The controversies of mechanical bowel and oral antibiotic preparation in elective colorectal surgery

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Although it has been shown conclusively that mechanical bowel preparation (MBP) alone offers no benefit to patients undergoing colorectal surgery when compared with no bowel preparation,¹ there is a resurgence in interest in oral antibiotic (OAB) preparation with or without MBP, as studies have shown that it may reduce the incidence of surgical site infection (SSI). Our recent meta-analysis² published in the *Annals of Surgery* examined this topic in adult patients undergoing elective colorectal surgery across 40 studies that included a total of 69,517 patients. This meta-analysis demonstrated that the combination of MBP and OAB was associated with a significant reduction in SSI [risk ratio (RR) 0.51, 95% confidence interval (CI) 0.46 to 0.56, $P < 0.00001$, $I^2 = 13\%$], anastomotic leak (RR 0.62, 95% CI 0.55 to 0.70, $P < 0.00001$, $I^2 = 0\%$), and 30-day mortality rates (RR 0.58, 95% CI 0.44 to 0.76, $P < 0.0001$, $I^2 = 0\%$), with no difference in *Clostridium difficile* infection rates, when compared with MBP alone. The four cohort studies³⁻⁶ comparing the combination of MBP and OAB with no preparation also showed that SSI was reduced significantly with the combined preparation (RR 0.54, 95% CI 0.43 to 0.68, $P < 0.00001$, $I^2 = 82\%$). When the combination of MBP and OAB was compared with OAB alone, there was no significant difference in the incidence of SSI (RR 0.98, 95% CI 0.64 to 1.50, $P = 0.92$, $I^2 = 77\%$) or anastomotic leak (RR 0.79, 95% CI 0.59 to 1.05, $P = 0.11$, $I^2 = 0\%$), although there was a significant reduction in 30-day mortality.² The two cohort studies^{3,5} comparing OAB alone with no preparation showed a significant benefit for OAB alone when the incidence of SSI (RR 0.56, 95% CI 0.38 to 0.83, $P = 0.004$, $I^2 = 81\%$) was considered. However, this evidence was largely gathered from retrospective cohort studies, as at the time of publication, there were no randomized controlled trials (RCT) comparing OAB alone or the combination of MBP and OAB with no preparation in elective colorectal surgery. In addition, in view of the I^2 values being $>50\%$ for

some of the analyses, denoting a high level of heterogeneity, the results should be interpreted with a degree of caution.

With the recent publication of the 'mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy (MOBILE)' RCT (n=396)⁷ and the ORALEV RCT (n=536),⁸ which compared OAB alone with no preparation in patients undergoing colonic surgery, the debate seems set to continue. We, therefore, aimed to determine whether the results of the MOBILE⁷ and ORALEV⁸ studies altered the conclusions of our recently published meta-analysis.²

We have updated the literature search and re-performed the previously published meta-analysis² in accordance with the PRISMA guidelines and following the methods used previously,² comparing OAB alone or combined MBP and OAB with no preparation. The end-points included SSI, anastomotic leak rate, 30-day mortality and development of postoperative ileus.

Of the 43 additional studies identified in the literature search, only the MOBILE⁷ and ORALEV⁸ studies provided additional data. When re-analyzed, the addition of these data to those from previously identified cohort studies³⁻⁶ did not alter the overall results when the four end-points of SSI, anastomotic leak rate, 30-day mortality and development of postoperative ileus were considered (Table 1).

The lack of impact of the MOBILE⁷ and ORALEV⁸ studies on the updated results of the meta-analysis is likely in part due to the large sample size of one paper arising from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) database.⁵ The MOBILE study found an overall incidence of SSI of 6.6% (n=13/196) in the MBP+OAB group *versus* 10.5% (n=21/200) in the no preparation, a non-significant difference

($P=0.17$). It is interesting to note that in the previously published meta-analysis,² the reduction in the incidence of SSI associated with combined MBP+OAB over no preparation was a statistically significant 4.4% [$n=894/21508$ (4.2%) *versus* $1300/15134$ (8.6%), $P<0.00001$]. The MOBILE study was powered to detect an 8% absolute difference in the incidence of SSI, with the authors' estimate of a 5% SSI rate in those receiving combined MBP and OAB *versus* 13% in the no preparation group. There is clearly significant discrepancy between the estimates used in the power calculation and data provided by other studies on the topic and the recently published meta-analysis, raising the question of a type II error. Based on a reduction of SSI from 11% with no bowel preparation to 7% with a combination of MBP and OAB, an RCT with an α error of 0.05 and a power of 80% would need to recruit approximately 900 participants in each arm to detect a statistically significant difference. The largest study on the use of MBP, OAB and no preparation arising from the ACS NSQIP® database⁵ concerning the incidence of SSI found that those patients receiving combined MBP and OAB ($n=16,860$) had an overall SSI rate of 2.9% *versus* a rate of 6.7% in those who received no preparation ($n=11,898$) *versus* 4.6% in those who received OAB alone ($n=1,791$). Other issues surrounding the generalizability of this study include the very high laparoscopic rate in the series (78%) as well as the significant preponderance of right sided resections (56%), both of which are likely to have a knock-on effect on the incidence of SSI in the study population. However, it must be emphasized that the data from the MOBILE study⁷ did not suggest any difference in overall postoperative morbidity as the mean Comprehensive Complication Index,⁹ which is currently thought to be most accurate method to measure postoperative morbidity, was 9.0 in the no preparation group and 10.0 in the combined MBP and OAB group ($P=0.46$). The MOBILE study⁷ is a well conducted study

and despite the possibility of a Type II error, it raises the question of whether the results of retrospective cohort studies should trump those of RCTs.

On the other hand, the ORALEV study⁸ found that the SSI rate was significantly lower in the OAB alone group when compared with the no OAB group [4.9% (n=13/267) *versus* 11.2% (n=30/269), P=0.013], along with an overall reduction in all complications (19.1% *versus* 28.3%, P=0.017). The sample size was calculated on the basis of an expected incidence in SSI of 17% with no OAB and of 7.5% with OAB. These data are also consistent with those obtained from retrospective cohort studies^{3,5} and suggest that OAB preparation alone is beneficial when compared with no preparation, and obviates the side effects and patient acceptability issues associated with the addition of MBP.

There are well defined benefits and potential limitations associated with the two differing study methodologies. RCTs are tightly controlled studies with prospectively defined inclusion and exclusion criteria, interventions and clear end-points. Hence, they are considered to be the 'gold standard' level of evidence. However, criticisms of this methodology include the potential limited generalizability of the study findings to real world practice. In contrast, observational studies tend to have considerably wider study populations without such strict eligibility criteria and as such are a more representative body of evidence which is transferrable to clinical practice. Although retrospective cohort studies use "real world" data, if the records used were not designed for the study, the available data may be of poor quality. In addition, there may also be a paucity of data on potential confounding factors and a selection bias cannot be ruled out.

A recent survey¹⁰ of 495 respondents from the Association of Coloproctology of Great Britain and Ireland found that OAB preparation and combined MBP and OAB was used

routinely in just 12-20% and 5.5-18.6% of patients undergoing elective colorectal surgery, respectively. This is despite 53% of respondents believing that combined MBP and OAB reduced SSI rates, and 32% believing that it resulted in a reduction in anastomotic leak rates. This practice is very much in contrast to that in the USA, where a recent survey of members of the American Society of Colon and Rectal Surgeons¹¹ found that 83.2% of respondents routinely administer preoperative OAB preparation, with 98.6% using MBP routinely. In the face of mounting evidence supporting the benefits associated with MBP and OAB administration in elective colorectal surgery, the adjustment of consensus statements to support their routine use¹² and a shift in the support for OAB preparation amongst surgeons, particularly in the USA, the practice appears to be gaining momentum. One remaining question is that of the comparability of combined MBP and OAB *versus* OAB alone, with previous observational studies^{5, 13} and a meta-analysis² providing potential support for the role of OAB alone in terms of the equivalent reduction of SSI and anastomotic leak rates.

The definitive evidence on the question of combined MBP and OAB or OAB alone remains elusive, but the debate is gaining momentum. The high heterogeneity ($I^2 > 50\%$) in some of the outcomes of the meta-analyses suggest that the current data are far from conclusive. A high quality, well-designed, appropriately powered multicenter (and even multi-national) study that randomizes participants to three groups to receive no preparation, OAB alone or a combination of MBP and OAB will, perhaps, provide a definitive answer to this question and resolve the debate.

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Table 1: Results of re-analysis of effect of combined mechanical bowel preparation and oral antibiotics or oral antibiotics alone *versus* no preparation in elective colorectal surgery

Combined mechanical bowel preparation (MBP) and oral antibiotics (OAB) <i>versus</i> no preparation			
Outcome measure	Data analyzed	Total sample size (n)	Risk ratio (RR)
Surgical site infection	5 studies ³⁻⁷	MBP+OAB: 21,704 No prep.: 15,334	RR 0.54, 95% CI 0.44 to 0.69, P<0.00001, $I^2=76\%$ (favors MBP+OAB)
Anastomotic leak	3 studies ⁵⁻⁷	MBP+OAB: 17,347 No prep.: 12,399	RR 0.52, 95% CI 0.46 to 0.59, P<0.00001, $I^2=3\%$ (favors MBP+OAB)
30-day mortality	2 studies ^{6,7}	MBP+OAB: 487 No prep.: 501	RR 0.54, 95% CI 0.17 to 1.74, P=0.30, $I^2=0\%$ (no difference)
Development of postoperative ileus	3 studies ^{4,5,7}	MBP+OAB: 18,013 No prep.: 13,055	RR 0.80, 95% CI 0.62 to 1.02, P=0.07, $I^2=59\%$ (no difference)
Oral antibiotics (OAB) alone <i>versus</i> no preparation			
Outcome measure	Data analyzed	Total sample size (n)	Risk ratio (RR)
Surgical site infection	3 studies ^{3,5,8}	OAB: 2,781 No prep.: 14,145	RR 0.54, 95% CI 0.39 to 0.74, P=0.0002, $I^2=66\%$ (favors OAB)
Anastomotic leak	2 studies ^{5,8}	OAB: 2,058 No prep.: 12,167	RR 0.69, 95% CI 0.53 to 0.91, P=0.008, $I^2=0\%$ (favors OAB)
30-day mortality	2 studies ^{5,8}	OAB: 2,058 No prep.: 12,167	RR 0.58, 95% CI 0.34 to 0.98, P=0.04, $I^2=0\%$ (favors OAB)

CI=confidence interval