5.2a Strategies to Optimize Delivery and Minimize Risks of EN: Motility Agents

Question: Compared to standard practice (placebo), does the routine use of motility agents improve clinical outcomes in critically ill patients?

Summary of Evidence: Of the total of 12 studies included, 8 studies looked at the use of a single motility agent compared to placebo (1 level 1 study, 7 level 2 studies). Of these, 3 studies compared erythromycin to placebo (Chapman 2000, Berne 2002, Reigner 2002, Makkar 2016), 2 compared metoclopramide to placebo (Yavagal 2000 and Nursal 2007, Makkar 2016), 1 compared a novel phase II motility agent, camicinal, to placebo (Deane 2018) and an earlier study compared the use of enteral naloxone to placebo (Meissner 2003). Note that the Makkar 2016 trial included 3 groups: erythromycin vs metoclopramide vs placebo. The data from four additional studies was not included in the meta-analysis as the interventions varied (MacLaren 2008 erythromycin vs. metoclopramide; Nguyen 2007 erthryomycin plus metoclopramide vs. erythromycin alone; Baradari 2016 neostigmine vs metoclopramide; Baradari 2017 neostigmine vs metoclogpramide vs neostigmine + metoclopramide). Given the uncertainty around the safety and efficacy of naloxone as a motility agent, the data from the Meissner 2003 study was not included. Boivin 2001, which was included in the 2015 CPGs, has been moved to section 5.2b (motility agents vs intestinal feeds).

Mortality: When the data from the six studies of metoclopramide or erythromycin alone compared to placebo were aggregated, the use of motility agents had no effect on mortality (RR 1.08, 95% CI 0.89, 1.31, p=0.42, heterogeneity I^2=0%; figure 1). Note that these results are with the Makkar 2016 group that received erythromycin, but similar results are seen if the metoclopramide group is analyzed instead (RR 1.10, 95% CI 0.90, 1.34, p=0.37, heterogeneity I^2=1%; figure not shown).

Infections: In the one study using naloxone, there was a significant reduction in pneumonia (Meissner 2003) and in the other study, metoclopramide had no effect on the incidence of pneumonia (Yavagal 2000). One study reported on the number of infections per group rather than the number of patients with infections and again there were no differences between the two groups (Berne 2002).

LOS, Ventilator days: There were no differences between the groups in the 7 studies that reported on these outcomes (Meissner 2003, Nursal 2007, Nguyen 2007, Baradari 2016, Makkar 2016, Baradari 2017, Deane 2018,), with the exception of Baradari 2016 who found a trend in the reduction of ICU LOS in their study of neostigmine vs metoclopramide.

Other: The time to development of pneumonia was statistically different in the one study (Yavagal) (5.95 days versus 4.46 days, p=0.006), however, the clinical significance of this difference is negligible. In the studies comparing a motility agent to placebo, 2 found significant improvements in GRVs or feeding tolerance in the motility agent group (Chapman 2000, Reignier 2002, Berne 2002) but 3 studies found no significant difference (Nursal 2007, Makkar 2016, Deane 2018). Two studies found no significant difference in the EN volume the groups received (Meissney 2003, Deane 2018) but one study found the control group received significantly more calories than the motility agent group (Nursal 2007).

Conclusion:

1) Motility agents have no effect on mortality, infectious complications, LOS or ventilation duration in critically ill patients.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized Studies Motility Agents in Critically Ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† Experimental	Mortality # (%)† Control	Infections # (%)‡ Experimental	Infections # (%)‡ Control	Nutritional Indices Experimental	Nutritional Indices Control
Placebo-controlled Trials									
1) Chapman 2000	Mixed ICU patient with GRV>250ml N=20	C.Random: Yes ITT: yes Blinding: Yes (12)	Erythro 200 mg IV vs placebo x 1 dose	NR	NR	NR	NR	Successful feeding defined as GRV <250 mo and continuing with feeds. Erythro 9/10 vs placebo 5/10, p=0.05	
2) Yavagal 2000	Mixed ICU N=305	C.Random: not sure ITT: yes Blinding: yes (10)	Metoclopramide 10 mg NG q 6 h vs. placebo	73/ 131 (56)	92/174 (53)	Pneumonia 22/131 (17)	Pneumonia 24/174 (14)	NR	
3) Berne 2002	Critically injured patients n=48	C.Random: not sure ITT: no Blinding: no (6)	Erythromycin 250 mg IV q 6 hrs vs. placebo	2/32 (6)	2/36 (6)	Pneumonia 13/32 per group*	Pneumonia 18/36 per group*	Feeds tolerated at 48 hrs 58% 44 % p=0.001 Feeds tolerated for the study 65% 59% p=0.06	
4) Reignier 2002	Mixed ICU patients N=48	C.Random: not sure ITT: yes Blinding: no (6)	Erythro 250 mg q 6h IV vs placebo x 5 days	6/20 (30)	8/20 (40)	NR	NR	EN discontinued if GRV>250 or vomited: Erythro 35% vs Placebo 70 p<0.001	
5) Meissner** 2003	ICU patients N=84	C.Random: yes ITT: no Blinding: double (11)	Naloxone 8 mg q 6 hrs via NG vs, placebo	6/38 (16)	7/43 (16)	Pneumonia 13/38 (34)	Pneumonia 24/43 (56)	Feeding volumes after day 3 Higher in naloxone group (trend) Amount of Reflux (mls) 54 129	
6) Nursal 2007	Traumatic Brain Injured patients N=19	C.Random: no ITT: no Blinding: double (10)	Metoclopramide 10 mg IV TID vs. saline IV TID	Hospital 3/10 (30)	Hospital 3/9 (33)	NR	NR	Patients with high GRV 5/10 (50) 2/9 (22) Days to target calories 5.8 ± 5.2 3.4 ± 1.4 Calorie intake/total calories 61.3% 92.2%	

7) Makkar 2016	Trauma pts with TBI, GCS >5 N=122	C.Random: yes ITT: no Blinding: double (8)	Erythromycin 250 mg tablet for 5 days vs Metoclopramide 10 mg tablet for 5 days vs placebo (vitamin C) for 5 days	Erythromycin Unknown type 4/38 Metoclopramide Unknown type 6/39	Unknown type 3/38 P=0.574	NR	NR	Number of patients w high GRVs erythro. metocl. Control 11/38 17/39 23/38 P=0.295 Feeding failures (2 consecutive high GRVs) 6/38 10/39 11/38 P=NS
8) Deane 2018	ICU patients on vasopressors or ISS $\geq$ 15 or GCS $\leq$12 or high dose opioids N=84	C.Random: yes ITT: no Blinding: double (11)	Camicinal (GSK) 50 mg given enterally vs 10 ml enteral placebo. EN as per standard practice in both groups.	All cause 11/42 (26)	All cause 7/38 (18)	NR	NR	Avg % goal volume delivered via EN 77% [71, 83] 68% [58, 78], p=NS % pts receiving $\geq$ 80% goal 67% 74% Incidence of feed intolerance 15% 14%
Head to Head Comparisons								
9) MacLaren 2008	Mixed ICU patient with GRV>150ml N=20	C.Random: not sure ITT: yes Blinding: no (9)	Erythro 250 mg q6h vs Meto 10 mg IV q 6h for 4 doses	NR	NR	NR	NR	Both agents resulted in significant reduction in GRV and increase in feeding rate
10) Baradari 2016	Mechanically ventilated ICU patients with NG in place and GRX >120 ml 3h after last gavage N=60	C.Random: yes ITT: no Blinding: double (6)	Neostigmine 2.5 mg IV at baseline and 6h later vs metoclopramide 10 mg at baseline and 6h later. EN in both groups given as bolus – feeds of 180 ml every 3h.	Neostigmine Unknown type 1/30	Metoclopramide Unknown type 2/30	NR	NR	Median time from intervention to GRV improvoment Nestigmine Metoclopramide 6h (CI 3.75-8.25) 9h (CI 7.38-10.17) p=NS Adverse affects 20.4% 7.2% Diarrhea 2 (6.8%) 0
11) Baradari 2017	EN fed mechanically ventilated ICU patients with GRVs >120 ml 3h after last gavage N=90	C.Random: yes ITT: yes Blinding: double (10)	Neostigmine 2.5 mg IV vs metoclopramide 20mg IV given over 60 minutes after enrollment. Standard EN for all groups: 250 ml EN every 4h. *Combo group shown in table below*	Neostigmine Unknown type 1/30	Metoclopramide Unknown type 2/30	NR	NR	Median time from intervention to GRV improvoment Nestigmine Metoclopramide 3h (CI 2.9-4.99) 6h (CI 4.83-7.17) Adverse affects 16.7% 3.3%

Combo vs Mono								
12) Nguyen 2007	Mixed ICU patients N=75	C.Random: yes ITT: yes Blinding: double (11)	Combination of Erythromycin 200 mg IV bid + Metoclopramide 10 mg IV qid vs. Erythromycin 200 mg IV bid alone	Hospital Combo 8/37 (22)	Hospital Mono 10/38 (26)	NR	NR	Failure of feeding (days) 6.5 ± 0.5 4.5 ± 0.5 Caloric intake % prescribed 7 days Higher in combination group (p=0.02) Gastric residual volumes Lower in combination group (p<0.05) Need for post-pyloric feeds 2/37 (5) 8/38 (21)
11) Baradari 2017 (continued)	*As above*	*As above*	*In addition to head to head comparison:* vs combo 2.5 mg neostigmine + 20 mg metoclopramide given over 60 mintes after enrollment	Combo Unknown type 1/30	*As above*	NR	NR	Median time from intervention to GRV improvement, combo group 3h (CI 2.01-3.3) Adverse affects, combo group 10%

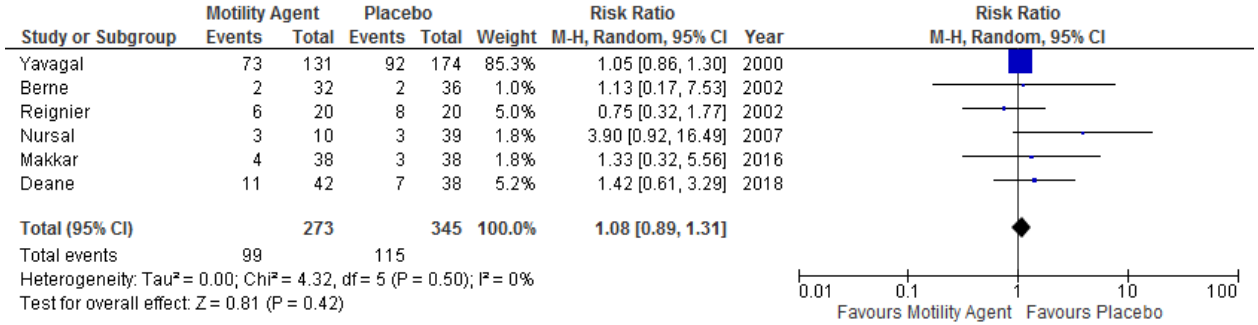
* infections reported as per group, not # patients with infections
**data from this study not included in the meta-analysis due to the uncertainty around the safety and efficacy of naloxone as a motility agent.

Table 1. Randomized Studies Motility Agents in Critically Ill Patients (continued)

Study	ICU LOS		Hospital LOS		Mechanical Ventilation	
	Experimental	Control	Experimental	Control	Experimental	Control
Placebo-controlled Trials						
1) Chapman 2000	NR	NR	NR	NR	NR	NR
2) Yavagal 2000	NR	NR	NR	NR	NR	NR
3) Berne 2002	NR	NR	NR	NR	NR	NR
4) Reignier 2002	NR	NR	NR	NR	NR	NR

5) Meissner** 2003	17.5 (11-26) P=0.61	19 (13.5-24)	24 (16-33) P=0.92	23 (14-34)	11.5 (7-20.5) P=0.35	13 (10-20)
6) Nursal 2007	16.8 ± 8.5 P=0.819	15.6 ± 11.1	NR	NR	NR	NR
7) Makkar 2016	Erythromycin 8.5 ± 3.59 Metoclopramide 8.9 ± 4.99 p=0.275	10.4 ± 7.17	NR	NR	Erythromycin 7.14 ± 3.23 Metoclopramide 7.85 ± 4.93 P=0.295	8.97 ± 7.1
8) Deane 2018	Mean and SE 14 ± 1 p-value NR	Mean and SE 12 ± 2	Mean and SE 27 ± 3 p-value NR	Mean and SE 24 ± 3	Mean and SE 11 ± 2 p-value NR	Mean and SE 8 ± 1
Head to Head Comparisons						
9) MacLaren 2008	NR	NR	NR	NR	NR	NR
10) Baradari 2016	Neostigmine 20 (16-20) P=0.072	Metoclopramide 17.5 (13-20)	NR	NR	Neostigmine 12 (6.5-15) P=0.58	Metoclopramide 11.5 (7-13)
11) Baradari 2017	Neostigmine 18.97 ± 6.25 P=0.4	Metoclopramide 16.8 ± 6.27	NR	NR	Neostigmine 12.17 ± 4.56 P=0.71	Metoclopramide 11.13 ± 3.84
Combo vs Mono						
12) Nguyen 2007	NR	NR	Combo 53.0 ± 6.1 P=NS	47.8 ± 9.1	NR	NR
11) Baradari 2017 (continued)	Combo 18.27 ± 6.3	*As above*	NR	NR	Combo 11.8 ± 5.91	*As above*

Figure 1. Mortality*



*Showing data for erythromycin motility agent group in Makkar study