MOTION

Methylnaltrex**o**ne for the **T**reatment of Opioid **I**nduced C**o**nstipation & Gastrointestinal Stasis in I**n**tensive Care Patients

Basic Results

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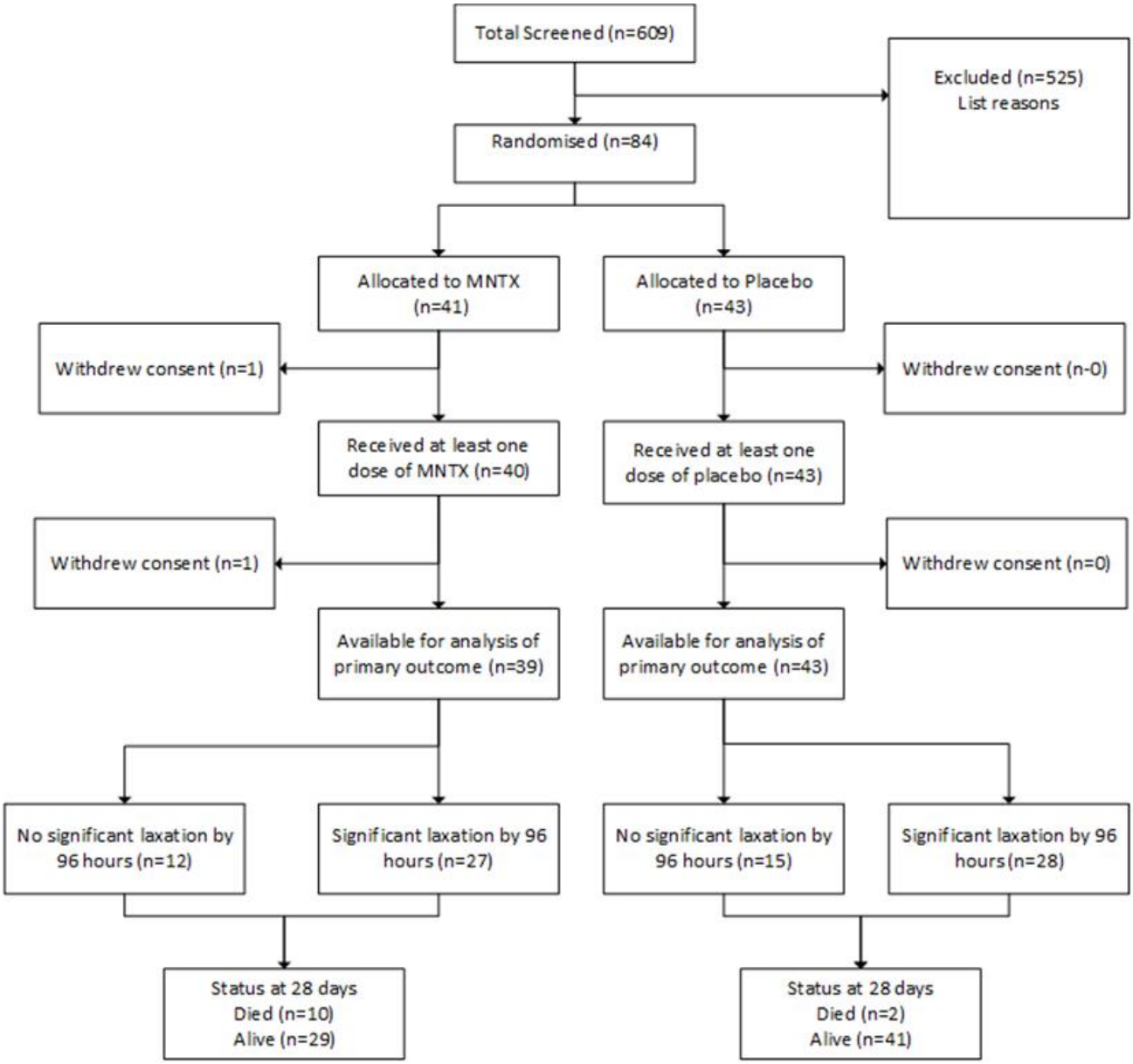
Figure 1. Participant Flow



n: number of participants, MNTX: Methylnaltrexone

Table 1. Baseline Characteristics

Demographics	MNTX (n)	Placebo (n)	All (n)
Gender, n=84 (male/female)	27/14	31/12	58/26
Mean age, n=84 (SD)	55.6 (14.8)	58.6 (17.3)	57.1 (16.1)
Median height in cm, n=84 (male/female)	176.0/163.0	176.0/162.5	176.0/163.0
Median weight in kg, n=84 (male/female)	80.0/65.0	76.0/70.0	77.5/69.0
Ethnicity, n=79			
Caucasian/Asian/Black	24/12/3	28/9/2	52/21/5
Other white or white background/Other	1/1	0/4	1/5
Clinical Characteristics	**MNTX (n)**	**Placebo (n)**	**All (n)**
Reason for Intensive Care Unit (ICU) admission, n=84			
Medical (Non-operative)	31	34	65
Surgical – emergency (operative)	10	6	16
Surgical – elective (operative)	0	3	3
Type of opioid, n=84			
Fentanyl/Remifentanil/Morphine	29/9/2	35/7/0	64/16/2
Remifentanil until 1h before randomisation/off opioids	0/1	1/0	1/1
Other sedatives reported used, n=84	34	36	70
Mean Arterial Pressure (MAP), n=84 [Median (IQR)]	86.0 (76.0, 96.0)	80.0 (74.0, 89.0)	83.0 (75.0, 92.0)
Heart rate, n=84 [Median (IQR)]	78.0 (66.0, 85.0)	78.0 (60.0, 89.0)	78.0 (64.5, 86.0)
SaO_2, n=84 [Median (IQR)]	98.0 (96.0, 99.0)	98.0 (96.0, 98.0)	98.0 (96.0, 98.5)
Lactate, n=84 [Median (IQR)]	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
Patients on vasoactive drugs, n=84	25	27	52
On Selective Digestive Decontamination (SDD), n=84	4	10	14
PaO_2 from lowest PaO_2/FiO_2 ratio, n=84 [Median (IQR)]	10.7 (9.6, 11.6)	10.5 (9.2, 12.8)	10.6 (9.6, 12.2)
FiO_2 from lowest PaO_2/FiO_2 ratio, n=84 [Median (IQR)]	0.35 (0.26, 0.40)	0.35 (0.25, 0.50)	0.35 (0.26, 0.48)
Moderate or severe ARDS, n=84	2	4	6
Creatinine, n=74 [Median (IQR)]	63.5 (55.0, 111.0)	68.5 (56.5, 103.5)	64.5 (55.0, 106.0)
Renal replacement therapy, n=84	4	4	8
Bilirubin, n=73 [Median (IQR)]	13.5 (7.0, 23.0)	10.0 (5.0, 24.0)	13.0 (6.0, 24.0)
Richmond Agitation Sedation Score (RASS), n=83 [Median (IQR)]	-5.0 (-5.0, -4.0)	-4.0 (-5.0, -4.0)	-5.0 (-5.0, -4.0)
Patients with traumatic brain injury, n=84	8	7	15
Patients on any muscle relaxant, n=84	6	5	11
Total APACHE II score, n=84			
Mean (SD)	18.0 (6.3)	18.2 (6.1)	18.1 (6.2)
Median (IQR)	20.0 (13.0, 23.0)	16.0 (14.0, 22.0)	17.0 (13.5, 22.0)
Baseline Opioids	**MNTX (n)**	**Placebo (n)**	**All (n)**
Fentanyl dose (mcg/h)			
N	29	35	64
Mean	137.1	142.1	139.8
Median (IQR)	100 (100, 200)	150 (100, 200)	100 (100,200)
Remifentanil dose (mcg/h)			
N	9	7	16
Mean	438.2	213.0	339.7
Median (IQR)	480 (292, 684)	158 (96, 301)	296 (111, 593)

SD: standard deviation, IQR: interquartile range, ARDS: acute respiratory distress syndrome, n: number of participants, MNTX: Methylnaltrexone

Outcome Measures

Primary Outcome

Table 2. Rescue-Free Laxation

Rescue-Free Laxation	MNTX (n)	Placebo (n)	All (n)
Randomised	41	43	84
Withdrawn	2	0	2
Available for analysis of primary outcome	39	43	82
Rescue free laxation achieved within 96 hours (events)	27 (69.2%)	28 (65.1%)	55 (67.1%)
Rescue free laxation not achieved	12	15	27
Laxation after rescue (censored at rescue or 96h)	10	13	23
No laxation (censor at last ICU date or 96h)	2	2	4

ICU: intensive care unit, n: number of participants, MNTX: Methylnaltrexone

Secondary Outcomes

Table 3.1 Average Number of Bowel Movements

Mean No. of Bowel Movements Per Day	MNTX		Placebo	
	Mean	Median (IQR)	Mean	Median (IQR)
Days 1-3				
No rescue	0.63	0.33 (0.00, 1.00)	0.91	0.67 (0.00, 1.67)
After 1 to 2 rescues	1.50	1.50 (0.50, 2.50)	0.97	1.33 (0.00, 1.50)
All days 1 to 3	0.69	0.67 (0.00, 1.00)	0.98	0.67 (0.00, 1.67)
P-value (Wilcoxon)		P=0.5765		
Days 4-28				
No rescue	1.34	1.08 (0.33, 1.80)	1.94	2.00 (1.44, 2.50)
After 1 to 2 rescues	1.23	1.18 (0.00, 2.00)	1.42	1.14 (0.40, 2.17)
After 3+ rescues	1.46	1.38 (0.00, 2.14)	1.83	1.63 (1.00, 2.42)
All days 4 to 28	1.60	1.38 (1.00, 2.00)	2.07	2.00 (1.54, 2.50)
P-value (Wilcoxon)		0.0055		

IQR: interquartile range, MNTX: Methylnaltrexone

Table 3.2 Escalation of Opioid Doses due to Antagonism/Reversal of Analgesia and Sedation

Opioid doses - patients on Fentanyl	MNTX (n)	Placebo (n)
Total on fentanyl at baseline	28	35
Remained on fentanyl	26	33
Dose reduced	1	0
Remained on same dose	22	30
Dose increase by less than 100%	0	3
Dose increase by 100% or more	3	0
Changed to remifentanyl	0	1
Stopped	2	1
Opioid doses - patients on Remifentanyl	**MNTX (n)**	**Placebo (n)**
Total on remifentanyl at baseline	9	7
Remained on remifentanyl	9	5
Dose reduction	3	0
Remained on same dose of fentanyl	3	3
Dose increase by less than 100%	1	1
Dose increase by 100% or more	0	1
Dose unknown	2	0
Changed to fentanyl	0	1
Stopped	0	1

n: number of participants, MNTX: Methylnaltrexone

Table 3.3 Incidence of Clostridium Difficile Infection

First day c. difficile infection reported	
MNTX (n=3)	**Placebo (n=7)**
Day 6	Day 1
Day 18	Day 2
Day 18	Day 10
	Day 11
	Day 12
	Day 12
	Day 21
7.7% of patients	16.3% of patients

n: number of participants, MNTX: Methylnaltrexone

Table 3.4 Incidence of Diarrhoea

Incidence of Diarrhoea	MNTX	Placebo	Total
Number of patients with information on bowel movements	39	43	82
Number of patients with type 7 stool diarrhoea at least once	23	36	59
Proportion of patients experiencing diarrhoea at least once	59.0%	83.7%	72.0%
P-value (Pearson's chi-sq) for difference	0.0152		
Number of bowel movements with stool type specified	854	1423	2276
Number of bowel movements with stool type 7	208	336	544
Proportion of movements with stool type 7	23.3%	23.6%	23.9%
P-value (Pearson's chi-sq) for difference	0.6937		-

MNTX: Methylnaltrexone

Table 3.5 Incidence of Ventilator Associated Pneumonia VAP Defined by the Clinical Pulmonary Infection Score

Incidence of Ventilator-Associated-Pneumonia (VAP)	MNTX	Placebo	All
Randomisation			
N	41	43	84
Mean	5.9	5.5	5.7
Median (IQR)	6.0 (5.0, 7.0)	6.0 (4.0, 6.0)	6.0 (5.0, 6.5)
Proportion>6, [n, %]	11 (26.8%)	10 (23.3%)	21 (25.0%)
Day 1			
N	39	43	82
Mean	5.9	5.6	5.7
Median (IQR)	6.0 (4.0, 7.0)	6.0 (5.0, 6.0)	6.0 (5.0, 7.0)
Proportion>6, [n, %]	12 (30.8%)	9 (20.9%)	21 (25.6%)
Day 4			
N	37	43	80
Mean	6.0	6.1	6.0
Median (IQR)	6.0 (5.0, 7.0)	6.0 (4.0, 7.0)	6.0 (5.0, 7.0)
Proportion>6, [n, %]	13 (35.1%)	16 (37.2%)	29 (36.3%)
Day 7			
N	29	39	68
Mean	6.7	5.8	6.2
Median (IQR)	7.0 (5.0, 8.0)	6.0 (5.0, 7.0)	6.0 (5.0, 8.0)
Proportion>6, [n, %]	14 (48.3%)	14 (35.9%)	28 (41.2%)

n: number of participants, IQR: interquartile range, MNTX: Methylnaltrexone

Table 3.6 Incidence of Positive Microbiology Blood Cultures

Incidence of Positive Microbiology Blood Cultures	MNTX	Placebo	Total
Number of patients	19	27	46
Number of days	70	178	248

MNTX: Methylnaltrexone

Table 3.7 28-Day Mortality

28-day Mortality	MNTX (n)	Placebo (n)	Total (n)
Survival status:			
Died <28 days	10	2	12
Alive at 28 days	29	41	70
Total	39	43	82

n: number of participants, MNTX: Methylnaltrexone

Table 3.8 Requirement of Prokinetics

Requirement of Prokinetics	MNTX (n=40)	Placebo (n=43)
Metoclopramide		
Number of patients with data on metoclopramide use	39	43
Number of patients given metoclopramide	15	13
Number of patient days with data on metoclopramide use	560	769
Number of patient days patients given metoclopramide	65	104
Erythromycin		
Number of patients with data on erythromycin use	39	43
Number of patients given erythromycin	10	7
Number of patient days with data on erythromycin use	560	769
Number of patient days patients given erythromycin	56	40

n: number of participants, MNTX: Methylnaltrexone

Table 3.9 Requirement of Rescue Laxatives

Requirement of Rescue Laxatives	MNTX (n)	Placebo (n)
Available for analysis	39	43
Rescue laxatives required	17	17
P value (Pearson's chi-squared)	0.74	
Rescue laxatives required before laxation	10	13
Rescue laxatives given after first laxation	7	4
Further rescue laxatives required	9	11

n: number of participants, MNTX: Methylnaltrexone

Table 3.10 Toleration of Enteral Feeds and Gastric Residual Volume

Summary of Enteral Feeding While on Study Drug and Gastric Residual Volume (GRV)	MNTX	Placebo
Number of patients for analysis	39	43
Number of patient days	561	769
Number of patient days with enteral feed 'Not applicable'	30	62
Number of patient days of enteral feeds available for analysis	531	707
Number of days when full enteral feed was achieved	174 (32.8%)	225 (31.8%)
Target enteral feed (mls) for the days on study drug		
[Mean]	1371.5	1325.8
[Median, (IQR)]	1460 (1240, 1680)	1346 (1152, 1538)
P-value (Wilcoxon) for difference in target enteral feed	<0.0001	
Gastric Residual Volume in mls		
[Mean]	80.1	70.7
[Median, (IQR)]	0.0 (0.0, 40.0)	0.0 (0.0, 25.0)
P-value (Wilcoxon) for difference in GRV between treatments	0.0535	

IQR: interquartile range, MNTX: Methylnaltrexone

Table 4. Adverse Events

Adverse Events (AEs)	MNTX		Placebo	
	No. of AEs	No. of Subjects	No. of AEs	No. of subjects
Metastatic rectal cancer	0	0	1	1
Diarrhoea	8	8	11	11
Patient developed rashes over his torso	1	1	0	0
Total	9	9	12	12
Serious Adverse Events (SAEs)	**MNTX**		**Placebo**	
	No. of SAEs	No. of Subjects	No. of SAEs	No. of subjects
Perforated abdominal viscous	0	0	1	1
Respiratory distress	1	1	0	0
Hypoxic cardiac arrest following displacement of newly inserted surgical tracheostomy	1	1	0	0
Self-terminating asystolic events	0	0	1	1
Total	2	2	2	2
Severity				
Moderate	0	-	1	-
Life threatening or disabling	2	-	1	-
Causality				
Not related	2	-	2	-
Expectedness				
Not expected	2	-	2	-

MNTX: Methylnaltrexone