

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

Question: Does the routine use of motility agents improve clinical outcomes in critically ill patients?

Summary of Evidence: There were 16 studies, (5 level 1 and 11 level 2) that compared motility agents to a placebo, standard of care, other motility agents or as a mono vs. combined approach. Of these, 8 studies looked at the use of a single motility agent compared to placebo (1 level 1 study, 7 level 2 studies) and one compared the motility agent to none (1 level 2 study). Three of these studies compared erythromycin to placebo (Chapman 2000, Berne 2002, Reigner 2002, Makkar 2016), two compared metoclopramide to placebo (Yavagal 2000 and Nursal 2007, Makkar 2016), two compared a novel phase II motility agent, one compared camicinal to placebo (Deane 2018), one compared the use of enteral naloxone to placebo (Meissner 2003) while one compared a higher dose of a traditional Japanese herbal medication to a standard dose and to none (Doi 2020). The Makkar 2016 trial included 3 groups: erythromycin vs. metoclopramide vs. placebo as did the Baradari 2017 study that compared neostigmine to metoclopramide to a combined approach. Given the uncertainty around the safety and efficacy of naloxone as a motility agent, the data from the Meissner 2003 study was not included. Five studies conducted a head to head comparison of motility agents but the data from these studies was not included in a meta-analysis as the interventions varied (MacLaren 2008 erythromycin vs. metoclopramide; Baradari 2016 & 2017 neostigmine vs. metoclopramide; Heyland 2019 Ulimorelin vs. metoclopramide; Chapman 2020 TAK-954 (Selective 5-HT4 receptor agonist) vs. metoclopramide). Three studies (Nguyen 2007, Baradari 2017 and Charoensareerat 2020) compared combined vs. monotherapy. Boivin 2001, which was included in the 2015 CPGs, was moved to section 5.2b (motility agents vs. intestinal feeds) in the 2018 update.

Mortality: When the data from the seven studies of a single motility agent compared to placebo/control that reported on mortality were aggregated, the use of motility agents had no effect on mortality (RR 1.06, 95% CI 0.87, 1.28, $p=0.56$, test for 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 1.07, 95% CI 0.88, 1.29, $p=0.50$, test for heterogeneity $I^2=0\%$; figure not shown). In the Doi 2020 study, the mortality data from both high dose and low dose intervention groups were combined.

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). 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. 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 groups receiving erythromycin vs. placebo (Berne 2002). Rates of ICU acquired/ventilator associated pneumonia were no different between the groups receiving Ulimorelin vs. metoclopramide (Heyland 2019) or those receiving combination metoclopramide and erythromycin vs. metoclopramide alone (Charoensareerat 2020).

LOS, Ventilator days: There were no differences between the groups in the 9 studies that reported on these outcomes (Meissner 2003, Nursal 2007, Nguyen 2007, Makkar 2016, Baradari 2017, Deane 2018, Heyland 2019, Doi 2020), with the exception of Baradari 2016 who found a trend in the reduction of ICU LOS in their study of neostigmine vs. metoclopramide.

Other: Nutritional outcomes and markers of enteral feeding intolerance were reported in all trials but the heterogeneity of how these outcomes were reported precludes formal statistical aggregation. In the controlled trials, three found significant improvements or strong trends towards improvements in feeding success or reduced feeding tolerance in the motility agent group (Chapman 2000, Reignier 2002, Berne 2002, Meissner 2003), three studies found no significant difference but numerically, better outcomes were observed in these underpowered trials (Makkar 2016, Deane 2018, Doi 2020), whereas one trial (Nursal 2007) showed better outcomes in the control group but results were not statistically significant in this small trial of 19 patients. In the head-to-head comparisons, based on one trial evaluating erythromycin and metoclopramide, nutritional and enteral feeding intolerance outcomes improved in both groups compared to baseline and there were no differences between groups (MacLaren 2008). When considering trials of combination vs. monotherapy, there are mixed results when considering the impact on nutritional or enteral feeding intolerance outcomes.

Conclusion:

- 1) Motility agents have no effect on mortality, infectious complications, LOS or ventilation duration in critically ill patients.
- 2) Motility agents may improve nutritional intake and/or reduce enteral feeding intolerance.

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 # (%)† | | Infections # (%)‡ | | Nutritional Indices | |
|----------------------------------|--|--|---|------------------------------|-----------------------------|--------------------------------------|--------------------------------------|--|---------|
| | | | | Experimental | Control | Experimental | Control | Experimental | 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 ml 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); p=0.22 Days to target calories 5.8 ± 5.2 3.5 ± 1.4; p=0.23 Calorie intake/total calories 61.3 ± 35.5% 92.2 ± 8.0%; p=0.04 | |

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|---------------------------------|--|---|--|---|--|-----------|-----------|---|
| <p>7) Makkar 2016</p> | <p>Trauma pts with TBI, GCS >5 N=122</p> | <p>C.Random: yes ITT: no Blinding: double (8)</p> | <p>Erythromycin 250 mg tablet for 5 days vs. Metoclopramide 10 mg tablet for 5 days vs. placebo (vitamin C) for 5 days</p> | <p>Erythromycin Unknown type 4/38 Metoclopramide Unknown type 6/39</p> | <p>Unknown type 3/38; p=0.574</p> | <p>NR</p> | <p>NR</p> | <p>Number of patients with high GRVs erythro. metocl. Control 11/38 17/39 23/38 p=0.30 Feeding failures (2 consecutive high GRVs) 6/38 10/39 11/38 p=NS</p> |
| <p>8) Deane 2018</p> | <p>ICU patients on vasopressors or ISS ≥ 15 or GCS ≤12 or high dose opioids N=84</p> | <p>C.Random: yes ITT: no Blinding: double (11)</p> | <p>Camicinal (GSK) 50 mg given enterally vs. 10 ml enteral placebo. EN as per standard practice in both groups.</p> | <p>All cause 11/42 (26)</p> | <p>All cause 7/38 (18)</p> | <p>NR</p> | <p>NR</p> | <p>Avg % goal volume delivered via EN 77% [71, 83] 68% [58, 78], p=NS % pts receiving ≥ 80% goal 67% 74% Incidence of feed intolerance 15% 14%</p> |
| <p>9) Doi 2019</p> | <p>Critically ill requiring gastric feeding for ≥ 5 days N=26</p> | <p>C.Random: no ITT: no Blinding: no (5)</p> | <p>Rikkunshito (traditional Japanese herbal medicine) high dose 5 gm TID vs. Rikkunshito standard dose 2.5 mg TID vs. None (no placebo) for 5 days</p> | <p>ICU 3/17 (17.6%) Hospital 3/17 (17.6%)</p> | <p>ICU 1/9 (11) Hospital 1/9 (11%)</p> | <p>NR</p> | <p>NR</p> | <p>Rikkunshito high dose vs. standard dose vs. none GRVs ≥ 300 mL/day, n (%) 1/9 (11) vs. 1/8 (13) vs. 2/9 (22); p=1.00 Diarrhea, n (%) 2/9 (22) vs. 2/8 (25) vs. 1/9 (11); p=0.84 Vomiting, n (%) None in all groups Day 5 % EN target reached, median, 62% (IQR 17–83%) vs. 40% (IQR, 26–61%) vs. 59% (IQR 39–63%); p=0.42</p> |
| Head to Head Comparisons | | | | | | | | |
| <p>10) MacLaren 2008</p> | <p>Mixed ICU patient with GRV>150ml N=20</p> | <p>C.Random: not sure ITT: yes Blinding: no (9)</p> | <p>Erythromycin 250 mg q6h vs. Metoclopramide 10 mg IV q 6h for 4 doses</p> | <p>NR</p> | <p>NR</p> | <p>NR</p> | <p>NR</p> | <p>Both agents resulted in significant reduction in GRV and increase in feeding rate Erythromycin vs. Metoclopramide GRV mL after dose 4 (mean SD) 36 ±48 (p<0.01 from baseline) vs. 21±23 (p<0.05 from baseline) Feeding rate mL/hr after dose 4 (mean SD) 45 ± 21 (p<0.05 from baseline) vs. 44 ± 22 (p<0.05 from baseline) % patients achieved goal feeding 4/10 (40%) vs. 3/10 (30%) Diarrhea 3/10 (30%) vs. 1/10 (10%)</p> |

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|----------------------------------|---|---|--|---|---|---|---|--|
| <p>11) Baradari 2016</p> | <p>Mechanically ventilated ICU patients with NG in place and GRX >120 ml 3h after last gavage N=60</p> | <p>C.Random: yes ITT: no Blinding: double (6)</p> | <p>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.</p> | <p>Neostigmine Unknown type 1/30</p> | <p>Metoclopramide Unknown type 2/30</p> | <p>NR</p> | <p>NR</p> | <p>Median time from intervention to GRV improvement Neostigmine 6h (CI 3.75-8.25) Metoclopramide 9h (CI 7.38-10.17) p=NS Adverse affects 20.4% 7.2% Diarrhea 2 (6.8%) 0</p> |
| <p>12a) Baradari 2017</p> | <p>EN fed mechanically ventilated ICU patients with GRVs >120 ml 3h after last gavage N=90</p> | <p>C.Random: yes ITT: yes Blinding: double (10)</p> | <p>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. <i>Combo group shown in table below as 12b</i></p> | <p>Neostigmine Unknown type 1/30</p> | <p>Metoclopramide Unknown type 2/30</p> | <p>NR</p> | <p>NR</p> | <p>Median time from intervention to GRV improvement Neostigmine 3h (CI 2.9-4.99) Metoclopramide 6h (CI 4.83-7.17) Adverse affects 16.7% 3.3%</p> |
| <p>13) Heyland 2019</p> | <p>Mechanically ventilated, intolerant to gastric tube feedings (GRV ≥ 500ml) N=122</p> | <p>C.Random: yes ITT: no Blinding: double (9)</p> | <p>Ulimorelin 600µg/kg in 50ml IV infusion vs. Metoclopramide 10mg in 50ml IV infusion. Both given for 30 mins, 8 hourly</p> | <p>Ulimorelin 5 day 5/62 (6.5%) 30 day 19/62 (30.6%) Due to adverse events 3/62 (4.8%)</p> | <p>Metoclopramide 5 day 1/58 (1.7%) 30 day 15/58 (25.9%) Due to adverse events 1/58 (1.7%)</p> | <p>Ulimorelin ICU-acquired pneumonia 11/62 (17.7%)</p> | <p>Metoclopramide ICU-acquired pneumonia 11/58 (19%)</p> | <p>Day 1-5 % daily protein target rate achieved, mean, IQR 82.9 (38.4,110.2) 82.3 (65.6, 11.2); p=0.49 Feeding success, n(%) 32 (51.6) 32 (55.2) GRV > 500ml, n(%) 31 (50) 33 (56.9) Vomiting or regurgitation, n(%) 14 (22.6) 10 (17.2) Tracheal aspirate positive for pepsin, n(%) 21 (33.9) 18 (31.0) Constipation, n(%) 2 (3.2) 0 (6.9)</p> |
| <p>14) Chapman 2020</p> | <p>Mechanically ventilated patients with enteral feeding intolerance (GRV>200ml) N=13</p> | <p>C.Random: yes ITT: yes Blinding: double (12)</p> | <p>TAK-954 (Selective5-HT4 receptor agonist) 0.5mg single dose IV over 1 hour and 0.9% NaCl QID vs. 0.9% NaCl single dose IV over 1 hour and Metoclopramide 10mg QID IV</p> | <p>TAK-954 2/7 (29%)</p> | <p>Metoclopramide 3/6 (50%)</p> | <p>NR</p> | <p>NR</p> | <p>4 hr GRV, ml, median (min,max) 0(0,24) 5.5 (0, 65) 10 hr GRV, ml, median (min,max) 20 (0,150) 27.5 (0, 160) 16 GRV, ml, median (min,max) 15 (0, 60) 10 (0,140) 22h GRV ml, median (min,max) 10 (0,300) 30 (0,420)</p> |

| Combo vs. Mono | | | | | | | | |
|---------------------------------|---|--|---|--|--|---------------------------|---------------------------------|---|
| 15) 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 | Combo Hospital 8/37 (22%) | Mono Hospital 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) |
| 12b) Baradari 2017 | <i>As above</i> | <i>As above</i> | <i>In addition to head to head comparison:</i> Combination of neostigmine 2.5 mg + metoclopramide 20 mg given over 60 minutes after enrollment | Combo Unknown type 1/30 | <i>As above</i> | NR | NR | Median time from intervention to GRV improvement, combo group 3h (CI 2.01-3.3) Adverse affects, combo group 10% |
| 16) Charoensareerat 2020 | Mechanically ventilated, critically ill patients with enteral feeding intolerance N=35 | C.Random: yes ITT: yes Blinding: double (13) | Metoclopramide 10mg IV every 6-8hrs (total 40mg) + erythromycin 250mg enterally vs. metoclopramide plus placebo every 6 hrs for 7 days | Hospital 11/17 (64.7%) 28 day 10/17 (58.8%) | Hospital 12/18 (66.7%); p=1.00 28 day 12/18 (66.7%); p=0.73 | VAP 1/17 (5.9%) | VAP 0/18 (0%); p=0.46 | Rate of successful feeding, n(%) 8 (47.1) 11 (61.1); p=0.51 Time to achieve successful feeding, median (IQR), h 44 (20-68) 44 (16-96); p=0.97 Average GRV, ml/d Day 1 377.5 ± 396.4 414.3 ± 326.2; p=0.77 Average GRV, ml/d Day 7 149.2 ± 92.8 227.5 ± 275.6; p=0.53 |

* 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.

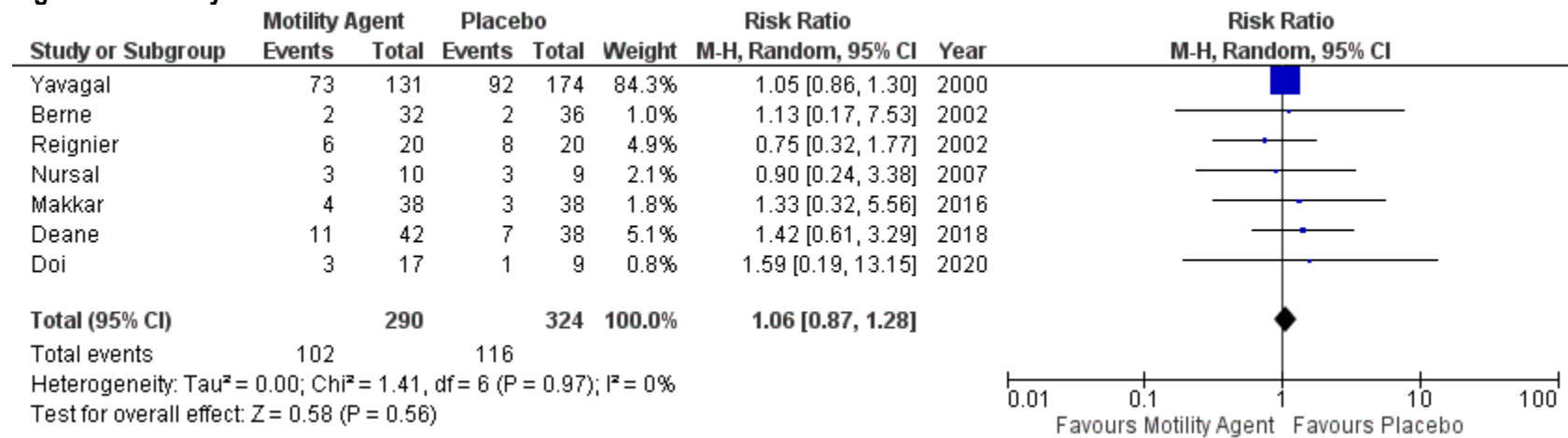
‡ mortality data from both interventional groups in this study (higher and standard doses) were combined

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 | Mean and SE 12 ± 2; p-value NR | Mean and SE 27 ± 3; p-value NR | Mean and SE 24 ± 3 | Mean and SE 11 ± 2 | Mean and SE 8 ± 1; p-value NR |
| 9) Doi 2019 | Rikkunshito high dose 5(4-14) . Rikkunshito standard dose 6(3-8) | 7 (4-9); p=0.92 | Rikkunshito high dose 42 (26-48) Rikkunshito standard dose 35 (30-40) | 56 (35-82); p=0.19 | NR | NR |

| Head to Head Comparisons | | | | | | |
|---------------------------------|--|--|--|--|--|---|
| 10) MacLaren 2008 | NR | NR | NR | NR | NR | NR |
| 11) Baradari 2016 | Neostigmine 20 (16-20) | Metoclopramide 17.5 (13-20); p=0.072 | NR | NR | Neostigmine 12 (6.5-15) | Metoclopramide 11.5 (7-13); p=0.58 |
| 12a) Baradari 2017 | Neostigmine 18.97 ± 6.25 | Metoclopramide 16.8 ± 6.27; p=0.4 | NR | NR | Neostigmine 12.17 ± 4.56 | Metoclopramide 11.13 ± 3.84; p=0.71 |
| 13) Heyland 2019 | Ulimorelin 14.9 (10.8, 20.8) | Metoclopramide 14.7 (11.8, 22.0) | Ulimorelin 33.7 (25.0, 43.8) | Metoclopramide 25.8 (18.1, 35.0) | Ventilator Free days 15.9 (0.0, 24.5) 15.5 (0.0, 23.3) | |
| 14) Chapman 2020 | NR | NR | NR | NR | NR | |
| Combo vs. Mono | | | | | | |
| 15) Nguyen 2007 | NR | NR | Combo 53.0 ± 6.1 | Mono 47.8 ± 9.1; p=NS | NR | NR |
| 12b) Baradari 2017 | Combo 18.27 ± 6.3 | <i>As above</i> | NR | NR | Combo 11.8 ± 5.91 | <i>As above</i> |
| 16) Charoensareerat 2020 | NR | NR | 13 (1-68) | 11.5 (1-62); p=0.57 | NR | NR |

Figure 1. Mortality*



*Showing data for erythromycin motility agent group in Makkar study

References

Included Studies

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Excluded Studies

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