Clinical trial results:
Multicenter study on the effect of the treatment of metabolic alkalosis with acetazolamide on the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease or obesity-hypoventilation syndrome.

Summary

EudraCT number	2010-022901-16
Trial protocol	ES
Global end of trial date	25 December 2016

Results information

Result version number	v1 (current)
This version publication date	25 June 2020
First version publication date	25 June 2020

Trial information

Trial identification

Sponsor protocol code	TRAMA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hospital Universitario Son Llàtzer. Conselleria de Salut i Consum del Govern de les Illes Balears
Sponsor organisation address	Ctra. Manacor, km 4, PALMA, Spain, 07198
Public contact	Gemma Rialp Cervera. Intensive Care Department. Hospital Son Llàtzer. grialp@hsll.es, Gemma Rialp Cervera. Intensive Care Department. Hospital Son Llàtzer. grialp@hsll.es, grialp@hsll.es
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of treatment of metabolic alkalosis with acetazolamide on the evolution of patients with COPD or with SOH connected to invasive MV due to acute respiratory failure.

Protection of trial subjects:

The study was approved by the Ethics Committee (CEIC-IB 1411/10PI) and was conducted in accordance with the amended Declaration of Helsinki. Patients or patients' next of kin provided written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	47
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

104 patients were enrolled between November 2011 and February 2014 in seven intensive care units in Spain. 47 patients were included in the study.

Pre-assignment

Screening details:

57 patients were excluded before assignment. 47 patients were allocated randomly on a 1:1 basis to Placebo and Acetazolamide.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule, hard
Routes of administration	Gastroenteral use

Dosage and administration details:

500 mg of placebo by nasogastric tube

Arm title	Acetazolamide

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACETAZOLAMIDA
Investigational medicinal product code	59-66-5
Other name	ACETAZOLAMIDE
Pharmaceutical forms	Capsule, hard
Routes of administration	Gastroenteral use

Dosage and administration details:

capsules of 500 mg of acetazolamide by nasogastric tube.

Number of subjects in period 1	Placebo	Acetazolamide
Started	23	24
Completed	23	24

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Acetazolamide
Reporting group description: -	

Reporting group values	Placebo	Acetazolamide	Total
Number of subjects	23	24	47
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	67	67	
standard deviation	± 11	± 10	-
Gender categorical Units: Subjects			
Female	3	8	11
Male	20	16	36
Systemic corticosteroids "Home treatment" Units: Subjects			
YES	1	3	4
NO	22	21	43
COPD (Chronic obstructive pulmonary disease) Units: Subjects			
YES	20	22	42
NO	3	2	5
Obesity hypoventilation syndrome Units: Subjects			
YES	5	6	11
NO	18	18	36
Heart failure Units: Subjects			
YES	3	3	6
NO	20	21	41
NYHA functional classification >/= III			

Units: Subjects			
YES	2	0	2
NO	21	24	45
Home oxygenotherapy "Home treatment" Units: Subjects			
YES	7	11	18
NO	16	13	29
Home NIV (non-invasive ventilation) Units: Subjects			
YES	2	5	7
NO	21	19	40
Home diuretic treatment Units: Subjects			
YES	5	13	18
NO	18	11	29
BMI >/= 30 kg/m2 Units: Subjects			
YES	10	10	20
NO	13	14	27
Failure of NIV before inclusion			
Failure of noninvasive mechanical ventilation			
Units: Subjects			
YES	17	15	32
NO	6	9	15
Reason of IMV			
Reason of invasive mechanical ventilation			
Units: Subjects			
COPD exacerbation	13	13	26
Hypercapnic encephalopaty	3	1	4
Heart failure	1	4	5
Pneumonia	6	5	11
Cardiac arrest	0	1	1
Weight Units: kilogram(s)			
arithmetic mean	83	82	
standard deviation	± 22	± 25	-
Height Units: centimeter			
arithmetic mean	167	166	
standard deviation	± 8	± 9	-
Simplified Acute Phisiology Score at ICU admission Units: number			
arithmetic mean	51	59	
standard deviation	± 16	± 16	-
BMI Units: kilogram(s)/square meter			
arithmetic mean	29.6	30.7	
standard deviation	± 6.7	± 9.7	-
FEV1 (Forced expired volume at 1s) Units: percent			

arithmetic mean	39	44	
standard deviation	± 12	± 20	-
FVC (Forced vital capacity)			
Units: percent			
arithmetic mean	60	64	
standard deviation	± 13	± 20	-
FEV1/FVC			
Units: percent			
arithmetic mean	50.4	50.1	
standard deviation	± 17.9	± 17.9	-
Previous baseline PaCO2			
Units: mm Hg			
arithmetic mean	53	49	
standard deviation	± 8	± 8	-
Previous baseline creatinine			
Units: milligram/dL			
arithmetic mean	0.90	0.75	
standard deviation	± 0.31	± 0.29	-
SOFA score at inclusion			
Sepsis-related Organ Failure Assessment score			
Units: points			
arithmetic mean	5.5	5.4	
standard deviation	± 2.6	± 2.4	-
Arterial lactate			
Serum laboratory tests at inclusion			
Units: millimole(s)/litre			
arithmetic mean	1.4	1.5	
standard deviation	± 0.6	± 0.6	-
Leukocyte count			
Serum laboratory tests at inclusion			
Units: 10^9/L			
arithmetic mean	11.9	14.0	
standard deviation	± 5.3	± 7.7	-
Hemoglobin			
Serum laboratory tests at inclusion.			
Units: g/dL			
arithmetic mean	13.9	14.1	
standard deviation	± 3.0	± 2.6	-
Albumin			
Serum laboratory tests at inclusion.			
Units: g/dL			
arithmetic mean	3.15	2.78	
standard deviation	± 0.47	± 0.47	-
Prothrombin activity			
Serum laboratory tests at inclusion.			
Units: percent			
arithmetic mean	80	74	
standard deviation	± 16	± 22	-
pH			
Blood gas analysis at inclusion.			
Units: points			
arithmetic mean	7.42	7.43	

standard deviation	± 0.04	± 0.06	-
PaCO2			
Blood gas analysis at inclusion			
Units: mm Hg			
arithmetic mean	52	52	
standard deviation	± 6	± 7	-
Bicarbonate			
Blood gas analysis at inclusion			
Units: millimole(s)/litre			
arithmetic mean	33	34	
standard deviation	± 2	± 4	-
PaO2/FiO2			
Blood gas analysis at inclusion			
Units: mm Hg			
arithmetic mean	228	202	
standard deviation	± 93	± 69	-
Minute ventilation			
Units: L/min			
arithmetic mean	9.1	9.0	
standard deviation	± 2.0	± 2.6	-
Respiratory rate			
Units: bpm			
arithmetic mean	18	19	
standard deviation	± 3	± 5	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Acetazolamide
Reporting group description: -	

Primary: Bicarbonate concentration	
End point title	Bicarbonate concentration
End point description:	
End point type	Primary
End point timeframe: day 3	

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mmol/L				
median (full range (min-max))	34 (32 to 35)	30 (29 to 31)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:
[1] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: Carbon dioxide partial pressure (PaCO2)	
End point title	Carbon dioxide partial pressure (PaCO2)
End point description:	
End point type	Primary
End point timeframe: day 3	

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mmHg				
median (full range (min-max))	54 (51 to 57)	50 (48 to 52)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: PaO2/FiO2

End point title	PaO2/FiO2

End point description:

End point type	Primary

End point timeframe:

day 3

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mm Hg				
median (full range (min-max))	230 (198 to 262)	234 (199 to 271)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.84 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: pH

End point title	pH

End point description:

End point type	Primary

End point timeframe:

day 3

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number				
median (full range (min-max))	7.41 (7.39 to 7.42)	7.40 (7.38 to 7.41)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: Minute volume

End point title	Minute volume

End point description:

End point type	Primary

End point timeframe:

day 3

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: L/min				
median (full range (min-max))	9.3 (8.6 to 10.0)	9.7 (8.7 to 10.7)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.53 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: Respiratory rate

End point title	Respiratory rate

End point description:

End point type	Primary

End point timeframe:

day 3

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: bpm				
median (full range (min-max))	19 (17 to 20)	20 (19 to 22)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.13 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: Daily volume intake

End point title	Daily volume intake

End point description:

End point type	Primary

End point timeframe:

day 3

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mL				
median (full range (min-max))	2853 (2570 to 3136)	2553 (2169 to 2937)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.22 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Primary: Daily diuresis

End point title	Daily diuresis

End point description:

End point type	Primary

End point timeframe:

day 3

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millilitre(s)				
median (full range (min-max))	2193 (1958 to 2428)	2065 (1825 to 2305)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.46 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Duration of invasive mechanical ventilation (IMV)

End point title	Duration of invasive mechanical ventilation (IMV)

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Day				
arithmetic mean (standard deviation)	8.2 (± 5.6)	6.8 (± 6.0)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.44 [9]
Method	t-test, 2-sided

Notes:

[9] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Weaning duration

End point title	Weaning duration

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: day				
arithmetic mean (standard deviation)	2.2 (± 2.6)	1.9 (± 1.9)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.72 [10]
Method	t-test, 2-sided

Notes:

[10] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Carbon dioxide partial pressure (PaCO2)

End point title	Carbon dioxide partial pressure (PaCO2)

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mm Hg				
median (full range (min-max))	55 (51 to 59)	48 (47 to 50)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Bicarbonate concentration

End point title	Bicarbonate concentration

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mmol/L				
median (full range (min-max))	34 (32 to 35)	29 (28 to 30)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:
[12] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: PaO2/FiO2

End point title	PaO2/FiO2

End point description:

End point type	Secondary

End point timeframe:
Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: mm Hg				
median (full range (min-max))	207 (174 to 239)	223 (190 to 258)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:
[13] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: pH

End point title	pH

End point description:

End point type	Secondary

End point timeframe:
Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number				
median (full range (min-max))	7.41 (7.39 to 7.42)	7.40 (7.39 to 7.41)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.31 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Minute volume

End point title	Minute volume

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: L/min				
median (full range (min-max))	9.7 (8.9 to 10.4)	10.6 (9.2 to 12.0)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.26 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Respiratory rate

End point title	Respiratory rate

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: bpm				
median (full range (min-max))	20 (19 to 22)	21 (19 to 22)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.67 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Daily volume intake

End point title	Daily volume intake

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: millilitre(s)				
median (full range (min-max))	2735 (2558 to 2913)	2600 (2285 to 2916)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.46 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Daily diuresis

End point title	Daily diuresis

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: millilitre(s)				
median (full range (min-max))	2546 (2244 to 2849)	2311 (1954 to 2670)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.33 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Length of ICU stay

End point title	Length of ICU stay

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: day				
arithmetic mean (standard deviation)	14.8 (± 13.8)	11.8 (± 10.6)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4 [19]
Method	t-test, 2-sided

Notes:

[19] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: day				
arithmetic mean (standard deviation)	25.6 (± 16.7)	21.5 (± 14.9)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.22 [20]
Method	t-test, 2-sided

Notes:

[20] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Hospital mortality

End point title	Hospital mortality

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	2	4		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.41 [21]
Method	Chi-squared

Notes:
[21] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Vasoactive drugs administration

End point title	Vasoactive drugs administration

End point description:
Treatment and techniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:
Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	8	12		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.09 [22]
Method	Chi-squared

Notes:
[22] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Antibiotic administration

End point title	Antibiotic administration

End point description:
Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:
Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	21	23		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.53 [23]
Method	Chi-squared

Notes:

[23] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Furosemide

End point title	Furosemide

End point description:

Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	16	17		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [24]
Method	Chi-squared

Notes:

[24] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Furosemide, total doses

End point title	Furosemide, total doses

End point description:

Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: milligram(s)				
arithmetic mean (standard deviation)	139 (± 194)	179 (± 270)		

Statistical analyses

Statistical analysis title	Experimental (Acetazolamide) vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.88 [25]
Method	t-test, 2-sided

Notes:

[25] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Prednisone, total doses

End point title	Prednisone, total doses

End point description:

Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: milligram(s)				
arithmetic mean (standard deviation)	1026 (± 869)	610 (± 800)		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1 [26]
Method	t-test, 2-sided

Notes:

[26] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Tracheostomy

End point title	Tracheostomy

End point description:

Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	5	3		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.46 [27]
Method	Chi-squared

Notes:

[27] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Postextubation NIV

End point title	Postextubation NIV

End point description:

Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	6	8		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Acetazolamide v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.59 [28]
Method	Chi-squared

Notes:

[28] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Secondary: Reintubation in 48 h

End point title	Reintubation in 48 h

End point description:

Treatment and tehcniques applied during mechanical ventilation period.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Acetazolamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: number	4	2		

Statistical analyses

Statistical analysis title	Acetazolamide vs Placebo
Comparison groups	Placebo v Acetazolamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.66 [29]
Method	Chi-squared

Notes:

[29] - All analyses were two-tailed and p < 0.05 was considered of statistical significance.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

PATIENTS WERE MONITORED DURING THE WHOLE STUDY PERIOD.

Adverse event reporting additional description:

the presence of: bicarbonate concentration < 23 mmol/L, serum potassium < 3.5 mEq/L serum sodium < 135 mEq/L paresthesia in extremities or mild rashes Creatinine > 2.5 g/dL bilirubin > 3.5 mg/dL prothrombin activity < 40 % leukocyte count < 4.0x109/L platelets < 150x109/L appearance of seizures or severe allergic reaction.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Acetazolamide

Reporting group description: -

Serious adverse events	Acetazolamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Acetazolamide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)		
General disorders and administration site conditions			
Somnolence			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
supraventricular tachycardia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Bicarbonate concentration <23 mmol/L			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1. Sample size.
2. Lack of measurement of central drive performance due to the multicentre study and the different equipment among hospitals.
3. No measurement of asynchrony episodes, respiratory muscles workload or duration of respiratory cycle

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28286047