Review Article

Neurally Adjusted Ventilatory Assist versus Pressure Support Ventilation during weaning: A meta-analysis of randomized trials

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Abstract

Background: Prolonged ventilatory support is associated with poor clinical outcomes. Pressure support ventilation modes, are frequently used in clinical practice but are associated with patient–ventilator asynchrony and deliver fixed levels of assist. Neurally adjusted ventilatory assist (NAVA), a mode of partial ventilatory assist that reduces patient–ventilator asynchrony compared with other partial support modes for patients with difficult weaning. **Objectives:** To conduct a meta-analysis comparing neurally adjusted ventilatory assist (NAVA) with pressure support ventilation (PSV), in adult ventilated patients & clinical outcomes. **Study design:** Meta-analysis was used to address this concern. **Sittings:** Meta-analysis-based study following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. **Methods:** Online databases (PubMed, Embase, BioMed, and the Cochrane Central Register of Controlled trials)- were used for randomized studies ever performed in humans with NAVA & PSV in any clinical setting. **Results:** Twelve studies (n = 799 patients) were included. Regarding the primary outcome, patients weaned with NAVA had a higher success rate compared with pressure support ventilation. For the secondary outcomes, NAVA may reduce duration of mechanical ventilation and hospital mortality and prolongs ventilator-free days when compared with other modes. **Conclusion:** Our study suggests that the (NAVA) mode may improve the rate of weaning success compared with pressure support ventilation for difficult weaning

Keywords: Mechanical ventilation*;* Neurally adjusted ventilatory assist (NAVA); pressure support ventilation (PSV); patient-ventilator interaction

Introduction:

Mechanical ventilation is a life-preserving intervention in a wide range of critical illnesses. It is only considered as a key in the resuscitation of patients with oxygenation or ventilatory failure from primary lung disease. It is also vital in the support of patients needing augmented oxygen delivery [1].

Patients require mechanical ventilation when their ability to support ventilator demands is outweighed by a disease process or when the respiratory drive is inadequate to maintain ventilation because of diseases or medications[2-3]. Ventilation can be discontinued after the need for mechanical ventilation has been resolved. This is typically a straightforward maneuver for most patients- the ventilator is simply disconnected from the patient and the endotracheal tube (ET) is removed-. About 80% of patients requiring temporary mechanical ventilation do not require a gradual withdrawal process, and can be disconnected within a few hours or days of initial support [4-5].

The term weaning is frequently used to describe the gradual reduction of ventilatory support from a patient whose condition is improving[2,3,5,6]. Some practitioners prefer terms such as discontinuation, gradual withdrawal, or liberation [2].

Neurally-adjusted ventilatory assist (NAVA)- is an assist mode of ventilation that uses electrical activity of diaphragm (EAdi), sensed by a special nasogastric catheter (EAdi catheter), to trigger and terminate the respiratory cycle. Neurally Adjusted Ventilatory Assist (NAVA), therefore, provides assistance that is proportional to the patient's effort and hence improves patient-ventilator interaction and minimizes patient-ventilator asynchrony[7,8].

Pressure support ventilation (PSV) is a special form of assisted ventilation. The ventilator provides a constant pressure during inspiration once it senses that the patient has made an inspiratory effort. It is important to recognize that the patient must have a consistent, reliable spontaneous respiratory pattern for PSV to be successful weaning process [9,10].

This study aimed to compare between Neurally Adjusted Ventilatory Assist (NAVA) vs Pressure Support Ventilation (PSV) during weaning.

Methods:

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[11].

Search Strategy:

Pertinent studies will be independently searched in PubMed, Embase, BioMed, Central and the Cochrane Central Register of clinical trials the study investigators. Our search strategy aimed to include any RCTs ever performed in humans with NAVA & PSV in any clinical setting. In addition, we employed backward snowballing- i.e., scanning of references of retrieved articles and pertinent reviews- to obtain further studies. No language

restriction was employed. The search strategy for PubMed is available as Supplementary Material.

Selection of studies and selection criteria:

This analysis was performed comparing NAVA & PSV during weaning. Relevant articles were distinguished using the following search terms: "NAVA" and "PSV" sufficient information regarding the efficacy and safety outcome- were available. Studies without any reference to the comparative assessment of the efficacy and safety of NAVA &PSV were excluded. If studies with the same results published in different journals, we selected the most complete report. Retrospective studies, reviews, animal studies, and studies lacking sufficient data- were excluded. Studies were limited to human and English language. Reference lists of related articles were also reviewed. Meta-analysis was used to address this concern. This highly anticipated cohort study was conducted from September 2022 to February 2023. The study was done after approval from the Ethical Committee Benha Faculty of Medicine (approval code: {M.S. 8.12.2021}).

Exclusion criteria:

Studies were excluded if they satisfied the following criteria:

1. They were systematic reviews, meta-analyses, observational studies letter to editors, or case studies.

2. Their data were absent or deficient.

3. The study authors were inaccessible or did not reply if extra data from their trials were required.

4. their outcomes not of interest.

Data extraction:

Data were independently extracted from each report by authors, using a data-recording form developed for this purpose. After extraction, data were reviewed and compared. Disagreements between the two extractors were solved by consensus among the investigators, whenever needed, additional information concerning a specific study was obtained by directly questioning the principal investigator.

Definition of endpoints:

The primary outcome was weaning success, which was defined as the absence of the requirement for ventilatory support, without reintubation, a cardiac arrest event, or mortality within 48 h after extubating or withdrawal. The secondary outcomes included duration of MV, ventilator-free days at day 28 (VFDs), hospital mortality, Asynchrony index, Ineffective effort of patients, Auto triggering of patients, Double triggering of patients.

The quality of trials will be assessed using the risk of bias tools recommended by the Cochrane collaboration. We will appoint an estimation of high, unclear, or low to the following items: Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Any disparities will be identified through discussion.

Statistical analysis:

We conducted this analysis to pool the results of trials comparing NAVA and PSV during weaning using Review Manager (RemikmvMan), Version 5.3. Copenhagen (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) with risk ratio (RR) and 95% confidence intervals (CI)- as the analytical parameters.

Heterogeneity will be assessed using the I_2 statistic. We will use random-effects models to pool results. The mean difference (MD) will be calculated for continuous outcomes, with their corresponding 95% confidence intervals (CIs). Statistical significance will be defined using a two-sided α of 0.05, and interpretations of clinical significance emphasized CIs.

Result:

Literature Search:

Our search identified 266 studies through database searching and other sources. Of these articles, 7 were excluded after the removal of duplicates. One hundred eighty-seven articles were screened. Of these articles, 170 were excluded after screening, and 22 were assessed for eligibility. Ultimately, 11 randomized trials & one non randomized were included for analysis, with the remainder excluded as outlined in the PRISMA flow diagram (Fig. 1).

This figure is essential for credibility of the research as it is Flow diagram of choosing the appropriated articles.
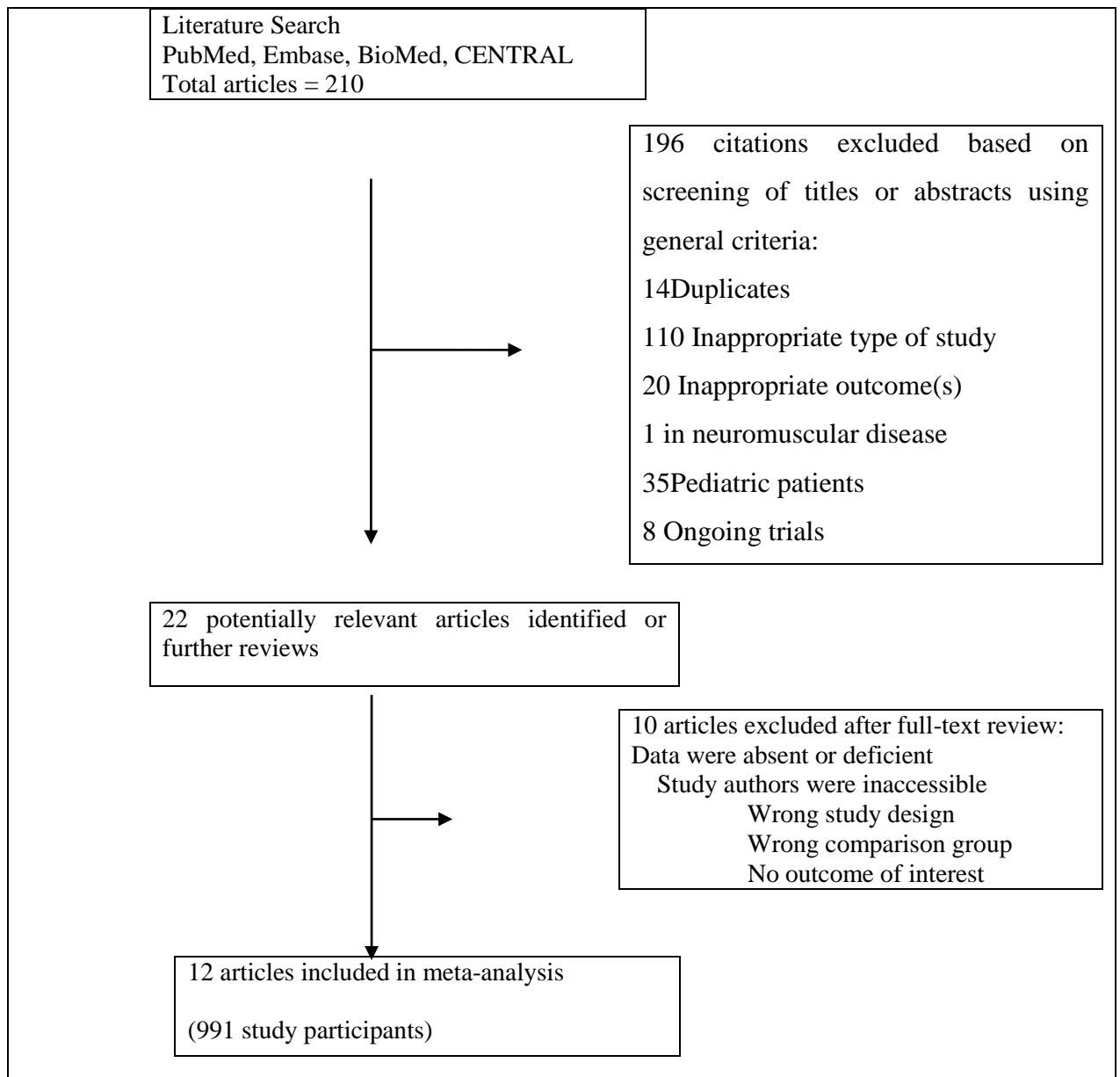

Figure 1: Literature search strategy

Characteristics and quality of studies included in the meta-analysis

The studies included in the analysis are detailed in **Table 1**. Eleven randomized[11,21] & one non randomized[22] studies- were identified for inclusion in this study, involving a total of 991 patients. Bias risk in the twelve trials was assessed to be generally low (**Figs. 2, 3**).

Table (1): Baseline characteristics of these studies

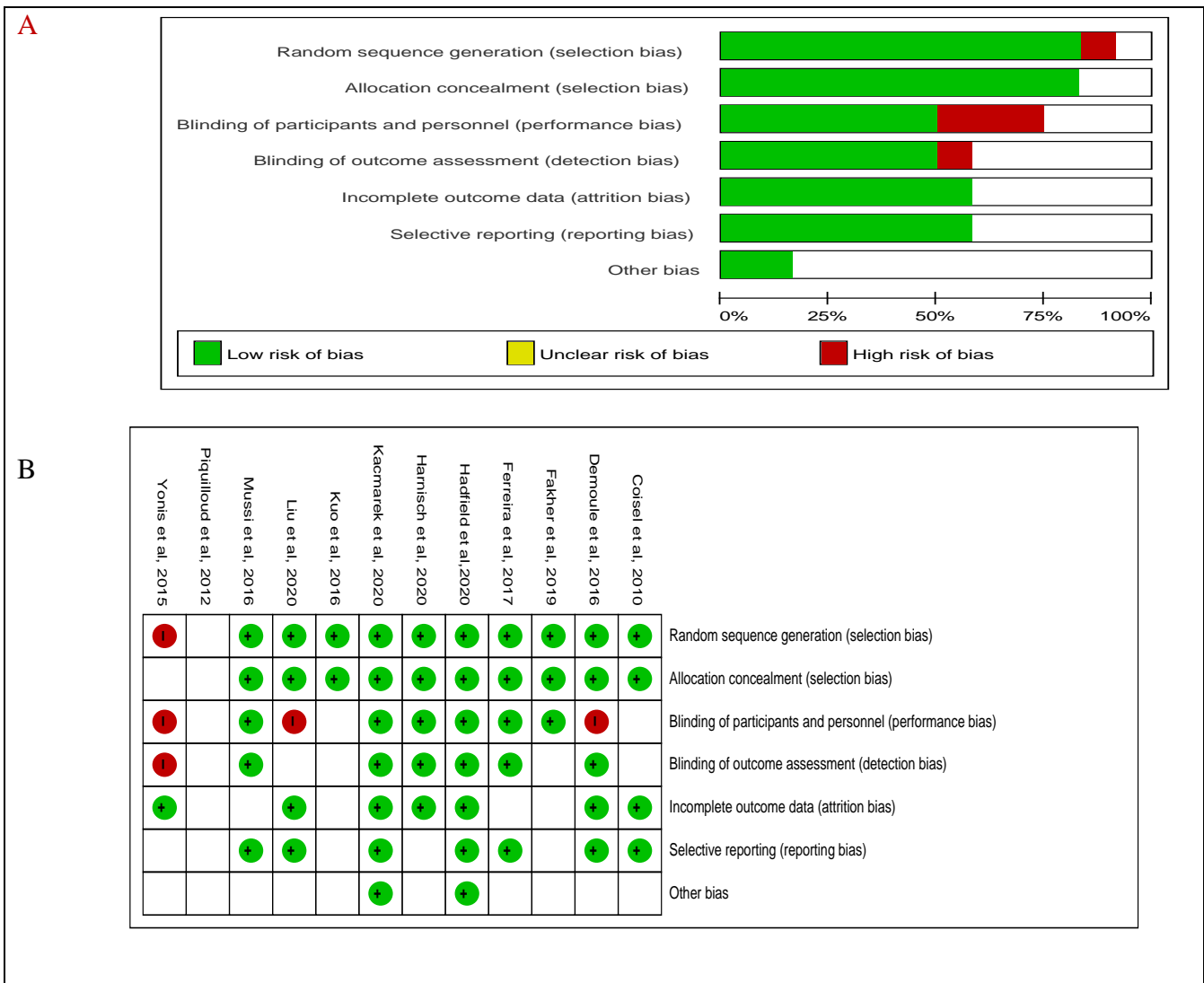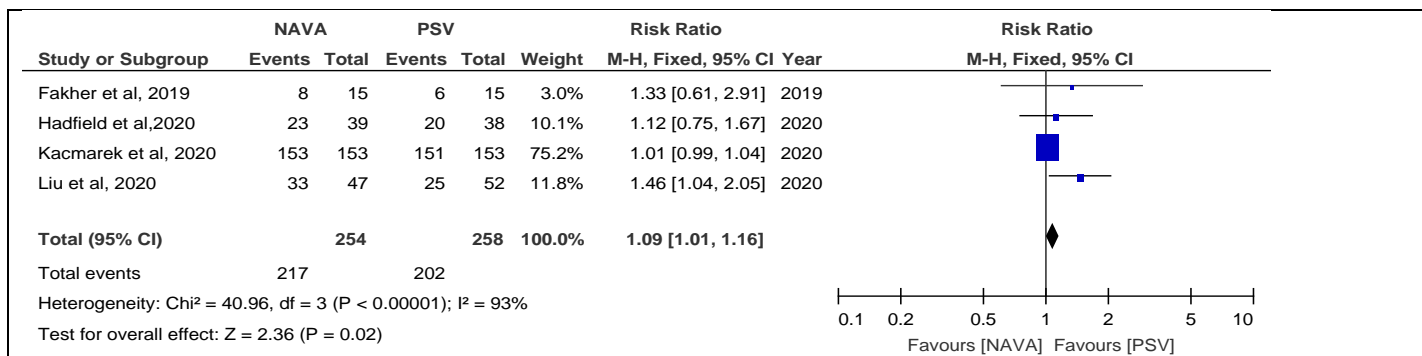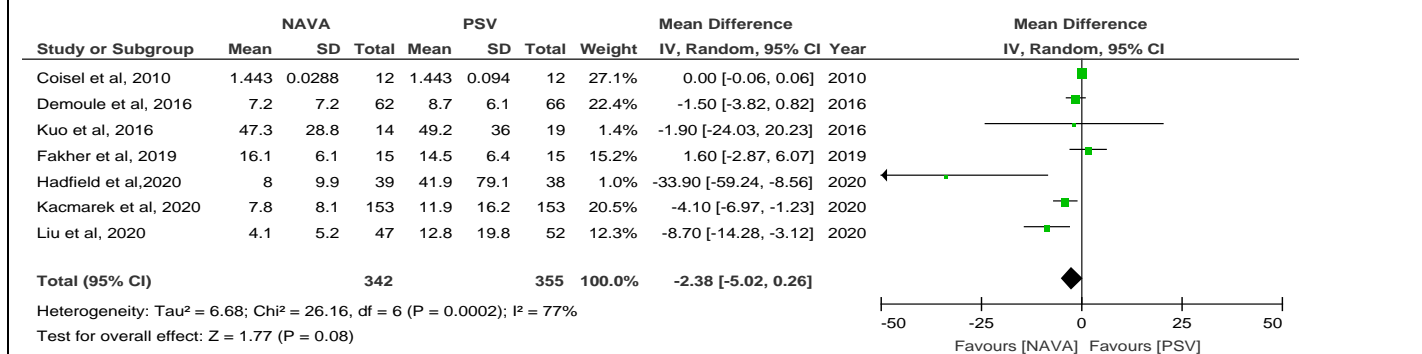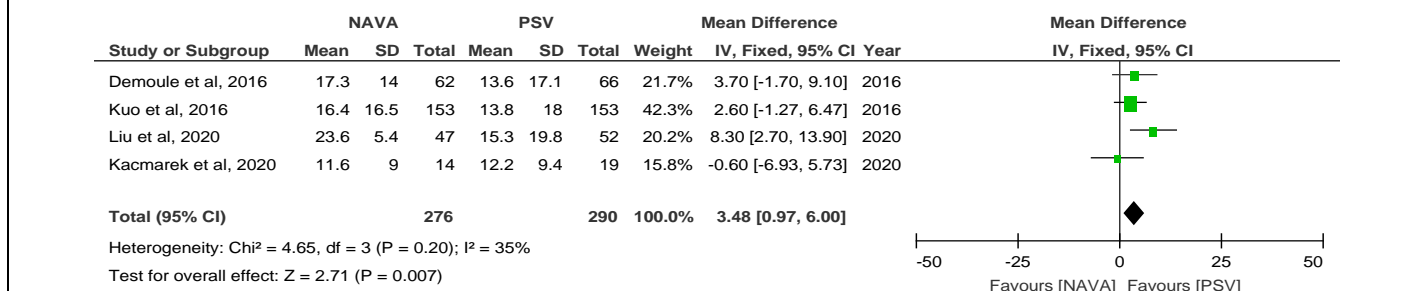| Study ID	Type	Time (Published)	Country	Participant	Age (NAVA vs. PSV)	Male/total (NAVA vs. PSV)	Invasive/non-invasive	Precondition
Coisel et al	Randomized crossover Study	2010	France	One ICU	76 [71—79]	7/12 crossover	invasive	PEEP= 2-10 cmH$_2$O PSV = 6-15 cmH$_2$O
Piquilloud et al	Randomized, cross-over	2012	Switzerland	2 center	70(64-78) (cross-over)	6/13 (cross-over)	non-invasive	NAVA level 0.5 Uv;30 min for placement of nasogastric tube,20 min for NIV
Yonis et al.	non-randomized cross-over	2015	France	One ICU	66.3±11 (cross-over)	19/30 crossover	invasive	V$_T$ = 6 and 8 ml/kg of PBW sedation was stopped; patents met the general and respiratory criteria for PSV
Kuo et al.	prospective, randomized, controlled study (RCT)	2016	China (Taiwan)	One RCC	79.3±6.2 vs. 76.9±9.3	11/14 vs. 13/19	Invasive (intubation or tracheotomy)	SBT was performed with PEEP =5 cmH$_2$O PSV = 8cmH$_2$O
Mussi et al.	RCT	2016	Italy	One ICU	66.8±17.3 vs. 69.8±15	5/13 vs. 9/12	Invasive	V$_T$ =5–8 mL/Kg (PBW); unsedated or moderate sedation
Demoule et al.	RCT	2016	France	11 centers	66 [61–77] vs. 64 [53–77] (baseline)	47/62 vs. 39/66 (baseline); event 53:50	Invasive	V$_T$ =6–8 mL/kg (ideal body weight) FiO$_2$, and PEEP according to guidelines
Ferreira et al.	Randomized, cross-over	2017	Brazil	One ICU	60 [19–82] (cross-over)	13/20 (cross-over)	Invasive	PEEP =5 cmH$_2$O PSV =5 cmH$_2$O
Fakher et al	RCT	2019	egypt	One ICU			Invasive	PS level: set to obtain a tidal volume of 5–8 ml/kg predicted body weight PEEP: NA
Ling Liu et al 2020	RCT	2020	China	One ICU	75 (61, 80) VS. 80 (65, 80)	30 (64) VS. 36 (69)	Invasive	PS level: set to obtain a VT of 6 to 8ml/kg predicted body weight PEEP: to maintain Spo2 ≥ 90%
Harnisch et al	single-blind prospective randomized crossover observational trial	2020	Germany	One ICU	65:7±12.25	16/22 Cross over	non-invasive	PEEP (cmH2O) 6:23±1:07 FiO2 40:54±4:54 NAVA level (cmH2O/µV) 0:77±0:45 Pressure support (cmH2O) 6:25±2:29 -PSV (%) 40±7:32 Tidal volume (ml/kg IBW) 8:30±1:86
Hadfield et al	RCT	2020	UK	multicenter	66.7(13.9)VS 67.1(12.9)	26/39 VS 28/38	Invasive	PS level: set to obtain a tidal volume of 6–8 ml/kg predicted body weight PEEP: N/a
Kacmarek et al	RCT	2020	Spain	multicenter	63.9 ± 15.4 VS 64.7 ± 14.1	100/153 VS 101/153	Invasive	N/a

Figure 2:

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

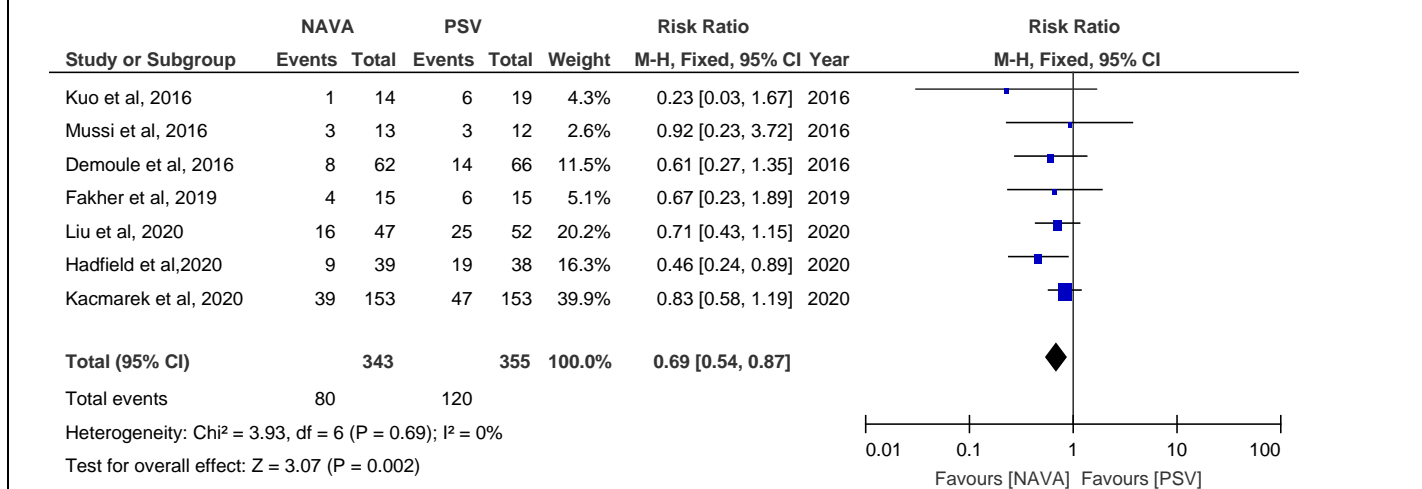B. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	NAVA		PSV			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Fakher et al, 2019	8	15	6	15	3.0%	1.33 [0.61, 2.91]	2019	
Hadfield et al,2020	23	39	20	38	10.1%	1.12 [0.75, 1.67]	2020	
Kacmarek et al, 2020	153	153	151	153	75.2%	1.01 [0.99, 1.04]	2020	
Liu et al, 2020	33	47	25	52	11.8%	1.46 [1.04, 2.05]	2020	
Total (95% CI)		254		258	100.0%	1.09 [1.01, 1.16]		
Total events	217		202					
Heterogeneity: Chi² = 40.96, df = 3 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 2.36 (P = 0.02)								

A : Weaning success

	NAVA			PSV				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Coisel et al, 2010	1.443	0.0288	12	1.443	0.094	12	27.1%	0.00 [-0.06, 0.06]	2010	
Demoule et al, 2016	7.2	7.2	62	8.7	6.1	66	22.4%	-1.50 [-3.82, 0.82]	2016	
Kuo et al, 2016	47.3	28.8	14	49.2	36	19	1.4%	-1.90 [-24.03, 20.23]	2016	
Fakher et al, 2019	16.1	6.1	15	14.5	6.4	15	15.2%	1.60 [-2.87, 6.07]	2019	
Hadfield et al,2020	8	9.9	39	41.9	79.1	38	1.0%	-33.90 [-59.24, -8.56]	2020	
Kacmarek et al, 2020	7.8	8.1	153	11.9	16.2	153	20.5%	-4.10 [-6.97, -1.23]	2020	
Liu et al, 2020	4.1	5.2	47	12.8	19.8	52	12.3%	-8.70 [-14.28, -3.12]	2020	
Total (95% CI)			342			355	100.0%	-2.38 [-5.02, 0.26]		
Heterogeneity: Tau² = 6.68; Chi² = 26.16, df = 6 (P = 0.0002); I² = 77%										
Test for overall effect: Z = 1.77 (P = 0.08)										

B : Duration of ventilation

	NAVA			PSV				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
Demoule et al, 2016	17.3	14	62	13.6	17.1	66	21.7%	3.70 [-1.70, 9.10]	2016	
Kuo et al, 2016	16.4	16.5	153	13.8	18	153	42.3%	2.60 [-1.27, 6.47]	2016	
Liu et al, 2020	23.6	5.4	47	15.3	19.8	52	20.2%	8.30 [2.70, 13.90]	2020	
Kacmarek et al, 2020	11.6	9	14	12.2	9.4	19	15.8%	-0.60 [-6.93, 5.73]	2020	
Total (95% CI)			276			290	100.0%	3.48 [0.97, 6.00]		
Heterogeneity: Chi² = 4.65, df = 3 (P = 0.20); I² = 35%										
Test for overall effect: Z = 2.71 (P = 0.007)										

C : Ventilator free-days at day 28)

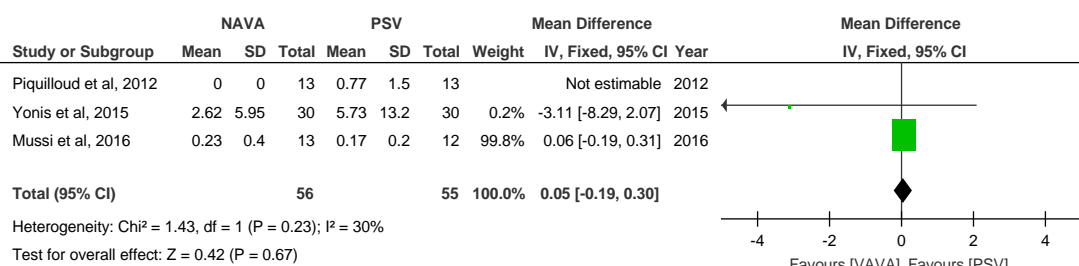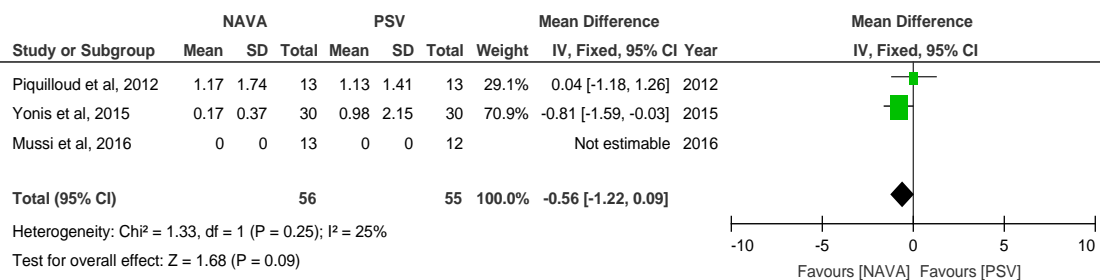|	NAVA		PSV			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Kuo et al, 2016	1	14	6	19	4.3%	0.23 [0.03, 1.67]	2016	
Mussi et al, 2016	3	13	3	12	2.6%	0.92 [0.23, 3.72]	2016	
Demoule et al, 2016	8	62	14	66	11.5%	0.61 [0.27, 1.35]	2016	
Fakher et al, 2019	4	15	6	15	5.1%	0.67 [0.23, 1.89]	2019	
Liu et al, 2020	16	47	25	52	20.2%	0.71 [0.43, 1.15]	2020	
Hadfield et al,2020	9	39	19	38	16.3%	0.46 [0.24, 0.89]	2020	
Kacmarek et al, 2020	39	153	47	153	39.9%	0.83 [0.58, 1.19]	2020	
Total (95% CI)		343		355	100.0%	0.69 [0.54, 0.87]		
Total events	80		120					
Heterogeneity: Chi² = 3.93, df = 6 (P = 0.69); I² = 0%								
Test for overall effect: Z = 3.07 (P = 0.002)								

D : Hospital mortalit

Figure (3) A: A total of 4 studies, involving 512 patients, were included in the analysis for the primary outcome. The meta-analysis using a fixed-effect model showed a statistically significant proportion of patients who received NAVA (217/254) weaned successfully, compared with patients who received other partial support modes (202/258) (Risk Ratio=RR =1.09 ; 95%confidence interval= CI [1.01, 1.16]P = 0.02) **B:** A total of 7 studies reporting about 697 patients, For all 7 studies, we found a statistically significant probability of lower duration of MV supporting patients undergoing NAVA comparing to other partial support modes (mean difference=MD = − 2.38; 95%confidence interval= CI[-5.02, 0.26]; P = 0.08), and the heterogeneity was moderate with I^2 = 77% **C:** For the 4 studies recruiting 566 patients , patients undergoing NAVA had a lesser VFDs compared with patients undergoing other partial support modes (MD = 3.48; 95% CI [0.97, 6.00]; P = 0.007) **D:** Hospital mortality was evaluated in 7 studies involving 698 patients and the results demonstrated that patients who were ventilated with NAVA(80/343) had lower hospital mortality compared to patients who were ventilated with other partial support modes (120/355) (RR = 0.69; 95% CI [0.54, 0.87]; P = 0.002).
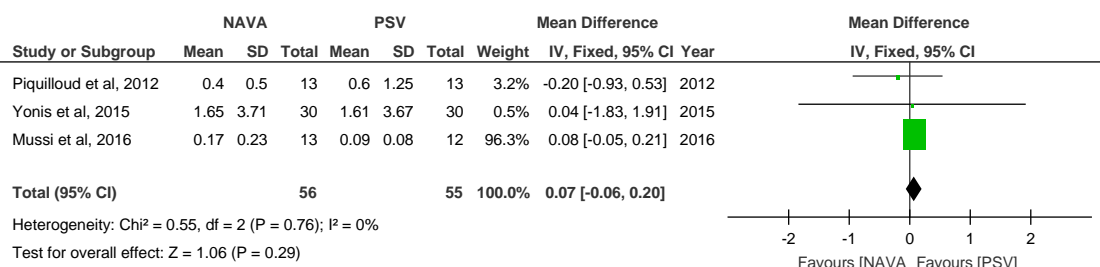
Study or Subgroup	NAVA Mean	SD	Total	PSV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Piquilloud et al, 2012	5.97	6.64	13	23.63	36.63	13	4.1%	-17.66 [-37.90, 2.58]	2012
Yonis et al, 2015	7.32	15.38	30	12.61	26.83	30	13.7%	-5.29 [-16.36, 5.78]	2015
Demoule et al, 2016	16.23	7.16	53	29.2	22.36	50	39.7%	-12.97 [-19.46, -6.48]	2016
Kuo et al, 2016	0	0	14	11.9	11.2	19		Not estimable	2016
Mussi et al, 2016	5.84	3.8	13	12.53	12.87	12	29.2%	-6.69 [-14.26, 0.88]	2016
Ferreira et al, 2017	11.8	12.37	20	21.63	22.34	20	13.4%	-9.83 [-21.02, 1.36]	2017
Total (95% CI)			143			144	100.0%	-9.86 [-13.95, -5.77]	

Heterogeneity: Chi² = 2.78, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 4.73 (P < 0.00001)

A: Asynchrony index

Study or Subgroup	NAVA Mean	SD	Total	PSV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Piquilloud et al, 2012	0	0	13	0.77	1.5	13		Not estimable	2012
Yonis et al, 2015	2.62	5.95	30	5.73	13.2	30	0.2%	-3.11 [-8.29, 2.07]	2015
Mussi et al, 2016	0.23	0.4	13	0.17	0.2	12	99.8%	0.06 [-0.19, 0.31]	2016
Total (95% CI)			56			55	100.0%	0.05 [-0.19, 0.30]	

Heterogeneity: Chi² = 1.43, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 0.42 (P = 0.67)

B: Ineffective effort of patients

Study or Subgroup	NAVA Mean	SD	Total	PSV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Piquilloud et al, 2012	1.17	1.74	13	1.13	1.41	13	29.1%	0.04 [-1.18, 1.26]	2012
Yonis et al, 2015	0.17	0.37	30	0.98	2.15	30	70.9%	-0.81 [-1.59, -0.03]	2015
Mussi et al, 2016	0	0	13	0	0	12		Not estimable	2016
Total (95% CI)			56			55	100.0%	-0.56 [-1.22, 0.09]	

Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%
Test for overall effect: Z = 1.68 (P = 0.09)

C: Auto triggering of patients

Study or Subgroup	NAVA Mean	SD	Total	PSV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Piquilloud et al, 2012	0.4	0.5	13	0.6	1.25	13	3.2%	-0.20 [-0.93, 0.53]	2012
Yonis et al, 2015	1.65	3.71	30	1.61	3.67	30	0.5%	0.04 [-1.83, 1.91]	2015
Mussi et al, 2016	0.17	0.23	13	0.09	0.08	12	96.3%	0.08 [-0.05, 0.21]	2016
Total (95% CI)			56			55	100.0%	0.07 [-0.06, 0.20]	

Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

D: Double triggering of patients

Figure (4) A: our study included 6 studies with a total of 287 adult patients; the results comparing groups were significantly lower in NAVA group (143 patients) than PSV group (144 patients) mean difference (MD) −9.86, 95% confidence interval CI [-13.95,-5.77]; P = 0.00001) **B:** For presenting the result of ineffective efforts, our study included 3 studies involving a total of 111events, and showed that NAVA (56 patients) was not significantly different from PSV (55patients) (MD 0.05, 95% CI [-0.19,0.30]; P = 0.67) **C:** For the result of Auto-triggering, our study enrolled 3 studies including a total of 111 events, and the result demonstrated that NAVA (56 patients) was significantly lower than the PSV (55patients) (MD −0.56, 95% CI [-1.22,0.09]; P = 0.09) **D:**For presenting the result of Double triggering, our study enrolled 3 studies including a total of 111 events, and demonstrated that NAVA (56 patients) was not significantly higher than PSV (55 patients) (MD 0.07, 95% CI[-0.06,0.20]; P = 0.29).

Discussion

The first use of mechanical ventilation was reported is in the 16th century, but it became widespread in the 20th century in patients that need respiratory care. Over the decades, optimal respiratory care and ventilator support have been supported by strong clinical evidence. Mechanical ventilation is triggered by either change in respiratory flow or pressure. Change in the respiratory flow- commonly termed as flow trigger- may cause false triggering or missed triggering. This produces patient-ventilator asynchrony, which occurs in approximately 25% of mechanically ventilated patients, thus, increasing the duration of mechanical ventilation and the length of ICU or hospital stays [23-24.]

In NAVA, the electrical activity of the diaphragm is measured using an electrode array inserted into a nasogastric tube placed in the lower esophagus; this information is then used to control the ventilator to generate flow, volume, and pressure- by applying pressure in proportion to diaphragm electrical activity [25,26]. With NAVA, therefore, the patient retains full control of the breathing pattern[27.] Unlike with the other

proportional mode, estimates of respiratory mechanics are not needed. With NAVA, the patient's respiratory center controls the assisted positive breaths in all phases of the ventilation cycle, from triggering to cycling-off of inspiration. Any change in patient ventilatory output is matched breath by breath by the ventilator, even in the presence of variations in respiratory mechanics. Neurally Adjusted Ventilatory Assist (NAVA) has been shown to decrease ineffective efforts (trigger asynchrony) and premature and delayed cycling (cycle asynchrony) compared to a pressure-controlled flow-cycled ventilation (i.e., PSV)[28-29]. Furthermore, demonstrated that, compared to pressure support, and NAVA improves patient-ventilator synchrony both by reducing trigger delay and the number of asynchronies events[30]. **Neurally Adjusted Ventilatory Assist (**NAVA) also, appears to improve patient-ventilator synchrony during helmet ventilation[31.] Finally, NAVA has one major advantage -compared to PAV- since air leaks do not interfere with its correct functioning [32.] According to our results in this meta-analysis, we found that patients weaned with NAVA had a higher success

rate compared with other partial support modes. Neurally Adjusted Ventilatory Assist (NAVA) may reduce duration of mechanical ventilation and prolongs ventilator-free days- when compared with other modes- and that agree with the line of several studies have reviewed changes that occur in ventilator parameters after a patient is switched to NAVA. Once NAVA is initiated, blood gases appear to return to the patient's normal levels. One hundred thirty-seven Oxygenation and compliance may also improve[33-35]. With NAVA, the patient establishes his or her own trans pulmonary pressures, volume, and respiratory rate[36]. In addition, NAVA allows a patient's respiratory center to maintain the biologically variable rhythm generation- compared to other modes such as pressure support- where the amount of support remains constant based on what the operator has selected for the patient[37]. Neurally Adjusted Ventilatory Assist (NAVA) is not affected by leaks, and in fact, is now available as noninvasive technique.

Early studies suggest that NAVA and the Edi catheter offer a promising alternative for the management of critically ill patients receiving mechanical ventilation[38,39]. The Edi waveform provides valuable information about a patient's respiratory center function, which in turn could ultimately improve patient-ventilator synchrony. It should be stated, however, that evidence-based practice dictates that additional studies will be required to better define the application and importance of NAVA in clinical practice.

There are several limitations to our meta-analysis. First, the lack of a detailed weaning protocol in the included studies.

In addition, the included studies involved heterogeneous populations and used variable definitions of outcomes (e.g., duration of MV) despite attempts to reduce clinical heterogeneity. Second, all studies in our analysis had a high risk of performance bias because of the inability to blind the investigators to the method of weaning. So, it is possible that the investigators' decisions and actions may be influenced, resulting in biased estimates of results. Third, not all the data on the patients with successful weaning were included. This may affect the results for the primary outcome in our study.

References:

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