burden of respiratory disease is increasing in India, and there is a need to manage this burden. A low-cost non-invasive portable ventilator can help in managing several respiratory disorders (Chronic obstructive pulmonary disease (COPD), Pneumonia, Severe bronchial asthma, Acute respiratory failure (ARF), Head trauma).

Respiratory muscle weakness is common in patients with neuromuscular diseases [5] LCPV could prolong survival and improve quality of life. Patients with neuromuscular diseases exhibit very often sleep-disordered breathing, which is frequently overlooked until symptoms become more severe leading to irreversible respiratory failure necessitating LCPV [6]

Acute respiratory infection is an infection that may interfere with normal breathing. It can affect upper respiratory system, which starts at sinuses and ends at vocal cords, or just lower respiratory system, which starts at vocal cords and ends at lungs. Chronic respiratory diseases (CRDs) are diseases of the airways and other structures of the lung. Some of the most common are chronic obstructive pulmonary disease (COPD), and Asthma. Pneumonia is also one of the major diseases that shows common among the elderly population and in those with comorbid conditions, such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal failure, congestive heart failure, chronic liver disease, etc. [7]

Epidemiology

Epidemiology is the distribution and determinants of health-related states among specified populations. While respiratory failure may be fairly easy to diagnose clinically. Acute respiratory failure, and the need for ventilation, remains one of the most common reasons for admission to the intensive care unit (ICU). The burden of acute respiratory failure is high in terms of mortality and morbidity as well as the cost of its principal treatment of ventilation. Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs 48 h later or thereafter following endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever and altered white blood cell count), changes in sputum characteristics, and detection of a causative agent [8]. The crude prevalence rates of these diseases increased by 29·2% (27·9–30·4) for COPD and 8·6% (6·1–11·4) for asthma in between 1990-2016 [9]. COPD became fourth leading cause of years of life lost in Empowered Action Group (EAG) States including Bihar, Jharkhand, Madhya Pradesh, Chhattisgarh, Odisha, Rajasthan, Uttar Pradesh and Uttarakhand [10]. Also, COPD ranked seventh among the North-East States including Assam, Mizoram, Arunachal Pradesh, Meghalaya, Nagaland, Tripura, Sikkim and Manipur. Bronchial asthma is the most common chronic respiratory disease, with a case burden of approximately 358.2 million in 2015.[11] In 2015, about 0·40 million people died from asthma, a decrease of 26·7% from 1990, and the age-standardized death rate decreased by 58·8%. The prevalence of asthma increased by 12·6%, whereas the age-standardized prevalence decreased by 17·7%. The prevalence of head injury in this study was found to be 105 (40.5%) among surgical emergency department visits. Among these 49 (46.7%) occurred due to assault/interpersonal fights. More than half of the patients sustained a mild head injury 56 (53.3%) and 67 (63.8%) an open head injury [12]. ventilators are required in 4.2 to 8.9% of all cases of heady injury [13].

Transmission of COVID-19 is primarily through droplet spread. These droplets are affected by gravity and may cause direct transmission from close contact or contribute to surface contamination (where the virus may remain active for hours to days). However, coughing and some airway management procedures can generate aerosols composed of smaller virus containing particles suspended in air. These airborne particles may travel greater distances and be inhaled, increasing the risk of transmission [14].

Initial reports suggest that COVID-19 is associated with severe disease that requires intensive care in approximately 5% of proven infections. In settings with limited access to invasive ventilation or prior to patients developing severe hypoxemic respiratory failure, there may be a role for high-flow nasal oxygen or LCPV [15]. However, the high gas flow of these 2 techniques is less contained than in the closed circuitry typical of invasive ventilators, which poses the risk of dispersion of aerosolized virus in the health care environment, such as in the setting of a poorly fitting face mask. Determining the magnitude of this risk, and mitigation strategies, is a crucial knowledge gap. The growing prevalence of respiratory diseases (Including COVID-19), increasing preference for cost-effective & portable ventilators in homecare, and growing applications of cost-effective & portable ventilators such as ambulatory services, emergency medical services, and home care are driving the growth of the portable ventilators segment in the market.

Rationale of the study

With a high burden of COPD, epidemics like COVID-19, respiratory failure and neuro muscular diseases in India, there is an urgent requirement of low-cost portable ventilation.

Economic Burden

With 18% of the world's population, India has 32% of the global DALYs from chronic respiratory diseases. The contribution of chronic respiratory diseases in total DALYs in India increased from 4.5% in 1990 to 6.4% in 2016. COPD was the second leading cause of disease burden in India contributing to 4.8% of DALYs. An Economic Analysis of a Randomized Controlled Trial by Plant et al. [16] found that a typical UK hospital which provides Non-Invasive ventilation service to patients suffering from acute exacerbation of COPD and mild to moderate acidosis would avoid 6 deaths, and 3 to 9 admissions to Intensive Care Units per year, with a cost reduction of £12000-53000. Another study by Tuggey et al., [17] found that a provision of a Home-based ventilator for COPD patients with recurrent admissions resulted in a mean saving of £8254 per patient per year along with reducing the number of days the patients had to spend in the ICU as well as the hospital.

Aim

Health Technology Assessment of Low-cost portable ventilators (LCPV) in Intensive care settings of Indian public health systems.

Objectives

- To assess clinical effectiveness of the new ventilators under review (low-cost portable ventilator) as compared with existing ventilators-portable and ICU based.
- To assess cost effectiveness of the new LCPV.
- To assess new LCPV in comparison to existing alternatives from the perspective of equity in access.
- *Population(P)*- Adult patients eligible for ventilation with the following diseases Chronic obstructive pulmonary disease (COPD), Pneumonia, Severe bronchial asthma, Acute respiratory failure (ARF), Neuromuscular diseases, Head trauma, Respiratory failure Guillain

barre syndrome (GBS)

- *Interventions(I)*- Low-Cost Portable ventilator.
- *Comparators(C)*- Mechanical Invasive ventilator
- **Outcomes (O)-Primary Outcomes:**
  Partial arterial carbon dioxide concentration
  Incremental Cost Effectiveness Ratio (ICER)
  Secondary Outcomes: Number of Adverse events,
  Other Outcomes: Ease of use, Level of comfort

Methodology

Literature search database

The systematic review was conducted by primary electronic database search. Searches were conducted in PubMed, Google scholar and Cochrane data bases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was developed for this project. The time taken to complete this study was approximately 5 months. The articles included in this study were from the period 2008-2019.

Inclusion criteria

Articles were considered for inclusion if the study met the following criteria Chronic obstructive pulmonary disease (COPD), Pneumonia, Severe bronchial asthma, Acute respiratory failure (ARF), Neuromuscular diseases, Head trauma, Respiratory failure Guillain barre syndrome (GBS)

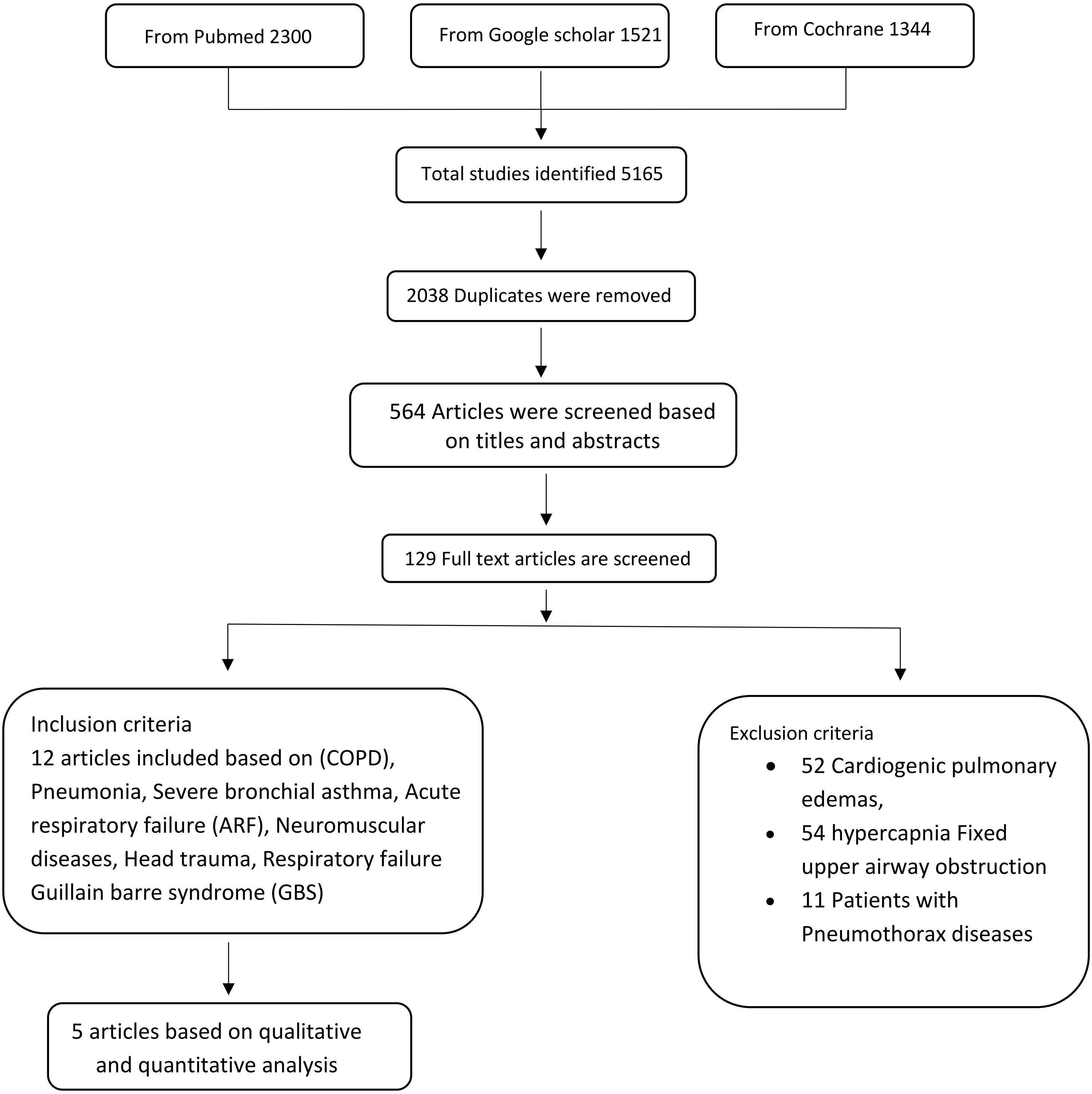
Exclusion criteria

Excluded studies from the data was cardiogenic pulmonary edema, hypercapnia Fixed upper airway obstruction and patients with Pneumothorax diseases.

Screening process

All articles identified by the search were initially screened for eligibility on title and abstracts. The search results were exported to the reference management software EndNote X7. Duplicate articles were removed and the remaining titles and abstracts were screened. Full-text articles were retrieved and assessed for eligibility using predefined criteria, for inclusion in the review. The target population was patients suffering with respiratory failure, COPD Asthma and Neuromuscular diseases.

PRISMA Flowchart



Key words: Respiratory failure, Neuro muscular diseases, COPD, pulse rate and Oxygen saturation

Types of studies

The studies like Prospective, Retrospective and Cohort studies

Data extraction

All articles were reviewed independently, extracted into a standard Excel file, or word file then all studies that fulfilled the inclusion criteria were included and those studies that are lacking required data were excluded.

Study quality Assessment:

Individual studies were evaluated for qualitative study where the PICO were taken into consideration. Acute respiratory failure usually shows difficulty in getting enough oxygen to the lungs, problems removing carbon dioxide from the lungs, or both. Respiratory failure can complicate a number of acute neuromuscular conditions [18]. Respiratory muscle weakness is common among patients who have neuromuscular disease. Symptoms will differ depending on the speed of onset of the respiratory muscle weakness. Careful monitoring of respiratory function is particularly important in acute disorders such as Guillain-Barré syndrome [19]. Patients with Guillain-Barré and other acute conditions may require short-term ventilatory support in the intensive care unit and it can be successfully treated with non-invasive ventilation. Asthma and chronic obstructive pulmonary disease (COPD) are disorders of the lungs characterized by airflow obstruction, inflammation and tissue remodeling. Management of patients with these diseases is complex and the improvement of diagnostic-therapeutic strategies represents a critical challenge for the healthcare system [20] Most of the patients preferring 70% noninvasive, and 58% invasive mechanical ventilation [21]. The increasing burden of obstructive lung diseases, such as Asthma and Chronic Obstructive Pulmonary Disease (COPD), appears to be caused, at least in part, by the ageing of the world's population [22].

Critical Appraisal

Risk of bias graph and summary

Risk of Bias: Risk of bias summary: review authors' judgements about each risk of bias item for each study included.

a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

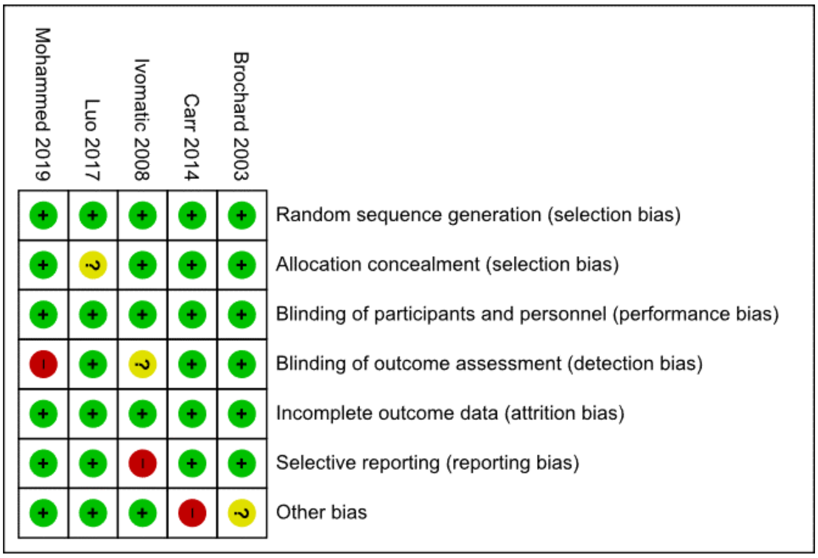


Figure.1 Risk of Bias graph

b) Risk of bias Summary: Review authors' judgements about each risk of bias item presented as percentages across all included studies. Both risk of bias Graph and risk of bias summary states that the selected studies have low risk of bias, and less unclear and high risk of bias

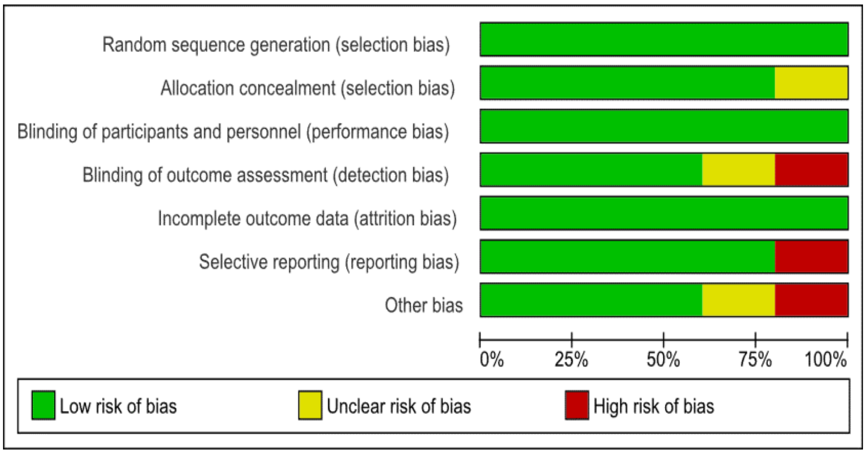


Figure. 2 Risk of Bias Summary

The analysis of risk was completed using Cochrane RevMan 5.0. This exercise is pivotal to knowing the quality of the data used.

Results

Study selection

A total of 5165 articles were identified by the search strategy of different databases like PubMed, Google scholar and Cochrane of which 2038 were removed based on duplicates, 564 articles were removed based the title and abstract. The full texts of 129 articles were screened, of which 14 articles met the inclusion criteria and were included in this review and 5 articles were taken into consideration based on the qualitative and quantitative analysis.

Study Characteristics

The study population with Chronic obstructive pulmonary disease (COPD), Pneumonia, Severe bronchial asthma, Acute respiratory failure (ARF), Neuromuscular diseases, Head trauma, Respiratory failure Guillain barre syndrome (GBS). In the present study, selection bias and incomplete outcome bias were taken as criteria. Patients were randomly allocated, and in two studies patients lost their follow up during the treatment.

Description of the included studies

Table: 1 Included studies for Mechanical Invasive ventilator

S.no	Author	Year	Total	Mechanical Invasive ventilator	Study design
1	Brochard	2003	60	43	Prospective
2	Carr	2014	55	46	Cohort
3	Ivomatic	2008	1311	614	Prospective
4	Luo	2017	85	47	Retrospective
5	Mohammed	2019	40	20	Prospective

Table: 2 Included studies for Portable ventilator (NIV)

S.no	Author	Year	Total	Portable ventilator (NIV)	Study design
1	Brochard	2003	60	17	Prospective
2	Carr	2014	55	09	Cohort
3	Ivomatic	2008	1311	697	Prospective
4	Luo	2017	85	38	Retrospective
5	Mohammed	2019	40	20	Prospective

Study outcome

Primary outcome

A prospective study of total 55 patients were identified with Guillain–Barré syndrome (GBS). Nine patients (16%) required non-invasive ventilation only, and 46 patients (84%) were intubated and ventilated [23].

An prospective, randomized trial was performed in a multidisciplinary intensive care unit with a total of 1311 patients of which 614 patients requiring mechanical invasive ventilator (MIV) and 697 were given with noninvasive mechanical ventilation (NIMV) for COPD patients. In NIMV an appropriate face mask was chosen and connected to the respirator. Starting respirator parameters were set to: continuous positive air pressure (CPAP) to

0cmH$_2$O, PSV 10cmH$_2$O and FiO$_2$ was adjusted to reach SatO$_2$ >90% [24]. After 12h of NIMV application, similar results were observed for respiratory frequency, minute volume and arterial blood gases. pH and PaCO$_2$ improvement after 12h were better in COPD patients and they reported the success for NIMV.

A Retrospective cohort of 85 patients admitted to ICU for acute neuromuscular respiratory failure, as compared to invasively ventilated patients 47 [25] with NIV treated patients 38 had a shorter length of stay. NIV has been increasingly used to manage both acute and chronic respiratory failure in a broad variety of conditions. Inpatients with amyotrophic lateral sclerosis (ALS), long term NIV may provide survival benefit and may improve patients' well-being and quality of life, increase in PaO2/FiO2, (PaO2/fraction of inspired oxygen) [26].

A prospective, randomized controlled study was conducted on 40 mechanically ventilated patients having chronic obstructive pulmonary disease with acute exacerbation and type 2 respiratory failures. As the patients were considered for weaning, those who failed the spontaneous breathing trial were randomly allocated into two groups each of 20 patients as follows: (1) Group 1: patients were extubated and received NIV. (2) Group 2: patients received invasive ventilation and were gradually weaned. NIV has a satisfactory arterial oxygen saturation (SaO$_2$) greater than or equal to 90% on FiO$_2$ 40% [27].

Sensitivity analysis

	LCPV		MIV			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**
Brochard 2003	17	60	43	60	19.6%	0.40 [0.26, 0.61]
Carr 2014	9	55	46	55	17.2%	0.20 [0.11, 0.36]
Ivomatic 2008	697	1311	614	1311	22.6%	1.14 [1.05, 1.23]
Luo 2017	38	85	47	85	21.1%	0.81 [0.60, 1.10]
Mohammed 2019	20	40	20	40	19.5%	1.00 [0.65, 1.55]
Total (95% CI)		**1551**		**1551**	**100.0%**	**0.62 [0.37, 1.04]**
Total events	781		770			

Heterogeneity: Tau² = 0.30; Chi² = 55.67, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.82 (P = 0.07)

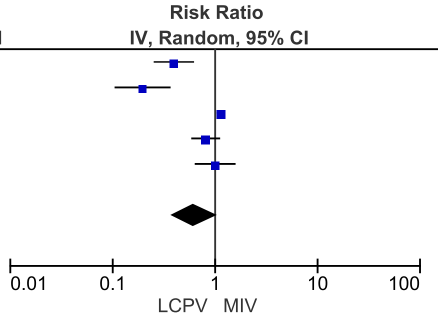


Figure. 3 Forest plot

Five studies were eligible for inclusion. The results of the meta-analysis comparing with invasive mechanical ventilator with non-invasive portable ventilator were presented in a forest plot. The forest plot showed out of 1551 participants 781 who received LCPV treatment and out of 1551 participants 770 received Low-cost portable ventilator treatment (risk ratio 0.62, 95% confidence interval 0.37 to 1.04). It is represented graphically by the diamond;

the centre of the diamond equals the total overall estimated risk ratio and the ends of the diamond indicate the limits of the 95% confidence interval. The vertical dotted line through the centre of the diamond represents the total overall estimated relative risk. The solid vertical line shows no significance and no relative risk. The p value is 0.00001 which is heterogenous and statistically significant.

Secondary outcome:

Secondary outcomes for respiratory failure and neuro muscular diseases are Tremors, Nervousness, Palpitations, Muscle cramps, Headache, Constipation, Unpleasant sensation in the mouth, Dry mouth. Dry throat, Urinary retention, Blurred vision.

Discussion:

In India, three out of five leading causes of mortalities constitute noncommunicable diseases whereas COPD is the second biggest cause of death. The prevalence of COPD has increased by 29.2% by 2016 which is a serious public health concern. The population-adjusted ARF-hospitalization rates increased in all age groups and patients 85 years and older had the highest age-specific hospitalization rate. While overall rates of mechanical ventilation (NIV or IMV) remained stable over the nine-year period, there was an important shift away from IMV (which decreased from 48% in 2001 to 42% in 2009) towards NIV (which increased from 4% in 2001 to 10% in 2009). [28]. Among patients hospitalized with asthma exacerbation and requiring ventilatory support (NIV or IMV), more than 40% received NIV. Although patients successfully treated with NIV appear to have better outcomes than those treated with IMV [29] ALS patients with mechanical ventilation quality of life QoL, is decreased but NIV improves QoL in terms of cognitive function, encouraging better sleep architecture and brain oxygenation [30].

Acute respiratory failure, COPD, asthma and neuromuscular disease are frequent and life-threatening complication in chest wall disorders. In all these disorders, invasive mechanical ventilation is the standard treatment when initial management with oxygen supplementation, physiotherapy, cough assistance, or antibacterial drugs are insufficient to stabilise the patient, although this may have potentially life-changing consequences for the patient with neuromuscular disease. Over the last decade, NIV has been increasingly used to manage both acute and chronic respiratory failure in a broad variety of conditions. In patients with amyotrophic lateral sclerosis (ALS), long term NIV may provide survival benefit and may improve patients' well-being and quality of life, [31].

Conclusion

LCPV minimizes length of ICU stay, hospital mortality in respiratory failure, COPD and Neuromuscular diseases. The success of LCPV is dependent on various clinical aspects and the organization of care, but also on a lot of technical issues [32]. LCPV should be considered as the first-line therapeutic approach for the management of acute respiratory failure, and neuromuscular disorders. Also, LCPV, if readily available in adequate numbers, may reduce the person's length of stay in the ICU, and potentially improve overall outcomes especially in resource constrained settings like in India. Also, LCPV may be lifesaving in COVID 19 and other flu epidemics.

Chapter 2: Clinical Evaluation of The Device

Description of the ventilator

As per the claim by the manufacturers, the device is as accurate as any high-end mechanical invasive ventilator. It has two components—a tablet size ventilator, a valve that attaches to patient's wind pipe and drives the air in and an android phone. This ventilator requires an external oxygen supply and it can also work with the air present around us. It takes the air steadily with the required quantity. The USP of the ventilator is at a fraction of non-invasive system. It can provide all features of a mechanical invasive ventilator.

There is an extremely sensitive FiO2 sensor incorporated with accuracy of +-2% which can display FiO2 from 10% to 100%. (The details of the device are provided in Annexure-I). Patients with head injuries, cervical and spinal injuries, respiratory problems often need ventilator at home. This ventilator will help them all."

- It uses electricity and can work on battery backup.
- It is portable and thus will provide mobility to patient's dependent on ventilator.

Applications

This device is used for ventilation, easy to carry with affordable price.

Technical Specifications

Modes available: PC-CMV PC-SIMV PSV VC-SIMV VC-CMV CPAP BPAP

Battery 50-watt hour Lithium-Ion Battery (4 hours backup)

Power Consumption 15watts (Nominal) 48 watts (Peak)

Peak Flow rate 100 Liters per minute

PEEP 0 cmH2O to 20 cmH2O (increments of 1 cmH2O)

Trigger Flow Sensitivity 1 Liter per minute to 20 Liter per minute

Volume Accuracy 10% of the full scale between (10 L/min - 80L/min)

Peak Pressure 60 cmH20

Peak Respiratory rate 40 or 60 Breath per minute

Minimum inspiratory time 0.5 to 2.5 seconds

Tidal Volume 50 ml to 1200 ml (increments of 1 ml)

FiO2 Capability

We collected data from the manufacturer regarding an observational study they did on fifty patients.

Based on this data, we did a retrospective case control study wherein we compared the performance of this ventilator with historical data on other ventilator for one-sided non-inferiority.

Essential features for COVID 19 Ventilator Globally:

Essential						
S. N	**Parameter**	**MHRA (UK)**	**Australia**	**USA (AARC)**	**Literature (Medscape-USA)**	**HLL**
1	Tidal Volume (Vt)	250- 600ml in steps of 50 ml or atleast 350 ml & 450ml options	200 mL to 800mL in steps of 50mL or smaller	4-8 mL/kg of predicated body weight So atleast range should be 300 to 600mL	5-8 mL/kg of ideal body weight	200-600 mL tidal volume
2	Peak Flow Rate	NA	upto 100 L/min	60 L/min	upto 100L/min	150L/min to 240 L/min
3	Respitatory Rate Breathe/min	10-30 breathes/min in increments of 2 (only in mandatory mode)	5 to 30 breaths per minute	atleast 10-15 breaths /min	atleast 8-12 breaths/min	60 breaths/min
4	I:E Ratio	1:2.0 (i.e expiration lasts twice as long as inspiration)	display	NA	1:2	1:4 to 4:1
5	Modes	CMV - PRVC/PCV/VCV, SIMV-PC	PCV or VCV	CMV (Continuous Mandatory Ventilation)	CMV, PSV	PC-CMV, PC-SIMV, PSV, VC-CMV, VC-SIMV, VC-CMC, PRVC, ACV, CPAP, BIPAP; Pressure Support & Volume Mode could be used in place of CPAP & BPAP
6	PEEP (Positive End Expiratory Pressure)	5-20 cm H20 adjustable in 5cmH2O increments	5 to 25cmH20	atleast 10-20 cm H20	≥10 cm H20	0cm H20 to 30cm H20 (increments of 1cmH20)

7	Plateau Pressure	< 30 cm H2O	NA	< 30 cm H2O	< 30 cm H2O	0-40 cmH20
8	FiO2	50% or 60% and 30-100% in 10% steps	range upto 100%	0.21-0.95	1	21%-100%

Aim: To establish non-inferiority of a new LCPV as compared to a Mechanical invasive ventilator

Methodology: A Retrospective Cohort Study

Population: Patients requiring ventilation

Intervention: A new low-cost portable ventilator (LCPV)

Comparator: Case arm from a randomized controlled trial [Khilani et al]. Patients suffering from Acute exacerbation of chronic obstructive pulmonary disease are given ventilation, and PaCO2 and pH is measured for these patients.

Outcomes to measure

Variation in PaCO2-

Adequacy of ventilation is best assessed "using partial arterial carbon dioxide concentration measurement" [Pretto et al]

The partial pressure of carbon dioxide (PCO2) is the measure of carbon dioxide within arterial or venous blood. It often serves as a marker of sufficient alveolar ventilation within the lungs. Generally, under normal physiologic conditions, the value of PCO2 ranges between 35 to 45 mmHg, or 4.7 to 6.0 kPa. [Messina et al.]

Based on the available data, we have tried to measure whether the mean variation between the control arm of Khilnani et al. and the New LCPV.

pH- "The respiratory centers contain chemoreceptors that detect pH levels in the blood and send signals to the respiratory centers of the brain to adjust the ventilation rate to change acidity by increasing or decreasing the removal of carbon dioxide (since carbon dioxide is linked to higher levels of hydrogen ions in blood)."[1]

[1] https://courses.lumenlearning.com/boundless-ap/chapter/respiration-control/

Study Design:

Based on the data provided by the manufacturers, we designed a retrospective cohort study

Hypothesis:

The Null Hypothesis for this test is whether there is a significant difference in the cross-sectional variation of partial pressure of carbon dioxide between the control group and comparator group.

$H_0 = \theta_1 - \theta_2 < \delta$

$H_1 = \theta_1 - \theta_2 > \delta$

Power of the test:

We have calculated the power of the test retrospectively. In this case, where the goal of the study was to make comparison between two different studies, hence we could calculate the power of the test retrospectively in order to quantify uncertainty [Thomas 1997].

We used sample size calculator for one sided non-inferiority hypothesis from the City University of Hong Kong

$N1 = (Z_\alpha + Z_\beta)^2 * [r\theta_1(1 - \theta_1) + \theta_2(1 - \theta_2)] / (\theta_1 - \theta_2 - \delta)^2$

$N2 = rN1$

Notations:

α: The probability of type I error (significance level) is the probability of rejecting the true null hypothesis.

β: The probability of type II error (1 – power of the test) is the probability of not rejecting the false null hypothesis.

θ1-θ2: The difference between the true mean response rates of a group1 (i.e., a test drug (θ1) and group2 (i.e., a control (θ2))), 0 for this case as θ1= θ2

r: The allocation ratio n2/n1. i.e., r=0.4 for this case

δ: The superiority for δ>0 or non-inferiority for δ<0. When δ>0, the rejection of the null hypothesis indicates the superiority of the test drug over the control. When δ<0, the rejection of the null hypothesis indicates the non-inferiority of the test drug against the control. We have taken this value as 0.1

Parameter	Value
α	0.1
β	0.25
θ1	0
θ2	0
δ	0.1
r	0.4

With N1 as 50, and N2 as 20 we retrospectively calculated the power of the test as 0.75

Base-Line characteristics:

The intervention had 50 patients with the following characteristics:

S.no	Age	Sex	Diagnosis
1	17	M	c1-c2 #
2	16	M	CVJ anomaly
3	12	M	Av Malformation (AVM)
4	15	M	Subdural haemorrhage (SDH)
5	11	M	Arteriovenous Malformation (AVM)
6	55	M	Subarachnoid Haemorrhage (SAH)
7	16	M	Infratentorial bleed
8	60	M	Subarachnoid Haemorrhage (SAH)
9	35	M	Post. fossa tumor
10	55	M	Subarachnoid Haemorrhage (SAH)
11	44	M	Arteriovenous Malformation (AVM)
12	17	M	Head Injury
13	45	F	Subdural haemorrhage (SDH)
14	55	M	Subdural haemorrhage (SDH)
15	58	M	Subarachnoid Haemorrhage (SAH)

16	60	F	Subarachnoid Haemorrhage (SAH)
17	49	F	Arteriovenous Malformation (AVM)
18	55	F	VOGM
19	48	M	Dorsal AVF
20	60	M	SAH Lt MCA ruptured Aneurysm
21	55	M	IVH with SAH
22	48	M	Tentorial Meningioma
23	68	F	Frontal Bleed k/c/o RHD with MS
24	55	M	Grade 4 Medulloblastoma
25	64	M	Large bifrontal SOL
26	14	F	Congenital hydrocephalus
27	34	M	C1-c2 neurofibroma
28	22	M	Pcom Aneurysm
29	36	F	Bifrontal SOL
30	14	M	Aqueduct Stenosis
31	11	F	Lt PO Bleed with ruptured AVM
32	16	F	Arnold Chiari Malformation with SyringoShunt
33	24	M	Subdural haemorrhage (SDH)
34	34	M	Subarachnoid Haemorrhage (SAH)
35	49	M	Glioma
36	44	M	Meningioma
37	54	M	Acom Aneurysm
38	62	F	Arteriovenous Malformation (AVM)
39	42	M	C3-c4 #
40	51	M	Subarachnoid Haemorrhage (SAH)
41	45	M	Tentorial Meningioma
42	18	M	Subdural haemorrhage (SDH)
43	55	m	Subarachnoid Haemorrhage (SAH)
44	66	M	POST Fossa SOL
45	57	F	Arteriovenous Malformation (AVM)
46	13	f	Congenital Hydrocephalus with Scoliosis
47	48	M	Decompressive craniectomy with Duraplasty

48	58	F	Subarachnoid Haemorrhage (SAH)
49	19	M	Glioma
50	17	M	Meningioma

The control arm has twenty patients, mean age 57.6 ± 10.8 years, 16 males and 4 females with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Results:

Mean PaCO2 for the patients on the new LCPV was 38.1 ± 7.83 mm of Hg, mean PaCO2 for the comparator arm in Khilnani et al. was 81.1 ± 11.6 mm of Hg.

We designed a study to find if there is a significant difference between the cross-sectional standard deviation of the PaCO2 two arms

H_0: $\sigma_{intervention} = \sigma_{comparator}$

H_1: $\sigma_{intervention} \neq \sigma_{comparator}$

Using methodology by Cho et al. (2008), we calculated the standard deviation of the sample variances of these two arms, and using these values we applied the independent t-test on the given hypothesis.

For the comparator arm, using the mean, standard deviation of PaCO2 and sample size values we have, and assuming normal distribution, we simulated the values of PaCO2 for the 20 patients in the comparator arm.

We fed the numbers on graph pad calculator[2] and found the following results:

P value and statistical significance:

1. The two-tailed P value equals 0.6350
2. By conventional criteria, this difference is considered to be not statistically significant.

Confidence interval:

1. The mean of Group One minus Group Two equals -3.7730775042100895
2. 95% confidence interval of this difference: From -19.5628461804851450 to 12.0166911720649670

Intermediate values used in calculations:

1. t = 0.4768

[2] https://www.graphpad.com/quickcalcs/ttest2/

2. df = 68
3. standard error of difference = 7.913

Conclusion:

Based on this analysis we can conclude that there is no significant cross-sectional variation in PaCO2 between the intervention and the comparator

Recommendations:

1. Although the clinical study number was small it found there is no significant cross-sectional variation in PaCO2 between the intervention and the comparator As the device is an indigenous low-cost version of mechanical invasive ventilator already available in the market, if it comes under the category of ***predicate medical device***, then the clinical testing may not necessary nor relevant. Testing the output parameters (like tidal volume, peak pressure, etc) of this LCPV using a test lung may be sufficient to check its functioning.
2. This LCPV may be particularly useful in the current COVID 19 epidemic to overcome ventilator shortage and resource constraints

Limitations:

1. The data was collected at one centre, we recommend a multicentric observational study to further validate the findings.
2. Since this is a retrospective cohort study, there is a possibility of selection bias and the absence of data on potential confounding factors as the data was recorded in the past.

Chapter 3: Economic Evaluation of domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD with a new lost cost ventilator in Indian healthcare setting.

The use LCPV can reduce the need for hospital and general practioners care in Indian healthcare setting.

Assuming that the new LCPV is non-inferior to the other available non-invasive ventilators, we calculate the annual cost saving from provider's perspective per Quality Adjusted Life Year (QALY) with the new low-cost ventilator.

Economic Model:

Based upon the available clinical evidence, we constructed a decision analytic tree in order to calculate the annual cost savings per QALY averted the provider incurs by switching to the new low-cost ventilator in domiciliary settings vis a vis any other available ventilator in the market.

Base-line characteristics of patients:

We assumed that the age of the patient is 50 years. The patient remains hypercapnic after acute respiratory failure requiring mechanical ventilation.

Transition Probabilities:

We used data from Funk et al., in the study on patients with COPD, after the run-in period of 6 month in which all the patients were put on ventilation, they were randomized to either continue ventilation or stop ventilation. The proportion of patients randomized to withdrawal vis a vis non-withdrawal was same.

After 12 months, clinical worsening was measured for both the groups. The probability of worsening with ventilator was 0.1538, and the probability of worsening without ventilator was 0.7629 respectively.

Assuming non-inferiority for the new ventilator, we calculated the cost savings and improvement in quality adjusted life years for a given patient if he/she is kept on the new ventilator.

Costing:

We did the costing from provider's perspective. There are three scenarios for a patient undergoing non-invasive ventilation: In Intensive Care unit, admitted to the hospital but not in ICU, and under ventilation while they are at home.

In order to calculate the cost of ICU stay per day for the patient, we used figures from Peter et al.(2016), and to calculate the cost of hospital stay, we took figures from the National Health system cost database for India, PGI School of Public Health.[3] In order to calculate the cost of domiciliary ventilation, we added the salary of nurse, cost of visit by the doctor, and the annual cost for ventilator and humidifier based on the facts that life of the device is 10 years, and assuming discount rate as 3% and annual maintenance cost as 8% [33-50].

We obtained the price and the maintenance cost of the new non-invasive ventilator from the receipts produced by the manufacturers, and the price of other non-invasive ventilator from the Government e-market place (GeM) portal[4].

Costing from the societal perspective:

Utilities:

The data for utilities was taken from Gani et al. [2010].

The utilities for mild, moderate and severe COPD were 0.787, 0.75 and 0.647 respectively. The disutility caused by severe and non-severe exacerbations was 0.5 and 0.15 respectively.

We calculated the Quality adjusted life years on the fact that average life expectancy in Andhra Pradesh is approximately close to 70 years, and hence the patients has expected 20 life years.

[3] National Health system cost database for India - https://www.healtheconomics.pgisph.in/costing_web/

[4] https://mkp.gem.gov.in/portable-ventilator/non-invansive-ventilator/p-5116877-67492746237-cat.html#variant_id=5116877-67492746237

Results:

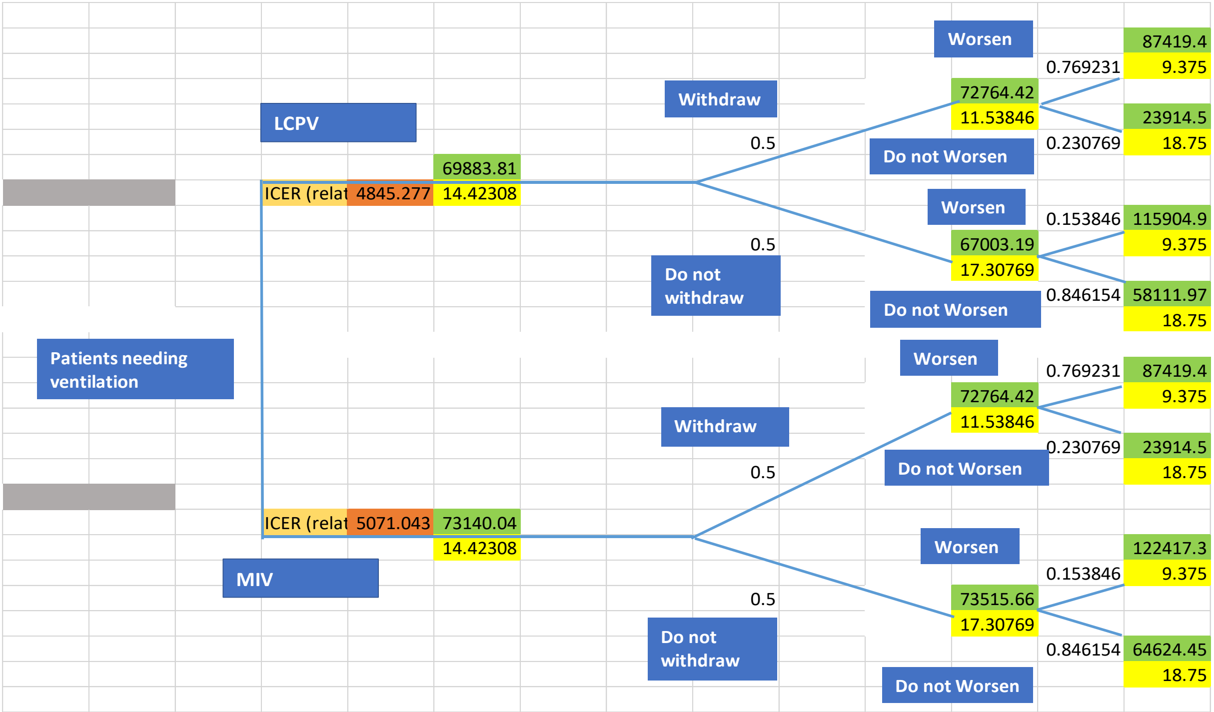


Figure. 4 Decision Tree

The new intervention is cost-effective at Rs 4845/- per QALY gained compared to sham strategy[5], while the standard of care is cost-effective at Rs 4859/- per QALY gained. The difference in Incremental Cost Effectiveness Ratio between the other non-invasive ventilator and the new ventilator turns out to be approximately Rs 14 per QALY gained per patient.

Taking the Willingness to pay threshold as GDP per capita per month and assuming non-inferiority in terms of clinical effectiveness, the new ventilator turns out to be cost-effective.

Net Monetary Benefit (NMB): The NMB is calculated as (incremental benefit x threshold) – incremental cost. The NMB for the new LCPV is Rs1588164.272/- and for the other NIV is Rs 1587965.106/- respectively. The difference in net monetary benefit between the two interventions is Rs 199/-

[5] The sham strategy is No Cost, No Effectiveness strategy: Xie, X., Falk, L., Brophy, J.M., Tu, H.A., Guo, J., Gajic-Veljanoski, O., Sikich, N., Dhalla, I.A. and Ng, V., 2019. A Non-inferiority Framework for Cost-Effectiveness Analysis. International journal of technology assessment in health care, 35(4), pp.291-297.

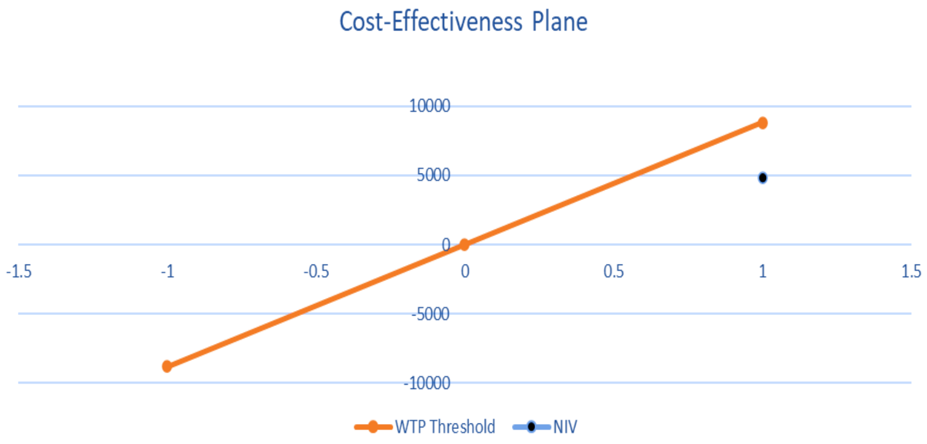


Figure. 5 Cost-Effectiveness Plane

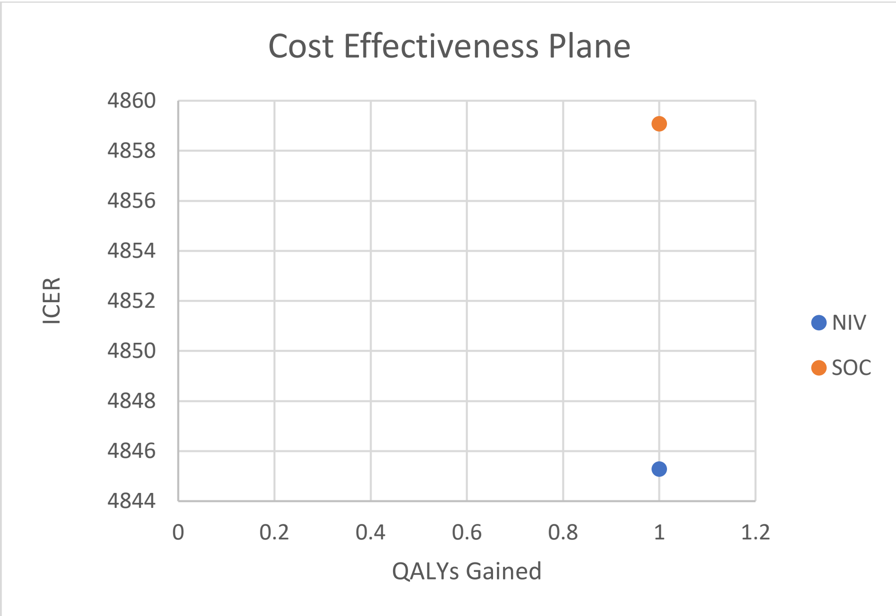


Figure. 6 Granular views of the CE plane

Sensitivity Analysis:

In order to check the robustness of our analysis we ran probabilistic sensitivity analysis. The cost functions were assumed to be gamma distributed, probabilities and utilities were assumed to be beta distributed and expected life years were assumed to be uniformly distributed for this analysis.

The results showed that the New non-invasive ventilator is cost effective at Rs 6000/- with 95% probability.

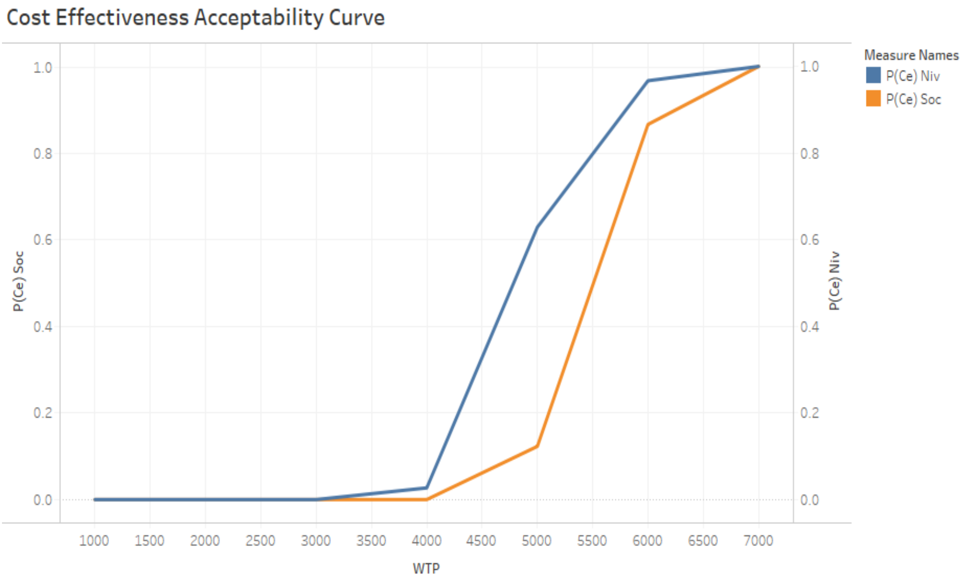


Figure. 7 Cost Effectiveness Acceptability Curve

Conclusion

Assuming non-inferiority, this ventilator turns out to be cost-effective as compared to a mechanical invasive ventilator. However, we don't have enough clinical data as we only have data for fifty patients from a retrospective cohort study. If non-inferiority is established then this device can be used for the patients requiring long term ventilation this device can be used at home. Ease of accessibility of the device makes it useful in other condition such as: In emergency situation it can be used in ambulance.

Appendix

Pubmed search strategy

1	((((((((((((adult) OR mature) OR patients) OR sick person) OR emergency) OR sufferer) OR ventilation) OR airing) OR respiratory failure) OR respiratory arrest) OR respiratory distress) OR neuromuscular diseases) OR neuromuscular disorder	10606243
2	((((((((((((((tidal volume) OR respiratory volume) OR lung volume) OR respiratory rate) OR breathing rate) OR rate of respiration) OR peak pressure) AND heart rate) OR pulse rate) OR heart beat) OR cardiac rate) AND blood pressure) OR stress) AND oxygen saturation) OR oxygenation	118829
3	((((((((((((adult) OR mature) OR patients) OR sick person) OR emergency) OR sufferer) OR ventilation) OR airing) OR respiratory failure) OR respiratory arrest) OR respiratory distress) OR neuromuscular diseases) OR neuromuscular disorder)) AND (Portable ventilator) OR respirator) OR breathing device)	32054
4	((((((((((((((adult) OR mature) OR patients) OR sick person) OR emergency) OR sufferer) OR ventilation) OR airing) OR respiratory failure) OR respiratory arrest) OR respiratory distress) OR neuromuscular diseases) OR neuromuscular disorder)) AND (((Portable ventilator) OR respirator) OR breathing device)) AND (((mechanical invasive ventilator ventilator) OR breathing machine) OR oxygen mask)	1604
5	((((adult) OR mature) OR patients) OR sick person) OR emergency) OR sufferer) OR ventilation) OR airing) OR respiratory failure) OR respiratory arrest) OR respiratory distress) OR neuromuscular diseases) OR neuromuscular disorder)) AND (((Portable ventilator) OR respirator) OR breathing device)) AND (((mechanical invasive ventilator) OR breathing machine) OR oxygen mask)) AND ((((((((((((((tidal volume) OR respiratory volume) OR lung volume) OR respiratory rate) OR breathing rate) OR rate of respiration) OR peak pressure) AND heart rate) OR pulse rate) OR heart beat) OR cardiac rate) AND blood pressure) OR stress) AND oxygen saturation) OR oxygenation)	243

Appendix: 2 Cochrane search strategy

1	((adult) OR (mature):ti,ab,kw OR (patient with ventilation):ti,ab,kw OR (respiratory disease and neuromuscular disease):ti,ab,kw AND (portable ventilator):ti,ab,kw	654421
2	(((((((((((((tidal volume) ti,ab,kw breathing rate) ti,ab,kw AND heart rate) ti,ab,kw OR pulse rate) ti,ab,kw AND blood pressure) ti,ab,kw OR stress) ti,ab,kw AND oxygen saturation) OR oxygenation	148025
3	(((portable ventilator) ti,ab,kw AND (((mechanical invasive ventilator) ti,ab,kw	667
4	((adult) OR (mature):ti,ab,kw OR (patient with ventilation):ti,ab,kw OR (respiratory disease and neuromuscular disease):ti,ab,kw AND (portable ventilator):ti,ab,kw (((mechanical invasive ventilator) ti,ab,kw AND tidal volume) ti,ab,kw breathing rate) ti,ab,kw AND heart rate) ti,ab,kw OR pulse rate) ti,ab,kw AND blood pressure) ti,ab,kw OR stress) ti,ab,kw AND oxygen saturation) OR oxygenation	238

Appendix: 3

Google scholar search strategy: **1521**

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