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**Pharmacological interventions for improved colonic anastomotic healing: A meta-analysis**

Øines MN *et al*. Pharmacological enhancement of anastomotic healing

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**Abstract**

**AIM:** To identify pharmaceuticals for the prophylaxis of anastomotic leakage (AL), we systematically reviewed studies on anastomosis repair after colorectal surgery.

**METHODS:** We searched PubMed and EMBASE for articles published between January 1975 and December 2012. We included studies in English with the primary purpose of promoting healing of anastomoses made in the colon or rectum under uncomplicated conditions. We excluded studies on adverse events from interventions, nutritional interventions or in situ physical supporting biomaterials. The primary outcome was biomechanical strength or AL. We performed meta-analyses on therapeutic agents investigated by three or more independent research groups using the same outcome. The DerSimonian-Laird method for random effects was applied with *P* < 0.05.

**RESULTS:** Of the 56 different therapeutic agents assessed, 7 met our inclusion criteria for the meta-analysis. The prostacyclin analog iloprost increased the weighted mean of the early bursting pressure of colonic anastomoses in male rats by 59 mmHg (95%CI: 30-89) *vs* the controls, and the immunosuppressant tacrolimus increased this value by 29 mmHg (95%CI: 4-53) *vs* the controls. Erythropoietin showed an enhancement of bursting pressure by 45 mmHg (95%CI: 14-53). The anabolic compound growth hormone augmented the anastomotic strength by 21 mmHg (95%CI: 7-35), possibly *via* the up-regulation of insulin-like growth factor-1, as this growth factor increased the bursting pressure by 61 mmHg (95%CI: 43-79) *via* increased collagen deposition. Hyperbaric oxygen therapy increased the bursting pressure by 29 mmHg (95%CI: 3-55). Broad-spectrum matrix metalloproteinase inhibitors increased the bursting pressure by 48 mmHg (95%CI: 31-66) on postoperative days 3-4. In the only human study, the AL incidence was not significantly reduced in the 103 colorectal patients treated with aprotinin (11.7%) compared with the 113 placebo-treated patients (9.7%).

**CONCLUSION:** This systematic review identified only one randomized clinical trial and seven therapeutic agents from pre-clinical models that could be explored further for the prophylaxis of AL after colorectal surgery.

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**Key words:** Anastomotic healing; Colorectal surgery; Experimental; Breaking strength; Bursting pressure; Collagen; Meta-analysis

**Core tip:** Anastomotic leakage after colorectal surgery is an ongoing challenge and results in high morbidity and mortality. Currently, there is no pharmaceutical compound specifically indicated for the improvement of anastomotic healing. This situation is remarkable considering the many interventions that have been assessed under experimental conditions. This study reviewed 56 therapeutic agents investigated in 75 separate studies. Iloprost, tacrolimus, erythropoietin, growth hormone, insulin-like growth factor-1, hyperbaric oxygen and matrix metalloproteinase inhibitor therapies reproducibly improved anastomosis stability in experimental models. These therapies, alone or in combination, should be explored further.

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**INTRODUCTION**

Surgical resection with primary anastomosis is a standard treatment for colorectal cancer and benign diseases, such as diverticulitis, ulcerative colitis and ischemia or for the reversal of an ostomy.

Surgical techniques have been optimized to restore intestinal continuity without compromising blood supply. Nevertheless, the incidence of anastomotic leakage (AL) is 3%-6% after colonic section and 10%-12% after rectal resection[1,2]. AL increases short-term morbidity, permanent stoma rates and mortality. Furthermore, AL contributes to the recurrence of malignant disease[3]. Risk factors for AL include age older than 60 years, male sex, low serum albumin, prolonged surgery, increased intraoperative blood loss and blood transfusions.

Although the negative impact of corticosteroids[4] and non-steroidal anti-inflammatory drugs[5] have been well documented, there have been no pharmaceutical compounds specifically indicated for the improvement of anastomotic healing. This is remarkable considering the many interventions that have been assessed under experimental conditions. It is even more surprising that this extremely valuable source of scientific data has not been assessed, either critically or systematically in terms of suitability for the prophylaxis of AL in patients.

One reason for this lack of data could be that spontaneous dehiscence and AL have been extremely rare in experimental models. Therefore, we have had to rely on surrogate outcomes of anastomotic repair. The most common measures are the bursting pressure (BPR) and the breaking strength (BST). BPR measurements reflect the resistance to increased intraluminal pressure, and BST indicates increased longitudinal load. BPR and BST are minimal in the early postoperative period, reflecting the fragility of the anastomosis at this stage, but they increase rapidly beginning on postoperative day 3[6-8]. Clinically, AL symptoms usually appear at postoperative days 5-8, while biochemical markers indicate that the intestinal connection dehisces earlier[9].

The aim of the present study was to provide a systematic and comprehensive review of pharmacological stimulation of anastomotic healing to identify compounds potentially capable of preventing AL.

**MATERIALS AND METHODS**

***Methods***

This systematic review followed the PRISMA guidelines[10].

***Data sources and searches***

The PubMed and EMBASE databases were searched for articles published between January 1975 and December 2012 using two different syntaxes: search 1, anastomo and (colon or rect) and (strength or pressure); and search 2, anastomo and (colon or rect) and leak not (strength or pressure) and experimental. The references of the included studies were searched manually.

***Inclusion and exclusion criteria***

We included controlled studies published in English that primarily investigated a therapeutic agent with the purpose of promoting colonic anastomotic healing under uncomplicated conditions, measured as BPR, BST or AL.

We excluded studies on interventions assessed under complicated conditions, such as intestinal ischemia, generalized peritonitis, colitis, large bowel obstruction, jaundice, diabetes, radiation, malnutrition or the presence of an ostomy. Furthermore, studies with the primary aim of investigating the adverse events associated with therapeutic agents were excluded. The influences of nutritional interventions were similarly excluded. Finally, the effects of mechanical enforcement, such as fibrin sealants, omental pedicle grafts or carboxymethylcellulose coatings, of anastomoses were recently reviewed and thus were excluded here[11].

***Data extraction***

The titles of the articles were retrieved and screened. Subsequently, the abstracts or the full texts of potentially relevant publications were scrutinized for eligibility. At least two authors decided whether a paper qualified. Disagreements were resolved by discussion among the four authors. The abstracted data included the investigated compound, dosage, route of administration, species, sex, sample size, assessment day and primary outcome of the study.

***Statistical analysis***

Therapeutic agents investigated by at least 3 independent research groups using the same primary outcome were subjected to meta-analysis. Pooled estimates were calculated using the inverse-variance weighting method with the DerSimonian-Laird random-effects model. Heterogeneity among the studies was determined using *I*2 tests. Analyses were conducted using Review Manager, version 5.1 (The Cochrane Collaboration). The level of statistical significance was *P* < 0.05.

**RESULTS**

We included 75 studies (Figure 1) that were performed in rats (*n* = 68), rabbits (*n* = 4), guinea pigs (*n* = 1), dogs (*n* = 1) and humans (*n* = 1). The most frequently reported outcome was BPR (*n* = 62), followed by BST (*n* = 19), whereas only one study used AL.

We identified 56 different compounds that were sub-grouped into immunomodulators (*n* = 20), hormones and growth factors (*n* = 14), miscellaneous (*n* = 15) and proteinase inhibitors (*n* = 7).

***Immunomodulators***

Of the 20 different immunomodulating compounds identified in the search, data for iloprost[12-14] and tacrolimus[15-17] were subjected to meta-analysis (Table 1). This analysis demonstrated that iloprost increased the weighted mean of the early bursting pressure by 59 mmHg (95%CI: 30-89, *P* < 0.0001) *vs* the controls (Figure 2A). The corresponding figure for tacrolimus was 29 mmHg (95%CI: 4-53, *P* = 0.02) (Figure 2B).

Recombinant human granulocyte macrophage-colony stimulating factor increased BPR on days 3 and 7 in one study[18], but this treatment was found to be ineffective in two other studies[19,20]. Interleukin-2 decreased both BPR and BST in male rats[21]. Both parthenolide and resveratrol increased BPR on day 7 but not on days 3 or 5 in one study[22,23], while resveratrol increased BPR on both day 3 and day 7 in another study[22,23].

Immunomodulating interventions assessed in single studies that reported increased anastomotic integrity included prostaglandin E1[24], cholera toxin[25], bacteria from rat colon[26] and noxythyoline[27]. CD18 antibody[28], *Escherichia coli*[26], *Lactobacillus* *acidophilus*[26], *Lactobacillus* *helveticus*[29], *Streptococcus thermophiles*[29], mesalamine[30], p38 mitogen-activated kinase protein inhibitor[8], activated protein C[31], pyrrolidine dithiocarbamate[32] and trapidil[33] showed no statistically significant effects on anastomotic biomechanical strength.

***Hormones and growth factors***

In this category, sufficient data for the meta-analysis were available for erythropoietin (EPO)[19,34-37], growth hormone (GH)[38-43] and insulin-like growth factor (IGF)-1[44-47] (Table 2). The meta-analyses showed that EPO increased BPR by 45 mmHg (95%CI: 14-53, *P* = 0.004) (Figure 2C), GH increased BPR by 21 mmHg (95%CI: 7-35, *P* = 0.004) (Figure 2D) and IGF-1 increased BPR by 61 mmHg (95%CI: 43-79, *P* < 0.00001) *vs* the controls (Figure 2E).

In addition to these substances, full-length or truncated keratinocyte growth factor increased anastomotic strength on postoperative days 2-7[44,48]. Compounds investigated in isolated studies reporting enhancement of anastomotic healing included triiodothyronine[49], epidermal growth factor[50], vascular endothelial growth factor[51], leptin[52] and platelet-rich-plasma[53]. In contrast, no significant effects on anastomotic strength were found with locally applied platelet-derived growth factor-BB[54], long-acting glucagon-like peptide-2[55], melatonin[56], octreotide[57] or ranitidine[58].

***Miscellaneous***

Although the results from animal studies on oxygen therapy were inconsistent[59-62] (Table 3), hyperbaric oxygen significantly increased BPR by 29 mmHg (95%CI: 3-55, *P* = 0.03) in the meta-analysis (Figure 2F). However, the sole human study on oxygen therapy that we retrieved was recently retracted by the journal that published it[63].

Gentamicin, administered systemically and locally, increased BPR on day 5 but not on day 3 in two separate studies[64,65]. Kanamycin in combination with erythromycin was more effective than kanamycin alone in increasing BS of colonic anastomoses on day 7 in dogs[66]. The calcium channel blocker nifedipine increased BPR on days 3 and 7 in one study[67]. Phenytoin increased BPR on days 3 and 7, either by oral or rectal administration at clinically relevant dosages[68]. Male rats that received pharmacological doses of vitamin A for five days preoperatively and for six days postoperatively showed increased BPR[69]. Simvastatin orally administered to rats resulted in increased BPR on days 3 and 7[70]. Zinc intraperitoneally administered to rabbits increased BPR on day 7[71] but showed no significant effect on BST on days 3 or 7 in male rats given an equivalent zinc dosage[72]. Heparin had no effect on BST, but low-molecular-weight heparin increased BST at day 7[73]. A dextran derivative with heparin-like properties increased BPR by more than two-fold on day 2 but not at later time points in two separate studies[74,75]. Albumin[76], colloid[77] and hydroxyethyl starch[76,78] had no significant impacts on anastomotic strength.

*Proteinase inhibitors*

Matrix metalloproteinase (MMP) inhibitors, including AG3340[8], BB-94[79], BB-1101[7], BE166227B[80], doxycycline[81,82] and GM6001[8], consistently resulted in improved anastomotic strength on postoperative days 3-4 but not later (Table 4). The meta-analysis of the three studies using the outcome of BPR showed a weighted mean increase in BPR of 48 mmHg (95%CI: 31-66 mmHg, *P* < 0.00001) *vs* the vehicle. The studies that used BST as an outcome measurement demonstrated a significant increase in the weighted mean of BST of 0.45 N (95%CI: 0.27-0.63, *P* < 0.00001) (Figure 3A). In a study on GM6001, light microscopic examination revealed a pronouncedly smaller longitudinal wound gap compared with vehicle-treated animals (Figure 3B)[8].

Aprotinin increased BPR in rabbits at postoperative days 4 and 7[83,84]. In addition, aprotinin treatment increased the absolute change in collagen concentration from day 0 more than in the controls[84]. In sharp contrast**,** aprotinin attenuated BPR in rats on day 15[85]. In the single human study, 103 patients were randomized to aprotinin and 113 to the placebo[86]. The incidence of AL in the placebo group (9.7%) was not significantly reduced with aprotinin (11.7%), which was administered in a dosage similar to that given in the experimental studies[83,84]. Post hoc analyses indicated reduced AL in the aprotinin-treated patients who underwent low anterior rectal resections, while those subjected to left hemicolectomy or sigmoid colectomy had more AL[86].

**DISCUSSION**

***Summary of results***

We reviewed the data on 56 different therapeutic agents intended to promote anastomotic wound healing with the purpose of identifying interventions with prophylactic potential in colorectal AL. Approximately half of these agents were assessed in one study only. To obtain more robust conclusions, we performed a meta-analysis of the products that were tested by three or more independent research groups. Meta-analyses were undertaken for iloprost, tacrolimus, EPO, GH, IGF-1, hyperbaric oxygen and MMP inhibitors. These therapies reproducibly improved anastomotic stability in uncomplicated pre-clinical models. Thus, exploration of these agents, alone or in combination, would be the next step in the search for effective interventions for AL prophylaxis.

***Anastomotic wound healing***

Anastomotic healing follows the chronological phases of tissue repair, which are largely regulated by cytokines and growth factors[6,87,88]. The initial hemostatic response results in a fibrin/fibronectin matrix that temporarily seals and connects the two bowel ends. Subsequently, inflammatory cell infiltration contributes to loss of the existing collagen of the adjacent submucosa by tissue-destructive proteinases, notably MMPs[89]. From postoperative day 3, the provisional matrix is gradually converted into granulation tissue, which contains many new blood vessels, macrophages and fibroblasts[89]. The collagen synthesis rate then increases dramatically and peaks on days 6-7[90]. BST, but not BPR, was correlated with the increase in collagen deposited in the anastomosis during the first week[90].

Anastomotic repair can be improved *via* different non-overlapping mechanisms, including inhibition of the degradation of submucosal collagen, promotion of angiogenesis and acceleration of granulation tissue deposition and epithelialization.

***Discussion of the seven candidate pharmaceuticals***

The prostacyclin analog iloprost enhanced anastomotic strength, possibly through increased neoangiogenesis and intestinal blood perfusion[13,14]. Tacrolimus also improved anastomotic healing, and light microscopy revealed reduced inflammatory cell infiltration and preserved morphology of the two colonic ends in the tacrolimus group[15]. However, tacrolimus is an immunosuppressive drug that targets T-cell activation and interleukin-2 transcription[15-17]. Based on these results, iloprost is a potential candidate for further exploration, while tacrolimus is not due to its general immunosuppressive effects.

Although the main indication for EPO is anemia, its non-hematopoietic properties could have positive effects on anastomotic healing[91]. EPO treatment also enhanced anastomotic strength under normal situations. Interestingly, improved BPR coincided with reduced MMP-8 expression in anastomotic wounds[35]. A more obvious place for EPO therapy would perhaps be under complicated situations, such as ischemia.

The beneficial effect of GH on anastomotic strength was reproduced on postoperative days 2-4 when administered at a dosage of 2.0 mg/kg/d or more[38-43]. The positive effects could be ascribed to earlier deposition and reorganization of neocollagen in anastomotic wound gaps[41,42]. Similarly, overexpression of GH profoundly stimulated early granulation tissue formation in wounds[92]. One caveat is that most of the studies were performed in female animals. GH treatment was seemingly less effective in male rats, possibly due to the negative influence of testosterone on wound healing[93]. GH stimulated hepatic synthesis of IGF-1, which is believed to mediate the local effects of GH[46]. Exogenous IGF-1 also raised anastomotic collagen levels and anastomotic strength when administered intraperitoneally[44-47]. However, the systemic adverse effects of GH and IGF-1 and the possible danger of using mitogenic substances in colorectal cancer patients might disqualify these agents from further exploration in clinical trials. To circumvent the risk of harm, IGF-1 could be delivered locally[94].

Oxygen therapy for anastomotic wound healing is theoretically attractive. In a series of elegant experiments, Shandall *et al*[95] demonstrated a strong positive correlation between tissue oxygen tension and the breaking strength of colon anastomoses, largely due to increased hydroxyproline. The results here were inconsistent, although there was a statistically significant, but mediocre, increase in BPR with hyperbaric oxygen therapy[59-61]. On the other hand, hyperbaric oxygen therapy increased intra-abdominal adhesions[96]. Interestingly, a more clinically useful regimen, with 50% oxygen at atmospheric pressure, was ineffective[61]. This outcome agrees with the findings of the PROXI trial, in which no significant effect of supplemental oxygen on anastomotic dehiscence was observed[97]. The PROXI trial was excluded here because AL was not the primary outcome, and patients undergoing emergency surgery were also enrolled.

MMPs comprise a 23-member family of human zinc-dependent endopeptidases[98]. While extracellular matrix remodeling by MMPs is part of the normal physiological response to injury[98], increased activity of MMPs could be deleterious to anastomotic strength due to excessive collagen degradation[89]. Synthetic MMP inhibitors unequivocally improved anastomotic integrity. Kiyama *et al*[80] attributed the increased mechanical strength to more collagen fibers in the wound gap connecting the large bowel ends. Morphologically, the smaller wound gap observed after administration of GM6001 strongly suggested that MMP inhibitors protected the existent submucosal collagen network from degradation[8]. Intuitively, this observation also indicated a decreased risk of leakage of the intraluminal content into the peritoneal cavity[8]. Interestingly, GM6001 treatment did not increase the formation of intra-abdominal adhesions[99].

***Limitations***

The pathogenesis of AL is multifactorial. The studies in our review used surrogate outcomes that could not be directly translated into clinical AL. Furthermore, there was only one study conducted in patients who were subjected to colorectal surgery.

Neither the quality nor publication bias of the included studies was evaluated here because the studies were too small in sample size and too few in number[100].

The efficacy of a therapeutic agent depends on the conditions in which the anastomoses are constructed. We chose to focus on studies investigating anastomotic healing under uncomplicated conditions because these cases are representative of the majority of patients with colorectal cancer[101-103].

To conclude, despite these limitations, our review indicated several promising therapeutic agents for the prevention of AL.

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**COMMENTS**

***Background***

Anastomotic leakage (AL) is a very serious and common complication that typically follows surgical removal of colorectal cancer. Any prophylactic intervention would thus have an enormous socioeconomic impact. However, to date, there have been no pharmaceutical interventions available, despite this urgent medical need. This situation is remarkable, considering the many interventions that have been assessed under experimental conditions.

***Research frontiers***

The study was the first to systematically review studies on compounds that could potentially improve anastomotic wound healing and prevent AL.

***Innovations and breakthroughs***

The search identified 56 different therapeutic agents. Sufficient published data for a meta-analysis were available for iloprost, tacrolimus, erythropoietin, growth hormone, insulin-like growth factor-1, hyperbaric oxygen therapy and broad-spectrum matrix metalloproteinase inhibitors.

***Applications***

This review identified 7 therapeutic substances from pre-clinical studies. These interventions were considered promising enough that they could be explored further, alone or in combination, for AL prophylaxis.

***Terminology***

Anastomotic leakage occurs when surgically joined intestinal ends dehisce, resulting in contamination of the abdominal cavity with intestinal contents, leading to peritonitis or sepsis.

***Peer review***

This study reviewed 56 therapeutic agents investigated in 75 studies, and it provides important information about possible pharmaceutical candidates. The results could be helpful in improving colonic anastomotic healing.

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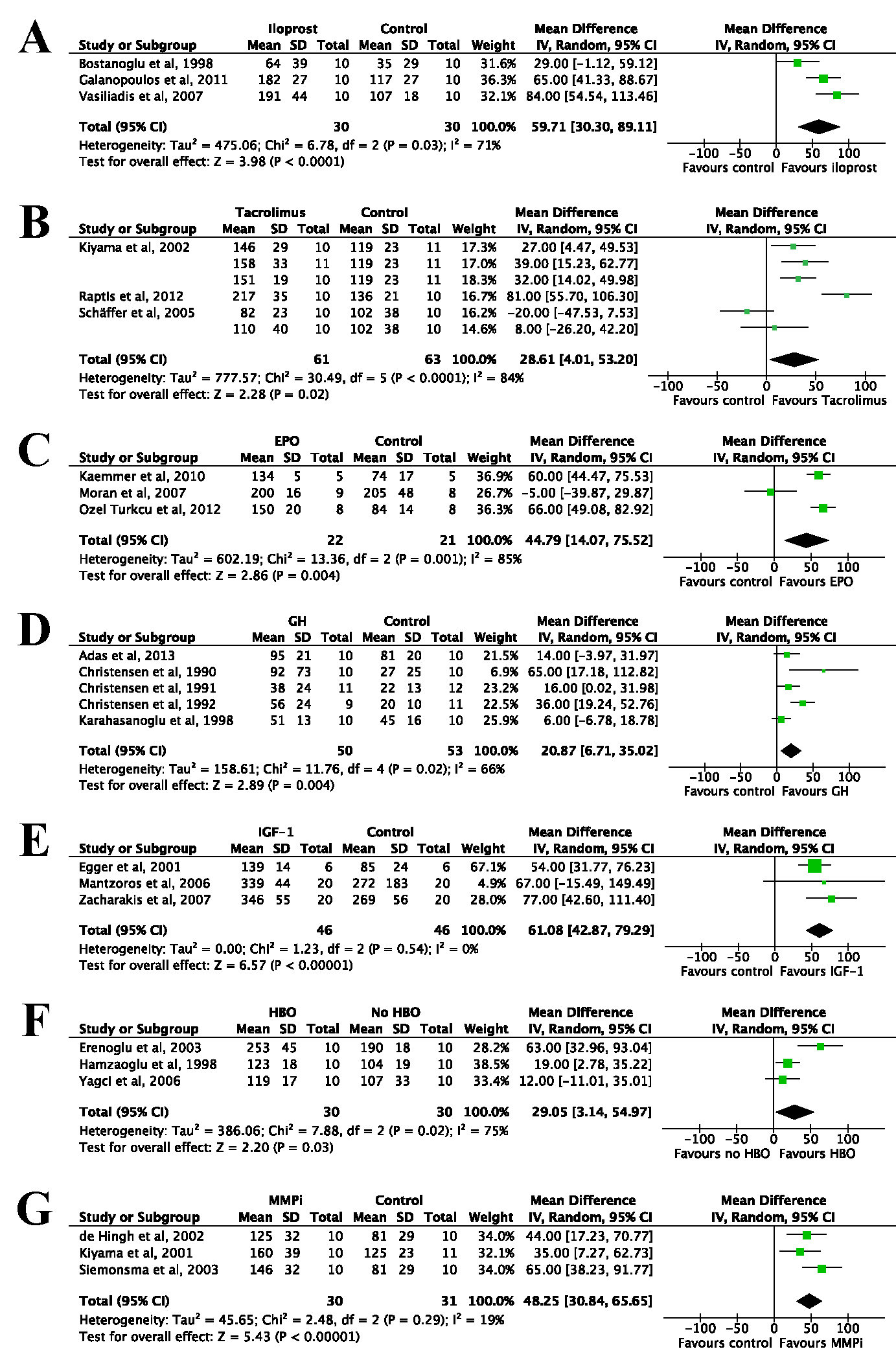
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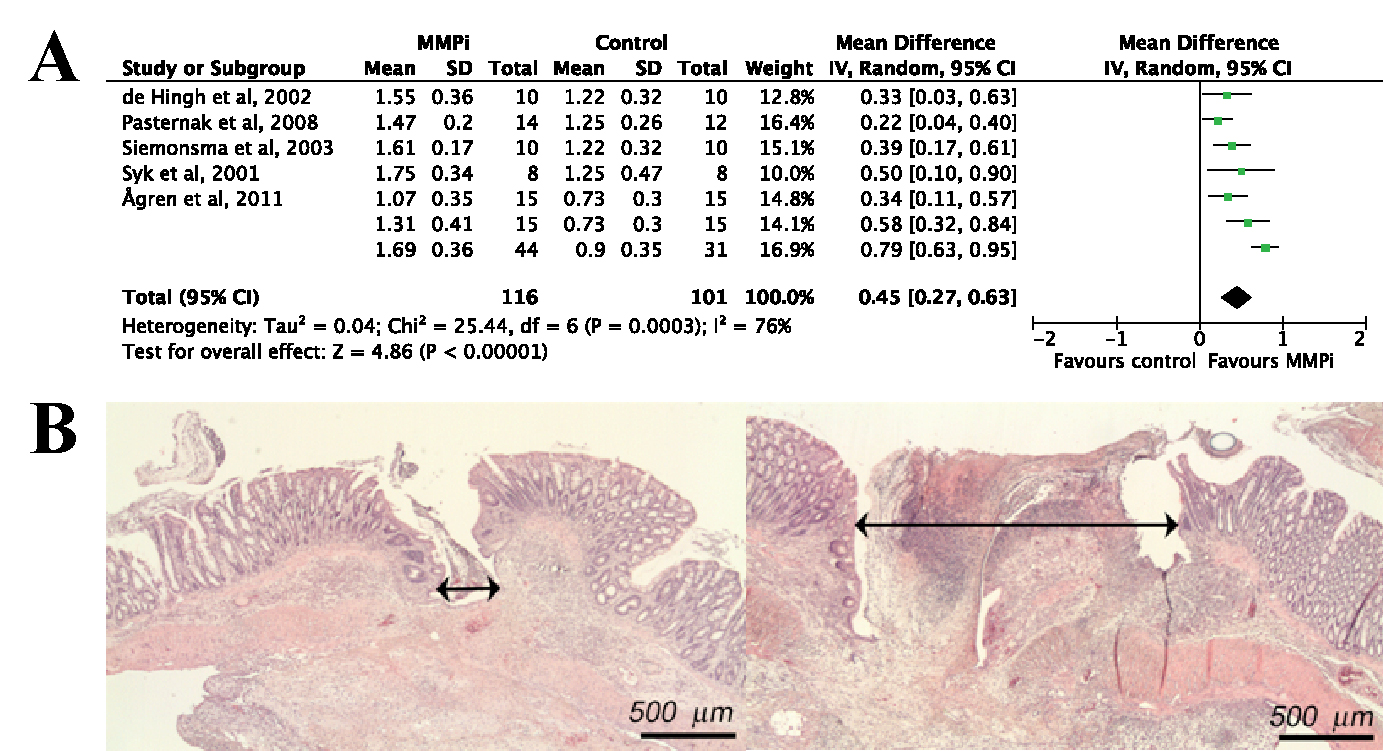
**P-Reviewers:** Regimbeau JM, Yu B **S-Editor:** Gou SX  **L-Editor: E-Editor:**

**Figure 1 Flow diagram of the studies that were identified and selected**.

**Figure 2 Forest plots of the bursting pressure in mmHg.** The results of the meta-analysis for A: Iloprost at days 3-5 (*cf.* Table 1); B: Tacrolimus (*cf.* Table 1); C: Erythropoietin (EPO) at days 5-7 (*cf.* Table 2); D: Growth hormone (GH) at day 4 (*cf.* Table 2); E: Insulin-like growth factor-1 (IGF-1) at days 4-7 (*cf.* Table 2); F: Hyperbaric oxygen (HBO) (*cf.* Table 3); G: Broad-spectrum matrix metalloproteinase inhibitors (MMPi) at days 3-4 (*cf.* Table 4).



**Figure 3 Effects of broad-spectrum matrix metalloproteinase inhibitors on anastomotic breaking strength (A) and morphology (B) on postoperative day 3.** A: Forest plot of the results of the meta-analysis in N (*cf.* Table 4); B: Diminution of the gap between the two large bowel ends after treatment with the broad-spectrum matrix metalloproteinase inhibitors (MMPi) GM6001 (left image) compared with the vehicle treatment (right image). The photomicrographs are representative of the overall significant (*P* < 0.05) effect of GM6001 (median: 320 μm) compared with the vehicle (median: 900 μm)[8].



**Table 1 Studies on the immunomodulators iloprost and tacrolimus in colonic anastomotic healing**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Compound** | **Species** | **Sex** | **Sample size1** | **Dosage (mg/kg)** | **Route** | **Test** | **Test day** | **Effects2** |
| Bostanoglu *et al*[12], 1998 | Iloprost | Rat | Male | 40 | 0.002 | IP | BPR | 3/7 | ↑82/NS |
| Galanopoulos *et al*[13], 2011 | Iloprost | Rat | Male | 40 | 0.002 | IP | BPR | 4/8 | ↑56/NS |
| Vasiliadis *et al*[14], 2007 | Iloprost | Rat | Male | 20 | 0.002 | IP | BPR | 5/8 | ↑78/NS |
| Kiyama *et al*[15], 2002 | Tacrolimus | Rat | Male | 42 | 0.01/0.1/1.0 | SC | BPR | 4 | ↑23/↑33/↑27 |
| Raptis *et al*[16], 2012 | Tacrolimus | Rat | Male | 40 | 0.1 | SC | BPR | 4/8 | ↑60/↑43 |
| Schäffer *et al*[17], 2005 | Tacrolimus | Rat | Male | 24 | 2.0 | SC | BPR | 5 | NS |

1Total number of animals; 2↑% increase (*P* < 0.05) or ↓% decrease (*P* < 0.05) *vs* controls; NS: Not statistically significant;

BPR: Bursting pressure; IP: Intraperitoneal; SC: Subcutaneous.

**Table 2 Studies on the hormones erythropoietin and growth hormone, and the growth factor insulin-like growth factor-1 in colonic anastomotic healing**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Compound** | **Species** | **Sex** | **Sample size1** | **Dosage2** | **Route** | **Test** | **Test day** | **Effects3** |
| Faruquzzaman *et al*[34], 2009 | EPO | Guinea pig | Male | 20 | 500 | SC | BPR | 7 | NS |
| Fatouros *et al*[19], 1999 | EPO | Rat | Male | 30 | 500 | SC | BST | 7 | ↑37 |
| Kaemmer *et al*[35], 2010 | EPO | Rat | Male | 20 | 5000 | SC | BPR | 3/5 | NS/↑82 |
| Moran *et al*[36], 2007 | EPO | Rat | Male | 20 | 500 | SC | BPR | 7 | NS |
| Ozel Turkcu *et al*[37], 2012 | EPO | Rat | Male | 16 | 500 | IM | BPR | 7 | ↑93 |
| Adas *et al*[38], 2013 | GH | Rat | Male | 20 | 2.0 | SC | BPR | 4 | ↑16 |
| Christensen *et al*[39], 1990 | GH | Rat | Female | 72 | 2.0 | SC | BPR | 2/4/6 | ↑104/↑232/NS |
| Christensen *et al*[40], 1991 | GH | Rat | Female | 72 | 2.0 | SC | BPR | 2/4/6 | ↑55/NS/NS |
| Christensen *et al*[41], 1992 | GH | Rat | Female | 50 | 0.125/0.5/2.0/8.0 | SC | BPR | 4 | NS/NS/↑270/↑430 |
| Christensen *et al*[42], 1994 | GH | Rat | Female | 36 | 2.04-6 | SC | BST | 4 | NS/↑34/↑59 |
| Karahasanoglu *et al*[43], 1998 | GH | Rat | Male | 20 | 2.0 | SC | BPR | 4 | ↑11 |
| Egger *et al*[44], 2001 | IGF-1 | Rat | Male | 76 | 1.0 | IP | BPR | 2/4/6 | ↑62/↑67/↑61 |
| Mantzoros *et al*[45], 2006 | IGF-1 | Rat | Female | 40 | 2.0 | IP | BPR | 7 | ↑25 |
| Petersen *et al*[46], 1996 | IGF-1 | Rat | Female | 26 | ~2.5 | SC | BST | 3 | NS |
| Zacharakis *et al*[47], 2007 | IGF-1 | Rat | Male | 40 | 2.0 | IP | BPR | 7 | ↑29 |

1Total number of animals; 2EPO: IU/kg; GH: mg/kg; IGF-1: mg/kg; 3↑% increase (*P* < 0.05) or ↓% decrease (*P* < 0.05) *vs* controls; NS: Not statistically significant; 4Preoperative; 5Postoperative; 6Preoperative and postoperative. BPR: Bursting pressure; BST: Breaking strength; EPO: Erythropoietin; GH: Growth hormone; IGF-1: Insulin-like growth factor-1; IM: Intramuscular; IP: Intraperitoneal; SC: Subcutaneous.

**Table 3 Studies on exogenous oxygen in colonic anastomotic healing**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Species** | **Sex** | **Sample size1** | **Dosage** | **Test** | **Test day** | **Effects2** |
| Erenoglu *et al*[59], 2003 | Rat | Male | 20 | Hyperbaric | BPR | 7 | NS |
| Hamzaoglu *et al*[60], 1998 | Rat | Male | 20 | Hyperbaric | BPR | 4 | ↑18 |
| Kirk *et al*[61], 1977 | Rat | Male | 36 | 50% | BWT | 7 | NS |
| Yagci *et al*[62], 2006 | Rat | Male | 40 | Hyperbaric3-5 | BPR | 5 | NS/NS/NS |

1Total number of animals; 2↑% increase (*P* < 0.05) or ↓% decrease (*P* < 0.05) *vs* controls; NS: Not statistically significant; 3Preoperative; 4Postoperative; 5Preoperative and postoperative. BPR: Bursting pressure; BWT: Bursting wall tension.

**Table 4 Studies on matrix metalloproteinase inhibitors in colonic anastomotic healing**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Compound** | **Species** | **Sex** | **Sample size1** | **Dosage (mg/kg)** | **Route** | **Test** | **Test day** | **Effect2** |
| de Hingh *et al*[79], 2002 | BB-94 | Rat | Male | 60 | 30 | IP | BPR/BST | 1 | NS/NS |
|  |  |  |  |  |  |  | BPR/BST | 3 | ↑54/↑27 |
|  |  |  |  |  |  |  | BPR/BST | 7 | NS/NS |
| Kiyama *et al*[80], 2001 | BE16627B | Rat | Male | 21 | About 10 | SC | BPR | 4 | ↑28 |
| Pasternak *et al*[81], 2008 | Doxycycline | Rat | Male | 40 | NA | LO | BST | 3 | ↑17 |
| Siemonsma *et al*[82], 2003 | Doxycycline | Rat | Male | 80 | About 40 | SC | BPR/BST | 1 | NS/NS |
|  |  |  |  |  |  | SC | BPR/BST | 3 | ↑93/↑27 |
|  |  |  |  |  |  | PO | BPR/BST | 3 | ↑36/NS |
|  |  |  |  |  |  | SC | BPR/BST | 5 | NS/NS |
| Syk *et al*[7], 2001 | BB-1101 | Rat | Male | 48 | 30 | SC | BST | 1/3/7 | NS/↑48/NS |
| Ågren *et al*[8], 2011 | AG3340 | Rat | Male | 80 | 10 | SC | BST | 3 | ↑43 |
|  | GM6001 | Rat | Male |  | 10/100 | SC | BST | 3 | ↑79/↑88 |

1Total number of animals; 2↑% increase (*P* < 0.05) or ↓% decrease (*P* < 0.05) *vs* controls; NS: Not statistically significant; BPR: Bursting pressure; BST: Breaking strength; IP: Intraperitoneal; LO: Local; NA: Not applicable; SC: Subcutaneous.