Perioperative non-hormonal Pharmacological Measures to Reduce Blood Loss During Open and Minimally Invasive Myomectomy: A Systematic Review and Network Meta-analysis

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Abstract

Background: To summarize evidence from randomized controlled trials(RCTs) on safety and efficacy of various blood loss-minimizing drugs during open(OM) and minimally invasive(MI) myomectomy.

Methods: We searched PubMed, Cochrane library, Scopus, Web of Science, and Google Scholar since inception till September 2023. We included RCTs of women undergoing OM or MI myomectomy(hysteroscopic or laparoscopic) who received vasopressin, misoprostol, oxytocin, carbetocin, tranexamic or ascorbic acids, and epinephrine. Study quality was assessed using Cochrane risk of bias 2(ROB2) tool. Effect measures were reported as risk ratios(RR) or mean differences[MD] with a 95% confidence interval[CI]. Primary outcomes were intraoperative blood loss & blood transfusion requirement.

Results: Sixty-one RCTs(n= 4932 patients) were included. In OM(48 RCTs, 3902 patients), Vasopressin plus Misoprostol were the best to decrease intraoperative blood loss(MD= -714.57, 95% CI -929.98 to -499.17),followed by Bupivacaine + Epinephrine(MD: -651.26, 95%CI -846.8 to -455.72). Also, Vasopressin + Misoprostol was the best in lowering need for blood transfusion(RR: 0.08, 95%CI 0.03 to 0.22),then Octreotide acetate(RR: 0.16, 95%CI 0.03 to 0.79). In MI myomectomy(13 RCTs, N=1030 patients), Oxytocin was the most effective in

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reducing operative blood loss(MD: -175.5, 95%CI -313.13 to -37.87), followed by Omipressin(MD: -149.6, 95%CI -212.8 to 86.4). Also, oxytocin is the most effective in lowering transfusion requirements(RR: 0.18, 95%CI 0.04 - 0.75),then vasopressin + misoprostol(RR: 0.17, 95%CI 0.01 to 4.27).

Conclusion: Vasopressin plus misoprostol and oxytocin could be beneficial in lowering need for blood transfusion and intraoperative blood loss during open and minimally invasive myomectomies, respectively. Nevertheless, quality of evidence is low(GRADE 2/4).

Synopsis: Vasopressin plus misoprostol and oxytocin were the best to decrease intraoperative bleeding and blood transfusion requirements in open and minimally invasive myomectomy, respectively.

Keywords: myoma/leiomyoma; myomectomy; blood loss; blood transfusion; pharmacological intervention.

Introduction

Uterine leiomyomas are benign monoclonal tumors developing from myometrial smooth muscle cells. Uterine leiomyomas are the most common pelvic tumors in females (1). Their frequency changes with age, and by age 50, they can be found in up to 80% of women, particularly in African American women (2). Clinically, fibroids cause one-third to half of all hysterectomies, leading to significant morbidity and healthcare costs for reproductive-age women (3). Symptomatic leiomyomas could be treated with medication therapy, myomectomy, hysterectomy, uterine artery embolization, radiofrequency ablation of fibroids, or High-intensity focused ultrasound (HIFU) (4). The choice of therapy should be individualized, considering family planning and desire for fertility or retaining the uterus (4).

Myomectomy is an operative procedure that involves surgical removal of leiomyomas from the uterus. This can be achieved by open/abdominal (OM), vaginal, or minimally invasive techniques, whether laparoscopic (LM) or hysteroscopic (HM) myomectomy. For individuals with symptomatic intramural, transmural, or subserosal leiomyomas who desire future childbearing, abdominal myomectomy is performed if hysteroscopic or laparoscopic myomectomy is non-feasible. Candidates for hysteroscopic myomectomy include FIGO type 0 or type 1 submucosal fibroids (≥50% within the uterine cavity) (3), while laparoscopic myomectomy is done for symptomatic intramural or subserosal leiomyomas with the intention of conserving the uterus or desire for future childbearing (5).

Myomectomy could be complicated by hemorrhage, fever and infection, adhesive disease, and, less commonly, visceral injury. Intraoperative blood loss is the most common complication, and hemorrhage could result from vascular injury, poor hemostasis, lack of surgeon experience, improper suturing, and variable characteristics of fibroids (6). Nearly 20% of myomectomy hemorrhages require blood transfusion, and up to 4 % of OM are converted to hysterectomy (7–10).

Several measures were developed to lower blood loss during abdominal or laparoscopic myomectomy(11). Preoperative measures include correction of anemia and preoperative GnRH agonists to reduce the likelihood of postoperative anemia. Intraoperative measures include pharmacological agents such as intramyometrial vasopressin, uterotonics, tranexamic acid, and carbetocin. Intraoperative mechanical techniques such as tourniquets, ligation of uterine or internal iliac arteries or embolization of uterine arteries, autologous blood transfusion, and intraoperative blood salvage were also used (9,12).

Samy et al. (11) studied safety and efficacy of various pharmacological therapies for myomectomy blood loss reduction; however, the small number of included studies constituted a limitation of their systematic review (26 trials). Moreover, multiple important studies have recently been published comparing

different hemorrhage-reducing drugs during myomectomy (13–15). Additionally, the optimal perioperative pharmaceutical strategy for myomectomy hemorrhage reduction remains unclear.

Therefore, we sought to update evidence regarding safety and effictiveness of several pharmacological measures in minimizing perioperative blood loss and blood transfusion requirements in patients having open, laparoscopic, or hysteroscopic myomectomy. Our aim was also to provide recommendations for the most suitable treatment in clinical practice.

Materials and Methods

We performed our network meta-analysis (NMA) following NMA extension of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (16). We followed guidelines provided by cochrane's handbook for systematic reviews of intervention for NMA (17). Study protocol was pre-registered on PROSPERO (ID; CRD42023477229). This study did not need formal ethical approval as a systematic review and meta-analysis.

2.1. Literature search

We systematically searched five electronic databases, namely PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar, from their inception till September 2023. Search strategy was based on finding all relevant articles about antihemorrhagic drugs in women undergoing myomectomy, whether open or minimally invasive. The search process was implemented by four experienced authors and revised by a specialized medical librarian. We searched all fields without limitations regarding study design or publication date (the search strategy is available through Supplemental Table 1). We searched reference lists of pertinent papers found throughout the search process for potentially eligible studies.

2.2. Eligibility criteria

We incorporated the subsequent PICOS criteria: (i) ***Population:*** symptomatic fibroid patients undergoing OM or MI myomectomy (LM or HM); (ii) Intervention; perioperative hemorrhage reducing drugs; misoprostol, vasopressin, oxytocics such as oxytocin or carbetocin, tranexamic acid, epinephrine, or ascorbic acid, (iii) ***Comparator***: placebo or no treatment or other active comparators with a reliable data for extraction; (iv) ***Outcomes***: primary outcomes were intraoperative blood loss and requirmenet for blood transfusion. Secondary outcomes included postoperative hemoglobin and hematocrit levels, hospital stay length, and postoperative fever incidence. (v) ***Study design***: RCTs. Excluded studies were those that did not meet the PICOS criteria. We excluded non-randomized trials, non-English articles, thesis and conference abstracts, abstracts where the main text was unavailable, unpublished studies, duplicate publications, and editorial materials.

Following the literature search, we exported search results to EndNote X8 for duplicate removal and then to an Excel sheet for formal screening. The screening method consisted of two sequential stages: evaluation by title and abstract screening, followed by a thorough examination of the full text for publications that met the criteria for possible eligibility. Five authors independently screened retrieved articles to check their network meta-analysis eligibility. We resolved any disagreements through discussion.

2.3. Data extraction

Two authors performed data extraction independently using a standardized form. Summary and participant characteristics of included trials were extracted: Author name, publication date, study design and country, study groups, sample sizes, myomectomy type, participants age and body mass index (BMI), uterine size (weeks), location of fibroid either intramural or subserosal, largest fibroid diameter (cm) and summary of study findings.

For efficacy endpoints, we extracted intraoperative blood loss (ml), preoperative and postoperative hemoglobin (g/dl), preoperative and postoperative hematocrit levels (%), length of hospital stays (days), and rate of blood transfusion. We grouped the results of laparoscopic and hysteroscopic myomectomy under the terminology of MI myomectomy as they fit in this definition, and the blood loss in those procedures is comparable.

For safety endpoints, we extracted rates of febrile morbidity and other complications. We extracted risk of bias (ROB) assessment domains and Grading of Recommendations Assessment Development and Evaluation working group (GRADE) score to evaluate evidence quality. Further missing data were requested from study authors. Two experienced reviewers settled six reviewers' differences during data extraction.

2.4. Risk of bias assessment and grading of evidence

We evaluated included papers' quality by cochrane risk of bias 2 (ROB2) tool. It concludes five domains: the randomization process, deviations from intended interventions, missing outcome data, measurements of outcomes, and selection of reported results. Each domain and overall quality received a "low," "some concerns," or "high" risk of bias score (18). Two assessors independently evaluated the quality, and any discrepancies were settled through discussion with senior author.

Grading of evidence:

We employed the GRADE methodology to evaluate the evidence quality for drugs that reduce blood loss (19). The final score was assessed based on the following criteria: study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, and publication bias.

2.5. Data synthesis

We performed our NMA by the frequentist statistical tool using package of Netmeta in R program 4.1.2 (20). We used risk ratio (RR) with 95% CI for categorical outcomes and mean difference (MD) with 95%CI for continuous outcomes. According to Cochrane Handbook for systematic reviews of interventions, we used I2 statistics and Chi-square p-values to measure heterogeneity. The interpretation of

I-square (I^2) statistic was as follows: (0–30%: mild; 30–60%: moderate; 50–90%: substantial; 75–100%: considerable heterogeneity) (21). The subjective nature of assessing the level of heterogeneity is reflected in the degree of overlap between these categories. Chi-square test was interpreted as having significant heterogeneity when $P < 0.1$ (21). A random effect model was performed for all outcomes.

Netsplit function in R package netmeta evaluated and measured the inconsistency between direct and indirect estimates, as Krahn et al.(22) determined, using generalized Cochran Q statistics for multivariate meta-analysis. We used P scores to rank different treatments. Higher P scores denote better performance (23). Also, league table presented a ranking for all regimens by combining direct and indirect comparisons. A graph was added to illustrate (I) number of direct comparisons between each group, which was represented by size of the line connecting the two groups, and (II) number of included patients in each group, which was represented by size of the nodes. We defined statistical significance as p-value < 0.05 for endpoints.

2.6. Publication Bias

For outcomes with ≥10 studies, Egger's test was employed to evaluate publication bias, while funnel plots were utilized to assess asymmetry(24).

Results

3.1. Results of the literature search and characteristics of included studies

Our database search retrieved 1399 records that were reduced to 951 studies after duplicate removal. After title & abstract screening, 824 records were excluded. Then, 127 arti-

cles' full texts were examined to determine their eligibility. Finally, we included 61 articles (n= 4,932) in our network meta-analysis (13,25–85). PRISMA flow diagram shows the reasons for exclusion **(Supplemental Figure 1).**

Characteristics of Included Studies

Regarding type of myomectomy, 48 studies performed OM technique, eight studies (n= 712) performed LM technique (39,52,55,56,77,79,82,83), and five studies (n= 318) performed HM technique (54,63,71,76,78). ***In OM group***, Misoprostol was evaluated in 18 studies for its potential to minimize blood loss during myomectomy; 11 studies compared vaginal (34,42,44,51,62,64,72,73,80,84) or rectal (27) misoprostol with placebo. Seven studies compared misoprostol with tourniquet (31,35,36,59), oxytocic drugs (62,65), or bilateral uterine artery ligation (26). One study compared combination of misoprostol and tourniquet with a tourniquet (13). All studies reported efficacy of misoprostol in decreasing intraoperative blood loss with different modes of administration; vaginal, rectal or sublingual over placebo, bilateral uterine artery ligation, or oxytocin. However, using a tourniquet alone or combined with misoprostol seemed as effective as (31) or more effective (35,36,59) than misoprostol. Another RCT proved the significant efficacy of carbetocin over misoprostol in lowering intraoperative blood loss (62).

On the other hand, six studies examined efficacy of vasopressin against tourniquet (46,50,70), placebo (47,53), or octreotide acetate (40). Two studies evaluated efficacy of combining vasopressin and misoprostol versus vasopressin (48) or tourniquet (45). Vasopressin alone or combined with misoprostol significantly decreased intraoperative blood loss compared with placebo, tourniquet, and octreotide acetate except for an open-label RCT, which revealed a non-significant difference between vasopressin and placebo (50).

Nine studies assessed efficacy of oxytocic drugs: oxytocin (32,33,38,61,69,74) or carbetocin (68,75,81) versus placebo. Six studies compared oxytocin with a combination of tranexamic acid and ethamsylate (28,58), with a tourniquet (25,37,49), or with tranexamic acid (57). All studies reported safety and significant efficacy of oxytocic drugs in decreasing intraoperative blood loss compared with placebo, tranexamic acid, or tourniquet. However, three studies reported a significant effect of tourniquet (25,37) or a combination of tranexamic acid and ethamsylate (58) over oxytocin alone in decreasing intraoperative blood loss. Two double-blinded RCTs reported a non-significant effect of oxytocin (28,32) or a combination of tranexamic acid and ethamsylate (28) in reducing blood loss intraoperatively compared with placebo.

Three studies evaluated efficacy of tranexamic acid compared to a placebo (41,66,67). Also, two studies assessed a combination of tranexamic acid and tourniquet with placebo (43) or a combination of tourniquet and placebo (29). All studies proved significant role of tropical or intravenous tranexamic acid in minimizing blood loss, except for one double-blind RCT, which stated a non-beneficial value of intravenous tranexamic acid (41).

Another two studies assessed efficacy of epinephrine and local anesthesia (lidocaine or bupivacaine) with placebo (30,60) or tourniquet (30). Both studies proved safety and significant efficacy of epinephrine combined with local anesthesia.

For MI myomectomy group; one study examined efficacy of misoprostol versus placebo (55). Three studies compared vasopressin with placebo (78,83) or a combination of vasopressin and misoprostol (82). Misoprostol or vasopressin given either transcervical or intramyometrial or a combination of them significantly decreases intraoperative blood loss.

Three studies assessed efficacy of oxytocin with tranexamic acid (54,63,76). The

three studies had different results; oxytocin had a lower, similar, or higher effect than tranexamic acid. Four studies compared oxytocin (79), tranexamic acid (71), ornipressin (39), or ascorbic acid (56) with placebo. Using oxytocin, ornipressin, or instillation of tranexamic acid had a significant role in decreasing intraoperative blood loss except for ascorbic acid, which could not reduce intraoperative bleeding.

Also, two studies compared epinephrine either alone (52) or added to bupivacaine (77) with placebo. Both proved epinephrine's safety and efficacy in decreasing intraoperative blood loss.

Regarding baseline characteristics of patients in included studies, the sample size ranged from ten to 100 patients. Included studies did not report any significant difference among study arms regarding the preoperative data. Preoperative hemoglobin (HB) and hematocrit values were comparable among included studies. They had a preoperative HB range of 7.7 ± 1.1 (34) and 13.64 ± 8.55 mg/dl (51). Also, studies of MI myomectomy had lower maximum diameter of uterine fibroid and fibroid volume than studies of OM. Uterine size ranged from 9.66 ± 2.64 (86) to 39.8 ± 2.33 weeks (76). On the other hand, studies of OM have more blood loss intraoperatively than those of MI myomectomy. Most patients had a fibroid located with a large percentage intramurally rather than subserosal (Supplemental Table 2).

3.2. Risk of bias assessment

All trials had some concerns regarding ROB except for twenty studies, which had an overall low risk of bias (28–30,36–38,41,43,45,49,64,68,71,73,74,76,77,87–89), and five studies had an overall high risk of bias (13,39,52,60,62). Additionally, The majority of studies did not provide sufficient randomization methodologies. **Supplemental Figure 2** details ROB assessment. Only 32 RCTs were double-blinded; the rest were single-blinded or open-label. Also, **Table 1** shows details of GRADE assessment for drugs decreasing blood loss during OM and MI myomectomy compared with placebo.

3.3. Outcomes

3.3.1. Intraoperative blood loss:

Regarding OM, intraoperative blood loss was reported in 44 studies (N= 3689 patients). **Figure 1A** shows the eligible comparisons network. In comparison to placebo, NMA showed that vasopressin + misoprostol (MD = -714.57, 95% CI -929.98 to -499.17, low evidence), bupivacaine + epinephrine (MD =-651.26 95% CI -846.80 to -455.72, low evidence), vasopressin (MD = -425.57, 95%CI -527.80 to -323.35, very low evidence), tranexamic acid + tourniquet (MD = -392.10, 95%CI -597.57 to -186.63, low evidence), octreotide acetate (MD = -374.02, 95%CI -558.41 to -189.64, very low evidence), misoprostol + tourniquet (MD= -337.48, 95%CI -540.89 to -134.06, very low evidence), carbetocin (MD= -294.49, 95%CI -369.98 to -219, low evidence), tourniquet (MD= -276.58, 95%CI -352.32 to -200.83, low evidence), tranexamic acid (MD= -258.88, 95%CI -346.08 to -171.69, very low evidence), tranexamic acid + ethamsylate (MD= -213.45, 95%CI -333.04 to -93.85, low evidence), misoprostol (MD= -181.97, 95%CI -232.89 to -131.04, low evidence) and oxytocin (MD= -125.94, 95%CI -197.57 to -54.32, low evidence) minimized intraoperative blood loss. No additional significant differences were found between compared treatments **(Figure 1B)**. Vasopressin plus misoprostol were ranked as the best treatment for reducing bleeding during surgery in a subgroup analysis (P= 0.97), followed by bupivacaine + epinephrine (P= 0.94), vasopressin (P= 0.77), tranexamic acid + tourniquet (P= 0.69), octreotide acetate (P= 0.66), misoprostol + tourniquet (P= 0.59), carbetocin (P= 0.53), tourniquet (P= 0.47), tranexamic acid (P= 0.42), tranexamic acid + ethamsylate (P= 0.31), misoprostol (P= 0.22) and the least ranked was oxytocin (P= 0.12) **(Figure 1B)**. The pooled analysis showed

substantial heterogeneity (I2 = 95.9%, P < 0.001), and the studies were inconsistent (P < 0.001). The net league table shows a head-to-head comparison among included interventions in **Figure 1C**.

Regarding MI myomectomy, intraoperative blood loss was reported in nine studies (N= 617 patients). **Figure 2A** displays the network of eligible comparisons. In comparison to placebo, NMA showed that oxytocin (MD =-175.5, 95% CI -313.13 to -37.87, low-quality evidence), ornipressin (MD =-149.6, 95% CI -212.8 to -86.4, very low evidence), misoprostol (MD =-91, 95% CI -154.32 to -27.68, very low evidence), bupivacaine + epinephrine (MD =-68.6, 95% CI -130.65 to -6.55, low evidence) and vasopressin (MD= -53.7, 95%CI -95.65 to -11.76, moderate evidence) decreased intraoperative bleeding. No additional significant differences were found between compared treatments **(Figure 2B)**. Ranking score of treatments showed that oxytocin (P= 0.9) ranked first in decreasing intraoperative bleeding, followed by ornipressin (P= 0.89), misoprostol (P= 0.64), bupivacaine + epinephrine (P= 0.51) and Vasopressin (P= 0.41) **(Figure 2B)**. Pooled analysis showed substantial heterogeneity (I2 = 90%, P = 0.0014). The net league table shows a head-to-head comparison among included interventions in **Figure 2C**.

3.3.2. Need for blood transfusion

Regarding OM, the requirement for blood transfusion was reported in 39 studies (N= 3007 patients). **Figure 3A** depicts the network of comparisons that are eligible for inclusion. In comparison to placebo, NMA illustrated that vasopressin + misoprostol (RR =0.08, 95%CI 0.03 to 0.22), octreotide acetate (RR = 0.16, 95%CI 0.03 to 0.79), vasopressin (RR = 0.22, 95%CI 0.12 to 0.40), carbetocin (RR = 0.31, 95%CI 0.20 to 0.49), Tourniquet (RR= 0.34, 95%CI 0.21 to 0.54), tranexamic acid (RR= 0.49, 95%CI 0.31 to 0.77), misoprostol (RR= 0.49, 95%CI 0.32 to 0.74) and oxytocin (RR= 0.68, 95%CI 0.48 to 0.96) decreased the risk of blood transfusion. There were no other significant differences between compared treatments **(Figure 3B)**. Ranking score of treatments showed that vasopressin + misoprostol ranked first in decreasing risk of blood transfusion (P= 0.97), then octreotide acetate (P= 0.8), Vasopressin (P= 0.78), carbetocin (P= 0.63), tourniquet (0.6), tranexamic acid (P= 0.36), misoprostol (P= 0.35) and oxytocin (P= 0.16) **(Figure 3B)**. Pooled analysis showed mild heterogeneity (I2 = 27.7%, P = 0.3), but the studies were inconsistent (P = 0.02). The net league table shows a head-to-head comparison among included interventions in **Figure 3C**.

Regarding MI myomectomy, risk of blood transfusion was reported in 11 studies (N=766 patients). **Figure 4A** shows network of eligible comparisons. In comparison to placebo, oxytocin (RR= 0.18, 95% CI 0.04 to 0.75) and vasopressin (RR= 0.52, 95%CI 0.3 to 0.9) significantly lowered requirement for blood transfusion. No other significant differences were found between compared treatments **(Figure 4B)**. Subgroup analysis showed that oxytocin ranked first in decreasing risk of blood transfusion (P= 0.81), followed by vasopressin (P= 0.52) **(Figure 4B)**. Pooled analysis was homogenous (I2 =0%, P = 0.99). The net league table showed a head-to-head comparison among included interventions **(Figure 4C).**

3.3.3. Postoperative HB:

Regarding OM, postoperative HB was reported in 44 studies (N=3646 patients). Eligible comparisons network is presented in Supplemental **Figure 3A**. Compared with placebo, bupivacaine + epinephrine (MD =2.16, 95% CI 1.21 to 3.11), lidocaine + epinephrine (MD =1.82, 95% CI 0.72 to 2.92]), vasopressin (MD = 1.40, 95% CI 0.89 to 1.92), tourniquet (MD =1.12, 95% CI 0.71 to 1.54), vasopressin + misoprostol (MD= 1.02, 95%CI 0.17 to 1.87), octreotide acetate (MD= 0.92, 95%CI 0.07 to 1.78), carbetocin (MD= 0.83, 95%CI 0.44 to 1.22), misoprostol (MD= 0.73, 95%CI 0.48 to 0.99) and tranexamic acid + ethamsylate (MD= 0.66, 95%CI 0.07

to 1.25) significantly lower the drop in postoperative HB. No other significant differences were found between compared treatments **(Supplemental Figure 3B)**. Ranking score of treatments showed that bupivacaine + epinephrine ranked first (P= 0.96), followed by lidocaine + epinephrine (P= 0.89), vasopressin (P= 0.82), tourniquet (P= 0.7), vasopressin + misoprostol (P= 0.61), octreotide acetate (P= 0.56), carbetocin (P= 0.52), misoprostol (P= 0.46) and lastly tranexamic acid + ethamsylate (P= 0.42) **(Supplemental Figure 3B)**. Pooled analysis showed substantial heterogeneity (I2 =77.4%, P <0.001), and the studies were inconsistent (P <0.001). The net league table showed a head-to-head comparison among included interventions **(Supplemental Figure 3C).**

Regarding MI myomectomy, postoperative HB was reported in six studies. Eligible comparisons network is presented in **Supplemental Figure 4C**. Compared with placebo, oxytocin significantly reduced the drop in postoperative HB (MD = 1.4, 95%CI 0.08 to 2.72) with a ranking score of P= 0.89. No other significant differences were found among compared treatments **(Supplemental Figure 4A)**. Ranking score of treatment showed that oxytocin ranked first (P= 0.89), followed by tranexamic acid (P=0.55), misoprostol (P= 0.49), and lastly, ascorbic acid (P=0.44) **(Supplemental Figure 4A)**. Pooled analysis showed substantial heterogeneity (I2 = 84.5%, P = 0.0016). The node split graph also showed non-significant results among included interventions **(Supplemental Figure 4B).**

3.3.4. Postoperative HCT after OM:

Twenty-six studies with 2258 patients reported postoperative HCT. Eligible comparisons network is presented in **Supplemental Figure 5A**. In NMA, the most effective intervention in lowering the drop of postoperative HCT was vasopressin (MD =4.14, 95% CI 1.70 to 6.57), followed by carbetocin (MD =3.38, 95% CI 1.17 to 5.59), then tranexamic acid + ethamsylate (MD = 3.29, 95% CI 0.83 to 5.74), and lastly misoprostol (MD = 2.72, 95% CI 1.45 to 3.98) compared with placebo. No other significant differences were found among compared treatments **(Supplemental Figure 5B)**. Ranking score of treatments showed that vasopressin ranked first (P= 0.79), followed by carbetocin (P= 0.65), tranexamic acid + ethamsylate (P= 0.63), Misoprostol (P= 0.5), tranexamic acid (P=0.31), and oxytocin (P=0.2) **(Supplemental Figure 5B).**

Pooled analysis showed substantial heterogeneity (I2 =91.6%, P <0.001), and the studies were inconsistent (P <0.001). Net league table showed a head-to-head comparison among included interventions **(Supplemental Figure 5C)**. We did not meta-analyze postoperative HCT in MI myomectomy as it was reported in a few studies that could not be pooled for metaanalysis.

3.3.5. Postoperative hospital stay after OM

Twenty studies with 1700 patients reported postoperative hospital stay. Eligible comparisons network is presented in **Supplemental Figure 6A**. The NMA showed that compared with placebo, the most effective intervention among included interventions was bupivacaine + epinephrine (MD = -0.58, 95%CI -0.89 to -0.27), Followed by carbetocin (MD = -0.26, 95%CI -0.45 to -0.07) and misoprostol (MD = -0.13, 95%CI -0.26 to -0.01). No other significant differences were found among compared treatments **(Supplemental Figure 6B)**. Ranking score of treatments showed that bupivacaine + epinephrine ranked first (P= 0.86), followed by carbetocin (P= 0.59), tranexamic acid + ethamsylate (P= 0.5), oxytocin (P=0.41), misoprostol (P= 0.36), and lastly tranexamic acid (P=0.34) **(Supplemental Figure 6B)**.

Pooled analysis showed moderate heterogeneity (I2 =52%, P = 0.007), and the studies were inconsistent (P = 0.02). The net league table showed a head-to-head comparison among included interventions **(Supplemental Figure 6C)**.

3.3.6. Postoperative fever:

Regarding OM, 11 studies (N=902 patients) reported risk of developing postoperative fever. Eligible comparisons network is presented in **Supplemental Figure 7A**. Misoprostol was the only drug that significantly increased risk of postoperative pyrexia compared to placebo (RR = 2.28, 95%CI 1.03 to 5.07). No other significant differences were found among compared treatments **(Supplemental Figure 7B)**. Ranking score of treatments showed that vasopressin ranked first (P= 0.94), followed by oxytocin (P=0.53), tranexamic acid + ethamsylate (P= 0.49), vasopressin + misoprostol (P= 0.31), and misoprostol (P=0.07) **(Supplemental Figure 7B)**. On the other hand, compared with misoprostol, NMA showed that vasopressin (RR= 0.16, 95%CI 0.04 to 0.61), tourniquet (RR= 0.34, 95%CI 0.16 to 0.74), and oxytocin (RR= 0.42, 95%CI 0.18 to 0.96) significantly reduced risk of postoperative fever **(Supplemental Figures 7C)**. Pooled analysis was homogenous (I2 =0%, P = 0.78), and the studies were consistent (P = 0.9).

Regarding MI, risk of postoperative fever was reported in two studies (n= 124 patients). No significant differences were found among the treatments compared with placebo **(Supplemental Figure 8A)**. Eligible comparisons network is shown in **Supplemental Figure 8B**. Ranking of included treatments showed that oxytocin ranked first (P= 0.64), followed by misoprostol (P= 0.6). The node split graph is presented in **Supplemental Figure 8C**.

3.3.7. Other complications:

Regarding OM, 16 studies (N= 1454 patients) reported risk of developing other complications. Eligible comparisons network is presented in **Supplemental Figure 9A**. Compared with placebo, NMA showed that misoprostol + tourniquet (RR =0.15, 95%CI 0.03 to 0.72) had a significantly lower risk of developing other complications. Meanwhile, carbetocin (RR = 2, 95%CI 1.42 to 2.82) and tranexamic acid (RR = 7, 95%CI 2.30 to 21.29) had a significantly higher risk of developing other complications than placebo. No additional significant differences were identified between treatments **(Supplemental Figure 9B)**. Ranking for the included treatments showed that misoprostol + tourniquet ranked first (P= 0.99), followed by tranexamic acid + ethamsylate (P= 0.74), oxytocin (P=0.62), misoprostol (P=0.51), octreotide acetate (P=0.29), carbetocin (P=0.27), vasopressin (P=0.27), and tranexamic acid (P= 0.06) **(Supplemental Figure 9B)**. Pooled analysis was homogenous (I2 =0%, P = 0.9), and the studies were consistent (P = 0.89). The net league table showed a head-to-head comparison among included interventions **(Supplemental Figure 9C)**.

Regarding MI myomectomy, four studies with 384 patients reported risk of developing other complications. Compared with placebo; NMA showed no significant differences among treatments **(Supplemental Figure 10 A)**. Ranking of included treatments showed that tranexamic acid ranked first (P= 0.74), followed by oxytocin (P= 0.59) and epinephrine (P= 0.56) **(Supplemental Figure 10A)**. The node split graph is presented in **Supplemental Figure 10B**, and network of eligible comparisons is shown in **Supplemental Figure 9C**.

3.4. Publication bias:

Regarding OM group, the following outcomes were free of publication bias: need for blood transfusion (Egger= 0.65), postoperative HB (Egger= 0.43), postoperative hospital stay (Egger= 0.71), and having other complications (Egger= 0.39). Conversely, the following outcomes had significant publication bias: intraoperative blood loss (Egger= 0.01) and postoperative HCT (Egger<0.01) **(Supplemental Figure 11)**. Regarding MI myomectomy, we could not assess publication bias as included studies for each outcome were less than ten.

Discussion

Summary of principal findings

Myomectomy may result in substantial blood loss, causing anemia, hypovolemia, and coagulation abnormalities. Therefore, it is imperative to implement strategies that minimize blood loss during myomectomy. Unfortunately, there is no agreement on the most effective pre- or intraoperative procedures to minimize blood loss or prepare for autologous blood transfusion.

Our network meta-analysis of 61 RCTs assessed and ranked pharmaceutical interventions to minimize blood loss and transfusions during myomectomy. In open myomectomy, Vasopressin, Epinephrine, Tranexamic acid, Octreotide acetate, Misoprostol, Carbetocin, and oxytocin alone or in combination significantly decreased intraoperative blood loss. Also, all except epinephrine and all except oxytocin, lowered need for blood transfusion and drop in postoperative HB, respectively. Vasopressin plus misoprostol ranked first in reducing blood loss and necessity for blood transfusion, with oxytocin being the least effective among studied drugs. On the other side, oxytocin was the most effective and ranked first in reduction of blood loss and transfusion requirements in MI myomectomy. Reducing blood transfusion is crucial in locations with little blood supply or high maternal hemorrhage mortality.

In open myomectomy, bupivacaine + epinephrine was the best in lowering the drop in postoperative HB, and tranexamic acid + ethamsylate was the least effective, while oxytocin was the one which significantly lowered the drop in postoperative HB compared to other treatments in MI myomectomy. Also, vasopressin in OM was the best to increase postoperative HCT, and bupivacaine + epinephrine was the best to decrease the postoperative hospital stay. In open myomectomy, misoprostol was the only drug significantly linked to postoperative pyrexia; however, misoprostol + tourniquet had the lowest odds of developing other complications in the OM group (Supplemental Table 3).

Interpretation of results and clinical implications

Our results were comparable to Samy et al.(11) network meta-analysis, which included 26 RCTs (N =1627). Their study revealed that oxytocin, ornipressin, bupivacaine plus epinephrine, and misoprostol were successful in decreasing blood loss in MI myomectomy. Similarly, vasopressin plus misoprostol, oxytocin, TXA, and misoprostol medications were beneficial in lowering blood loss during open myomectomy. Their study lacked newly studied drugs such as carbetocin and octreotide acetate, which we included and proved effective. Agreed with us, vasopressin combined with misoprostol ranked first in lowering blood loss and need for blood transfusion during open myomectomy and oxytocin in minimally invasive procedures.

Additionally, the decrease in blood loss and the need for transfusions are larger in our study than in Samy et al. study. It may be because of our inclusion of larger numbers of RCTs. In our network metanalysis, bupivacaine + epinephrine was the best to lower drop in postoperative HB after OM. However, Samy et al. (12) study ranked oxytocin first. This difference could be attributed to different patient characteristics and number of included studies.

According to a survey of gynecologists, The main intraoperative measures commonly employed to minimize blood loss during myomectomy (unspecified route) included vasopressin (94.1%), vasopressin with epinephrine (26.6%), intravenous tranexamic acid (73.5%), mechanical tourniquet (66.2%), misoprostol (33.8%), uterine artery ligation (22.1%), topical sealant (17.6%), and intraoperative blood salvage (11.8%)(90).

In our study, combined bupivacaine + epinephrine is ranked the second for lowering intraoperative blood loss during OM. Bupivacaine, a local anesthetic, produces vasodila-

tion at clinical dosages but causes vasoconstriction at lower concentrations (≤ 0.25%) for local infiltration, lasting 4-24 hours (91). A combination of bupivacaine and low-dose epinephrine minimizes cardiovascular effects without affecting hemostasis. Being a potent drug for decreasing the amount of blood loss, it is suitable for raising the HB values postoperatively.

Vasopressin plus misoprostol reduced open myomectomy blood loss better than oxytocin, tranexamic acid, or misoprostol alone, According to a new network meta-analysis conducted by Samy et al . Vasopressin is a potent vasoconstrictor with a short half-life (<30 minutes) and action duration (<60 minutes). It induces antihemorrhagic effects by intraoperatively stimulating myometrial contraction and vascular bed vasospasm (92). Alomar et al.(93) meta-analysis (11 studies; n=1067 patients) found that vasopressin administration significantly lowered intraoperative blood loss, hemoglobin and hematocrit levels, duration of surgery, and perioperative blood transfusion rates compared to control group. There was no significant difference in duration of hospitalization and occurrence of drug-related cardiovascular adverse events across the groups.

The posterior pituitary gland secretes the peptide hormone oxytocin, which increases uterine contraction during childbirth and reduces the risk of postpartum hemorrhage (94). Fibroids have a higher number of oxytocin receptors than normal myometrium, making oxytocin an effective intraoperative blood loss-minimizing therapy (95). In Samy et al.(11) network meta-analysis, Oxytocin was found to be the most effective in improving postoperative hemoglobin and hematocrit levels and the second most effective in shortening the length of hospitalization. Albazee et al.(96) examined six RCTs that investigated the impact of oxytocics on abdominal myomectomy. Compared to the placebo, oxytocin and carbetocin administration considerably lowered blood loss intraoperatively, lenghth of hospitalization, and transfusion requirements. Oxytocin, but not carbetocin, lowered postoperative hemoglobin, hematocrit, and operation time compared to control group. However, A continuous intravenous infusion of oxytocin is necessary because of its short half-life (4-10 min). The antidiuretic properties of oxytocin can result in hypotension, coronary artery spasms, and water intoxication when administered in large doses.

Tranexamic acid substantially decreased intraoperative blood loss by 213.1 mL (95% CI -242.4 to -183.7) in Fusca et al. meta-analysis (97). However, decrease in blood transfusions did not show any statistically significant patterns. No differences were found for postoperative HB and length of hospitalization. In Samy et al.(11) study, All meta-analyses supported prophylactic effectiveness of TXA during myomectomy despite the small number of trials and low power.

Misoprostol is a synthetic prostaglandin E1 analog that decreases leiomyoma blood supply by contracting the myometrium and directly constricting the uterine arteries (98,99). In Wali et al.(99) metanalysis (8 studies; n=385 patients), misoprostol before open myomectomy significantly reduced blood loss by -170.32 ml (95% CI -201.53 to -139.10), drop in hemoglobin level by -0.48 g/dl (95% CI -0.65 to -0.31), blood transfusion need, and duration of surgery by -11.64 minutes (95% CI -15.73 to -7.54) with no significant difference in postoperative fever or hospital stay. Misoprostol is affordable, has little acceptable adverse effects, and is widely available.

Furthermore, this network meta-analysis uncovered a significant degree of heterogeneity. This suggests potential bias in certain studies included, resulting in methodological diversity in the meta-analysis. Possible factors contributing to the observed variability could include variations in the surgical procedure, the anesthetic method employed, and the patient demographics. Therefore, It is important to interpret this study's results with caution.

Strengths and Limitations

Our strength points are we followed the Cochrane Handbook for the systematic reviews and meta-analysis and the statement of PRISMA-NMA; we adopted a thorough search approach employing several databases without language or publication date limitations; Our thorough search method has successfully gathered all relevant studies that meet the criteria, ensuring the most current analysis; including minimally invasive myomectomy technique into the search strategy; A priori protocol registration in the International Prospective Register of Systematic Reviews; only RCTs were included, which helped to produce high-quality evidence.

However, our major limitation is that several outcomes were heterogeneous. Heterogeneity of various meta-analyzed endpoints may be due to differences in perioperative variables, such as patient characteristics, surgical technique, length of procedure, and medication dosage and volume. These factors could have indirectly affected meta-analyzed endpoint summary effect sizes such as intraoperative blood loss and need for blood transfusion. Some RCTs have unclear or high risk of bias, lowering outcome quality. Also, the limited studies that assess the impact of different modifiers did not allow us to compare different parameters feasibly.

Conclusion

SThere are many effective treatment options; selection of therapy will depend on individual patient characteristics, and those at higher risk may benefit from multimodal therapy. Our data conclude that using vasopressin + misoprostol and oxytocin was the best way to reduce intraoperative bleeding and the need for transfusion in OM and MI myomectomy, respectively. Also, the use of bupivacaine + epinephrine was the best to increase postoperative HB in OM. Also, vasopressin in OM was the best to increase postoperative HCT, and bupivacaine + epinephrine was the best to decrease the postoperative hospital stay. Misoprostol + tourniquet had the lowest odds of developing other complications in the OM group.

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Conflict of interest

The authors declare no conflict of interest

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Figure 4: The need for blood transfusion MI myomectomy

Table 1: Summary of findings for the main comparison. Interventions to reduce blood loss during myomectomy for fibroids compared to placebo

Supplementary materials:

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Supplemental Table 3: summary of the results of NMA, comparing Placebo with other different drugs

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Supplemental Figure 6: Postoperative hospital stay OM

Supplemental Figure 7: Postoperative fever OM

Supplemental Figure 8: Postoperative fever MI myomectomy

Supplemental Figure 9: Postoperative other complications OM

Supplemental Figure 10: Postoperative other complications MI myomectomy

Supplemental Figure 11: Publication bias of different outcomes; A) Intraoperative blood loss OM, B) Need for blood transfusion OM, C) Postoperative HB OM, D) Postoperative HCT OM, E) Postoperative hospital stay OM and F) Postoperative other complications OM

Table 1: Summary of findings for the main comparison. Interventions to reduce blood loss during myomectomy for fibroids compared to placebo

Intervention	Illustrative comparative risks (95% CI) on blood loss		Relative effect	No of participants	Quality of the evidence	Comments
	Placebo	Interventions	(95% CI)	(studies)	(GRADE)	
Open Myomectomy						
Vasopressin + misoprostol	Mean blood loss with placebo was	Mean blood loss with Vasopressin + misoprostol was	MD -714.57 (-929.98, -499.17)	154	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	680.24 ml	714.57 ml lower		(2 study)	Low	
Bupivacaine +epinephrine	Mean blood loss with placebo was	Mean blood loss with Bupivacaine +epinephrine was	MD -651.26 (-846.80, -455.72)	60	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	680.24 ml	651.26 ml lower		(1 study)	Low	
Vasopressin	Mean blood loss with placebo was	Mean blood loss with Vasopressin was	MD -425.57 (-527.80, -323.35)	366	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of some risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	680.24 ml	425.57 ml Lower		(6 study)	Very low	
Tranexamic acid +tourniquet	Mean blood loss with placebo was	Mean blood loss with Tranexamic acid +tourniquet was	MD -392.10 (-597.57, -186.63)	211	⊕⊕⊖⊖	We rated the quality of evidence (by 2) because of the wide confidence interval (Imprecision) and presence of publication bias.
	680.24 ml	392.10 ml lower		(2 study)	Low	
Octreotide acetate	Mean blood loss with placebo was	Mean blood loss with Octreotide acetate was	MD -374.02 (-558.41, -189.64)	60	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of some risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	680.24 ml	374.02 ml lower		(1 study)	Very low	
Misoprostol + tourniquet	Mean blood loss with placebo was	Mean blood loss with Misoprostol + tourniquet was	MD -337.48 (-540.89, -134.06)	126	⊕⊖⊖⊖	We rated the quality of evidence (by 3) because of the high risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	680.24 ml	337.48 ml lower		(1 study)	Very low	

Carbetocin	Mean blood loss with placebo was	Mean blood loss with Carbetocin was	MD -294.49 (-369.98, -219.0)	686	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the high risk of bias, and the presence of publication bias.
	680.24 ml	294.49 ml lower		(7 study)	Low	
Tourniquet +placebo	Mean blood loss with placebo was	Mean blood loss with Carbetocin was	MD -300.63 (-670.93, -69.67)	80	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	680.24 ml	300.63 ml lower		(1 study)	Low	
Tourniquet	Mean blood loss with placebo was	Mean blood loss with Tourniquet was	MD -276.58 (-352.32, -200.83)	949	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of some risk of bias, and the presence of publication bias.
	680.24 ml	276.58 ml lower		(13 study)	Low	
Tranexamic acid	Mean blood loss with placebo was	Mean blood loss with Tranexamic acid was	MD -258.88 (-346.08, -171.69)	434	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of some risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	680.24 ml	258.88 ml lower		(4 study)	Very low	
Tranexamic acid + ethamsylate	Mean blood loss with placebo was	Mean blood loss with Tranexamic acid + ethamsylate was	MD -213.45 (-33.04, -93.85)	270	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	680.24 ml	213.45 ml lower		(2 study)	Low	
Bilat. Ut. A. ligation	Mean blood loss with placebo was	Mean blood loss with Bilat. Ut. A. ligation was	MD -190.94 (-391.54, 9.76)	60	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	680.24 ml	190.94 ml lower		(1 study)	Low	
Misoprostol	Mean blood loss with placebo was	Mean blood loss with Misoprostol was	MD -181.97 (-232.89, -131.04)	1091	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of some risk of bias, and the presence of publication bias.
	680.24 ml	181.97 ml lower		(17 study)	Low	

Oxytocin	Mean blood loss with placebo was	Mean blood loss with Oxytocin was	MD -125.94 (-197.57, -54.32)	1036	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of some risk of bias, and the presence of publication bias.
	680.24 ml	125.94 ml lower		(10 study)	Low	
	Minimally-invasive Myomectomy					
Oxytocin	Mean blood loss with placebo was	Mean blood loss with Oxytocin was	MD -175.50 (-313.13, -37.87)	306	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	349.56 ml	175.50 ml lower		(5 study)	Low	
Ornipressin	Mean blood loss with placebo was	Mean blood loss with Oxytocin was	MD -149.60 (-212.80, -86.40)	38	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of some risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	349.56 ml	149.60 ml lower		(1 study)	Very low	
Misoprostol	Mean blood loss with placebo was	Mean blood loss with Oxytocin was	MD -91 (-154.32, -27.68)	64	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of some risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	349.56 ml	91 ml lower		(1 study)	Very low	
Bupivacaine + Epineph-rine	Mean blood loss with placebo was	Mean blood loss with Bupivacaine + Epinephrine was	MD -68.60 (-130.65, -6.55)	60	⊕⊕⊖⊖	We rated down the quality of evidence (by 2) because of the wide confidence interval (Imprecision), and the presence of publication bias.
	349.56 ml	68.60 ml lower		(1 study)	Low	
Vasopressin + misopros-tol	Mean blood loss with placebo was	Mean blood loss with Vasopressin + misoprostol was	MD -63.70 (-150.04, -22.36)	60	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of some risk of bias, wide confidence interval (Imprecision), and presence of publication bias.
	349.56 ml	63.70 ml lower		(1 study)	Very low	

Epinephrine	Mean blood loss with placebo was	Mean blood loss with Epinephrine was	MD -57.60 (-138.94, -23.73)	190	⊕⊖⊖⊖	We rated down the quality of evidence (by 3) because of high bias, wide confidence interval (Imprecision), and presence of publication bias.
	349.56 ml	57.60 ml lower		(1 study)	Very low	
Vasopressin	Mean blood loss with placebo was	Mean blood loss with Vasopressin was	MD -53.70 (-95.65, -11.76)	233	⊕⊕⊕⊖	We rated the quality of evidence (by 1) because of the presence of publication bias.
	349.56 ml	53.70 ml lower		(2 study)	Moderate	
Ascorbic acid	Mean blood loss with placebo was	Mean blood loss with Ascorbic acid was	MD -33.80 (-94.50, -162.10)	46	⊕⊕⊕⊖	We rated the quality of evidence (by 1) because of the presence of publication bias.
	349.56 ml	33.80 ml lower		(1 study)	Moderate	

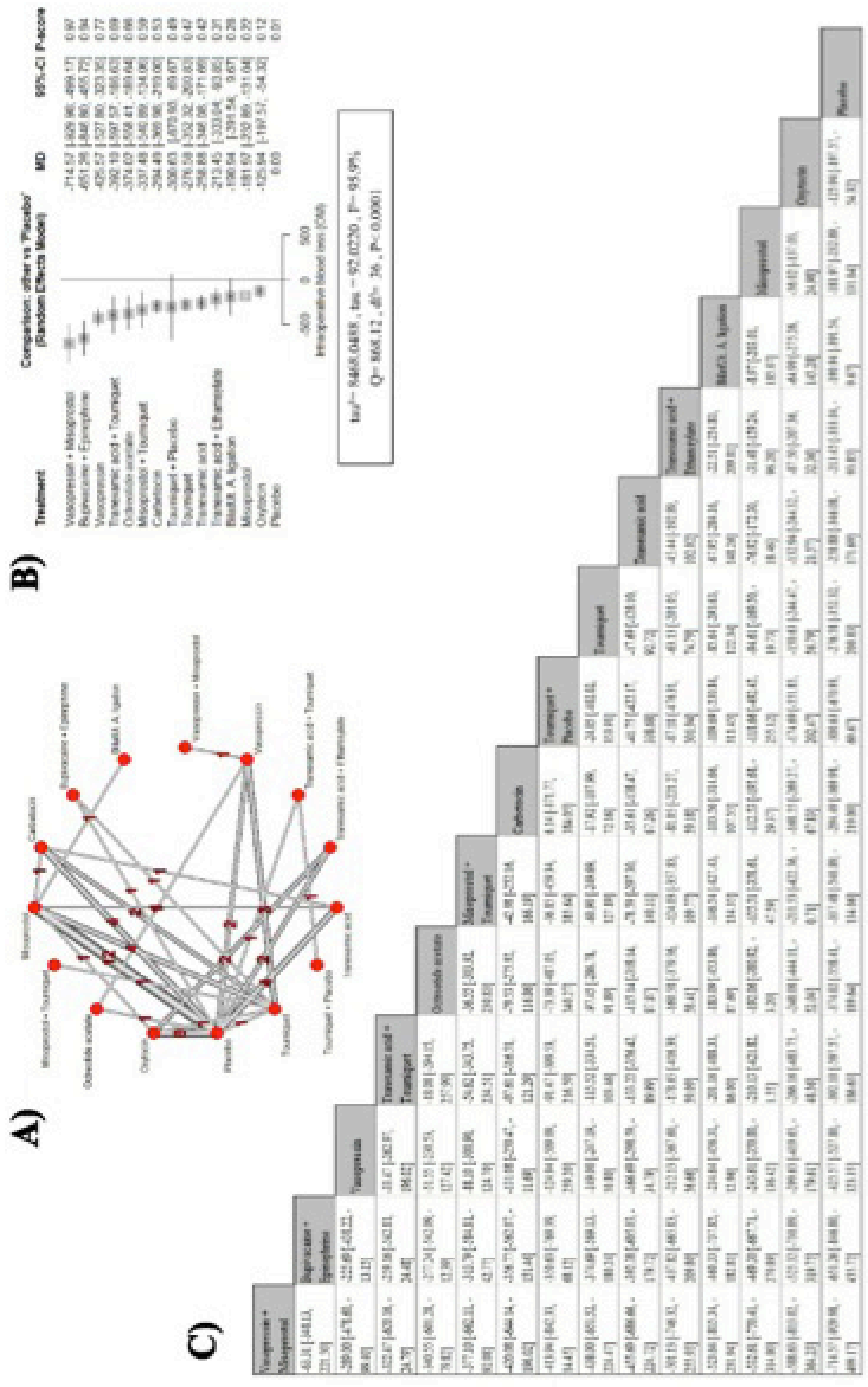
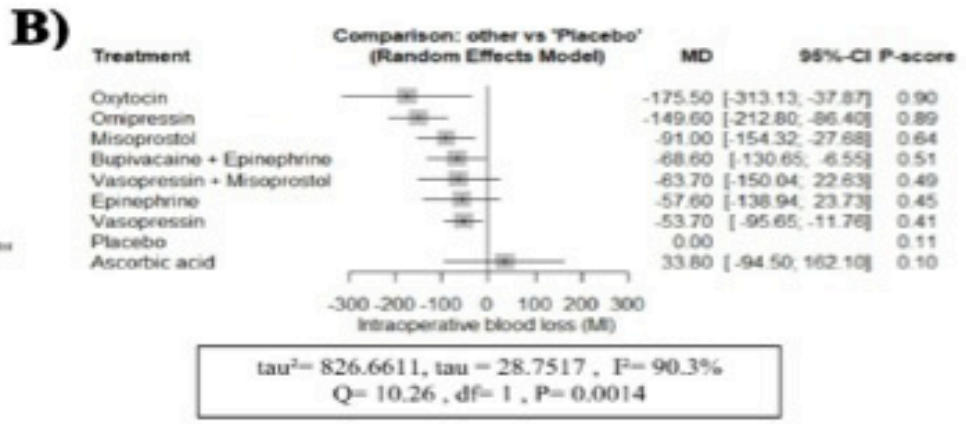


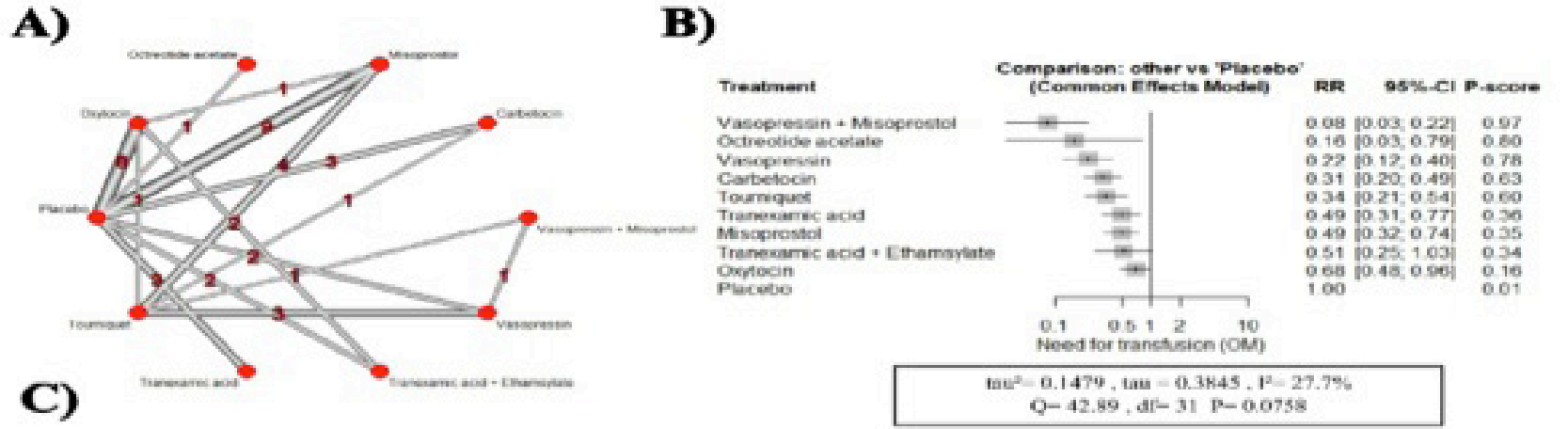
Figure 1: Intraoperative blood loss OM



C)

Oxytocin								
-25.90 [-177.35, 125.55]	Ompressin							
-84.50 [-236.00, 67.00]	-58.60 [-148.06, 30.86]	Misoprostol						
-106.90 [-257.87, 44.07]	-81.00 [-169.57, 7.57]	-22.40 [-111.05, 66.25]	Bupivacaine + Epinephrine					
-111.80 [-274.27, 50.67]	-85.90 [-192.89, 21.10]	-27.30 [-134.36, 79.77]	-4.90 [-111.21, 101.42]	Vasopressin + Misoprostol				
-117.90 [-277.76, 41.97]	-92.00 [-195.00, 11.01]	-33.40 [-136.47, 69.68]	-11.00 [-113.29, 91.30]	-6.10 [-108.82, 96.62]	Epinephrine			
-121.80 [-265.68, 22.08]	-95.90 [-171.75, -20.04]	-37.30 [-113.25, 38.66]	-14.90 [-89.79, 60.00]	-10.00 [-85.46, 65.46]	-3.90 [-73.58, 65.78]	Vasopressin		
-175.50 [-313.13, -37.87]	-149.60 [-212.80, -86.40]	-91.00 [-154.32, -27.68]	-68.60 [-130.65, -6.55]	-63.70 [-150.04, 22.63]	-57.60 [-138.94, 23.73]	-53.70 [-95.65, -11.76]	Placebo	
-209.30 [-397.46, -21.14]	-183.40 [-326.43, -40.37]	-124.80 [-267.88, 18.28]	-102.40 [-244.92, 40.12]	-97.50 [-252.15, 57.14]	-91.40 [-243.31, 60.51]	-87.50 [-222.49, 47.48]	-33.80 [-162.10, 94.50]	Ascorbic acid

Figure 2: Intraoperative blood loss MI myomectomy



Vasopressin + Misoprostol									
0.53 [0.08, 3.49]	Octreotide acetate								
0.38 [0.13, 1.08]	0.71 [0.13, 3.96]	Vasopressin							
0.27 [0.09, 0.78]	0.50 [0.09, 2.69]	0.71 [0.34, 1.47]	Carbetocin						
0.23 [0.10, 0.59]	0.47 [0.09, 2.51]	0.66 [0.34, 1.26]	0.93 [0.49, 1.76]	Tourniquet					
0.17 [0.06, 0.50]	0.32 [0.06, 1.71]	0.45 [0.22, 0.94]	0.64 [0.34, 1.21]	0.69 [0.36, 1.33]	Tranexamic acid				
0.17 [0.07, 0.44]	0.32 [0.06, 1.60]	0.45 [0.23, 0.87]	0.64 [0.35, 1.16]	0.69 [0.48, 0.98]	1.00 [0.54, 1.84]	Misoprostol			
0.16 [0.05, 0.54]	0.31 [0.05, 1.78]	0.43 [0.17, 1.07]	0.61 [0.27, 1.40]	0.66 [0.29, 1.51]	0.96 [0.42, 2.20]	0.96 [0.43, 2.14]	Tranexamic acid + Ethamsylate		
0.12 [0.04, 0.34]	0.23 [0.04, 1.20]	0.33 [0.17, 0.65]	0.46 [0.26, 0.81]	0.50 [0.29, 0.85]	0.72 [0.41, 1.27]	0.72 [0.44, 1.19]	0.75 [0.38, 1.51]	Oxytocin	
0.08 [0.03, 0.22]	0.16 [0.03, 0.79]	0.22 [0.12, 0.40]	0.31 [0.20, 0.49]	0.34 [0.21, 0.54]	0.49 [0.31, 0.77]	0.49 [0.32, 0.74]	0.51 [0.25, 1.03]	0.68 [0.48, 0.96]	Placebo

Figure 3: The need for blood transfusion OM

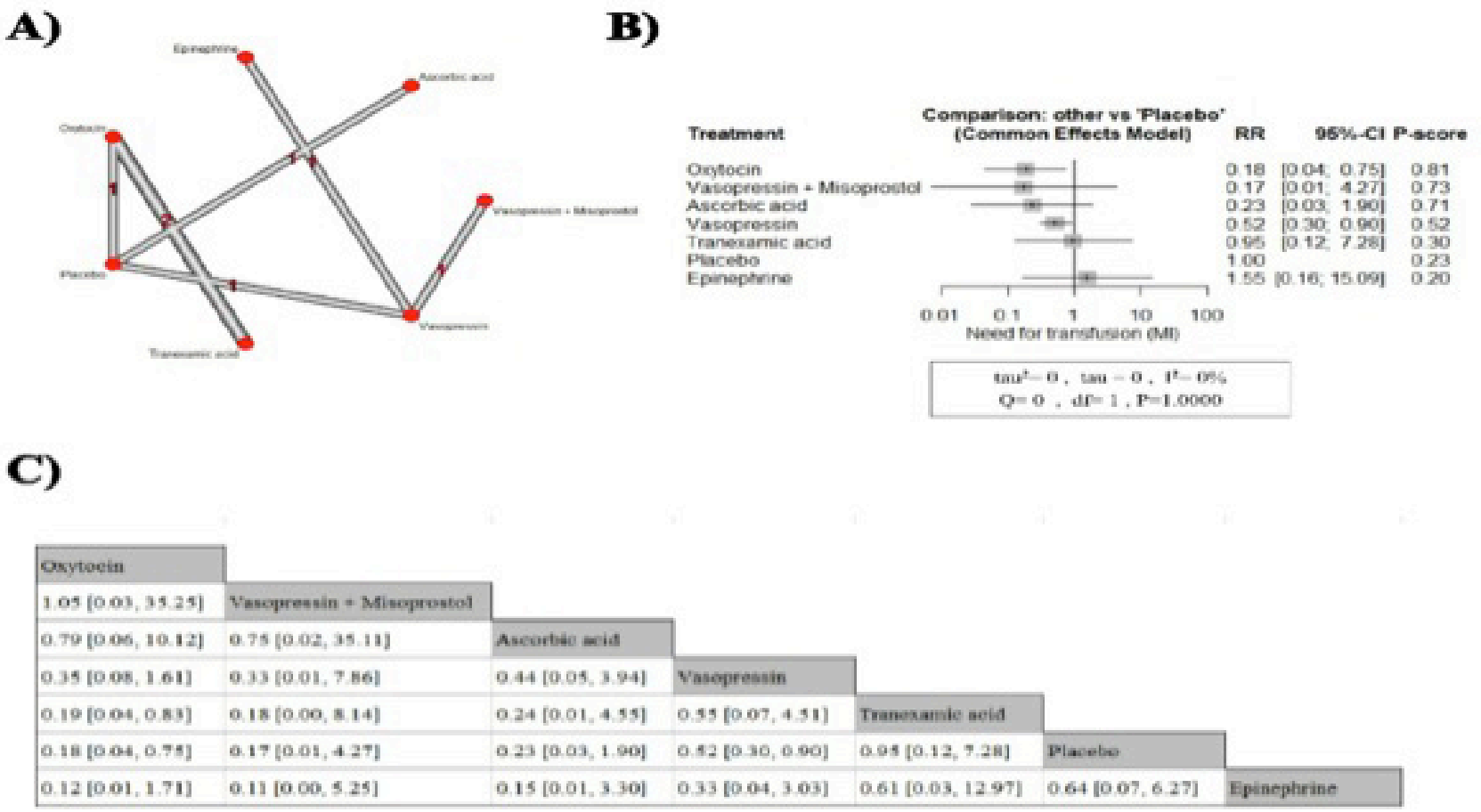


Figure 4: The need for blood transfusion MI myomectomy

Supplemental table 1: Details of search strategy

Pubmed	("Uterine Myomectomy"[Mesh] OR Uterine Myomectomy OR Uterine Myomectomies OR Myomectomy OR Myomectomies OR Fibroidectomy OR Fibroidectomies) AND ("Oxytocin"[Mesh] OR Oxytocin OR Syntocinon OR Pitocin OR OT OR OXT OR "carbetocin" [Supplementary Concept] OR dcomot OR Depotocin OR Depotocin OR Duratocin OR Pabal OR "Ascorbic Acid"[Mesh] OR Ascorbic Acid OR L-Ascorbic Acid OR L Ascorbic Acid OR Vitamin C OR Hybrin OR Magnorbin OR Sodium Ascorbate OR Ferrous Ascorbate OR Magnesium Ascorbate OR Magnesium di-L-Ascorbate OR Magnesium di-L-Ascorbate OR Magnesium Ascorbicum OR Ascor OR Ester-C OR Protexin OR "Tranexamic Acid"[Mesh] OR Tranexamic Acid OR AMCHA OR t-AMCHA OR AMCA OR Anvitoff OR Cyklokapron OR Ugurol OR KABI 2161 OR Spotof OR Transamin OR Amchafibrin OR Exacyl OR Lysteda OR "Vasopressins"[Mesh] OR Vasopressin OR Antidiuretic Hormone OR anti-diuretic hormone OR Antidiuretic Hormones OR anti-diuretic hormones OR beta-Hypophamine OR beta Hypophamine OR Pitressin OR arginine vasopressin OR argipressin OR ornipressin OR terlipressin OR glypressin OR selepressin OR desmopressin OR DDAVP OR Vasostrict OR "Epinephrine"[Mesh] OR Epinephrine OR Adrenaline OR Epinephrine Acetate OR Medihaler-Epi OR Epinephrine Hydrochloride OR Adrenaline Hydrochloride OR Epitrate OR Lyophrin OR Epifrin OR Epinephrine Bitartrate OR Adrenaline Acid Tartrate OR Epinephrine Hydrogen Tartrate OR Adrenaline Bitartrate OR Adrenaclick OR "Misoprostol"[Mesh] OR Misoprostol OR Novo-Misoprostol OR Novo Misoprostol OR SC-29333 OR SC 29333 OR SC29333 OR SC-30249 OR SC 30249 OR SC30249 OR Apo-Misoprostol OR Apo Misoprostol OR Glefos OR Cytotec OR Misodel OR "Dinoprostone"[Mesh] OR Dinoprostone OR PGE2 alpha OR Prostaglandin E2alpha OR Prostaglandin E2 OR Prostaglandin E2 alpha OR PGE2 OR PGE2alpha OR Prepidil Gel OR Prostenon OR Cervidil OR Prostin E2)
Cochrane	1. TITLE-ABS-KEY ("Uterine Myomectomy" OR "Uterine Myomectomies" OR "Myomectomy" OR "Myomectomies" OR "Fibroidectomy" OR "Fibroidectomies") 2. TITLE-ABS-KEY ("Oxytocin" OR "Syntocinon" OR "Pitocin" OR "OT" OR "OXT" OR "carbetocin" OR "dcomot" OR "Depotocin" OR "Depotocin" OR "Duratocin" OR "Pabal" OR "Ascorbic Acid" OR "L-Ascorbic Acid" OR "L Ascorbic Acid" OR "Vitamin C" OR "Hybrin" OR "Magnorbin" OR "Sodium Ascorbate" OR "Ferrous Ascorbate" OR "Magnesium Ascorbate" OR "Magnesium di-L-Ascorbate" OR "Magnesium di-L-Ascorbate" OR "Magnesium Ascorbicum" OR "Ascor" OR "Ester-C" OR "Protexin" OR "Tranexamic Acid" OR "AMCHA" OR "t-AMCHA" OR "AMCA" OR "Anvitoff" OR "Cyklokapron" OR "Ugurol" OR "KABI 2161" OR "Spotof" OR "Transamin" OR "Amchafibrin" OR "Exacyl" OR "Lysteda" OR "Vasopressin" OR "Antidiuretic Hormone" OR "anti-diuretic hormone" OR "Antidiuretic Hormones" OR "anti-diuretic hormones" OR "beta-Hypophamine" OR "beta Hypophamine" OR "Pitressin" OR "arginine vasopressin" OR "argipressin" OR "ornipressin" OR "terlipressin" OR "glypressin" OR "selepressin" OR "desmopressin" OR "DDAVP" OR "Vasostrict" OR "Epinephrine" OR "Adrenaline" OR "Epinephrine Acetate" OR "Medihaler-Epi" OR "Epinephrine Hydrochloride" OR "Adrenaline Hydrochloride" OR "Epitrate" OR "Lyophrin" OR "Epifrin" OR "Epinephrine Bitartrate" OR "Adrenaline Acid Tartrate" OR "Epinephrine Hydrogen Tartrate" OR "Adrenaline Bitartrate" OR "Adrenaclick" OR "Misoprostol" OR "Novo-Misoprostol" OR "Novo Misoprostol" OR "SC-29333" OR "SC 29333" OR "SC29333" OR "SC-30249" OR "SC 30249" OR "SC30249" OR "Apo-Misoprostol" OR "Apo Misoprostol" OR "Glefos" OR "Cytotec" OR "Misodel" OR "Dinoprostone" OR "PGE2 alpha" OR "Prostaglandin E2alpha" OR "Prostaglandin E2" OR "Prostaglandin E2 alpha" OR "PGE2" OR "PGE2alpha" OR "Prepidil Gel" OR "Prostenon" OR Cervidil OR "Prostin E2") 3. TITLE-ABS-KEY (#1 AND #2)

Scopus	(“Uterine Myomectomy” OR “Uterine Myomectomies” OR “Myomectomy” OR “Myomectomies” OR “Fibroidectomy” OR “Fibroidectomies”) AND (“Oxytocin” OR “Syntocinon” OR “Pitocin” OR “OT” OR “OXT” OR “carbetocin” OR “dcomot” OR “Depotocin” OR “Depotocin” OR “Duratocin” OR “Pabal” OR “Ascorbic Acid” OR “L-Ascorbic Acid” OR “L Ascorbic Acid” OR “Vitamin C” OR “Hybrin” OR “Magnorbin” OR “Sodium Ascorbate” OR “Ferrous Ascorbate” OR “Magnesium Ascorbate” OR “Magnesium di-L-Ascorbate” OR “Magnesium di-L-Ascorbate” OR “Magnesium Ascorbicum” OR “Ascor” OR “Ester-C” OR “Protexin” OR “Tranexamic Acid” OR “AMCHA” OR “t-AMCHA” OR “AMCA” OR “Anvitoff” OR “Cyklokapron” OR “Ugurol” OR “KABI 2161” OR “Spotof” OR “Transamin” OR “Amchafibrin” OR “Exacyl” OR “Lysteda” OR “Vasopressin” OR “Antidiuretic Hormone” OR “anti-diuretic hormone” OR “Antidiuretic Hormones” OR “anti-diuretic hormones” OR “beta-Hypophamine” OR “beta Hypophamine” OR “Pitressin” OR “arginine vasopressin” OR “argipressin” OR “ornipressin” OR “terlipressin” OR “glypressin” OR “selepressin” OR “desmopressin” OR “DDAVP” OR “Vasostrict” OR “Epinephrine” OR “Adrenaline” OR “Epinephrine Acetate” OR “Medihaler-Epi” OR “Epinephrine Hydrochloride” OR “Adrenaline Hydrochloride” OR “Epitrate” OR “Lyophrin” OR “Epifrin” OR “Epinephrine Bitartrate” OR “Adrenaline Acid Tartrate” OR “Epinephrine Hydrogen Tartrate” OR “Adrenaline Bitartrate” OR “Adrenaclick” OR “Misoprostol” OR “Novo-Misoprostol” OR “Novo Misoprostol” OR “SC-29333” OR “SC 29333” OR “SC29333” OR “SC-30249” OR “SC 30249” OR “SC30249” OR “Apo-Misoprostol” OR “Apo Misoprostol” OR “Glefos” OR “Cytotec” OR “Misodel” OR “Dinoprostone” OR “PGE2 alpha” OR “Prostaglandin E2alpha” OR “Prostaglandin E2” OR “Prostaglandin E2 alpha” OR “PGE2” OR “PGE2alpha” OR “Prepidil Gel” OR “Prostenon” OR “Cervidil” OR “Prostin E2”)
Web of science (WOS)	1. TITLE-ABS-KEY ("Uterine Myomectomy" OR "Uterine Myomectomies" OR "Myomectomy" OR "Myomectomies" OR "Fibroidectomy" OR "Fibroidectomies") 2. TITLE-ABS-KEY ("Oxytocin" OR "Syntocinon" OR "Pitocin" OR "carbetocin" OR "dcomot" OR "Depotocin" OR "Duratocin" OR "Pabal" OR "Ascorbic Acid" OR "L Ascorbic Acid" OR "Vitamin C" OR "Hybrin" OR "Magnorbin" OR "Sodium Ascorbate" OR "Ferrous Ascorbate" OR "Magnesium Ascorbate" OR "Magnesium di-L-Ascorbate" OR "Magnesium di-L-Ascorbate" OR "Magnesium Ascorbicum" OR "Ascor" OR "Ester-C" OR "Protexin" OR "Tranexamic Acid" OR "Spotof" OR "Transamin" OR "Amchafibrin" OR "Exacyl" OR "Lysteda" OR "Vasopressin" OR "Antidiuretic Hormone" OR "anti-diuretic hormone" OR "beta Hypophamine" OR "Pitressin" OR "arginine vasopressin" OR "argipressin" OR "ornipressin" OR "terlipressin" OR "glypressin" OR "selepressin" OR "desmopressin" OR "Vasostrict" OR "Epinephrine" OR "Adrenaline" OR "Epinephrine Acetate" OR "Medihaler-Epi" OR "Epinephrine Hydrochloride" OR "Adrenaline Hydrochloride" OR "Epitrate" OR "Lyophrin" OR "Epifrin" OR "Epinephrine Bitartrate" OR "Adrenaline Acid Tartrate" OR "Epinephrine Hydrogen Tartrate" OR "Adrenaline Bitartrate" OR "Adrenaclick" OR "Misoprostol" OR "Novo-Misoprostol" OR "Novo Misoprostol" OR "Apo-Misoprostol" OR "Apo Misoprostol" OR "Glefos" OR "Cytotec" OR "Misodel" OR "Dinoprostone" OR "PGE2 alpha" OR "Prostaglandin E2" OR "Prostaglandin E2 alpha" OR "PGE2" OR "Prepidil Gel" OR "Prostenon" OR "Cervidil") 3. TITLE-ABS-KEY (#1 AND #2)

Supplemental table ٢: Summary characteristics of the included studies

Author, year	Drugs used	Study Design	No	Type of Procedure	Age	BMI	Uterine Size (weeks)	Preoperative HB	Preoperative Hematocrit	Location of fibroid		Maximum diameter (cm)	Blood Loss in mL	Need for transfusion (%)	Summary of Findings
										Intramural (%)	Subserosal (%)				
Open Myomectomy Studies															
Niroomand et al., 2015	Misoprostol	Double-blind RCT	40	OM	35.3 ± 6.1		11.9 ± 1.1			72.5%	27.50%	8.7 ± 4.6	458 ±287	0.00%	A single dose of vaginal misoprostol is effective in reducing hemorrhage during myomectomy.
	Placebo		40		33 ± 5.1		11.9 ± 1.5			85%	15 %	8 ± 2.8	696 ±411	22.5 %	
Abdel-Fattah et al., 2017	Misoprostol	Single-blind RCT	30	OM	35.35 ± 4.87	28.35 ± 1.81		11.32 ±1.1		71.7%	20 %		447.4 ±133.23		Misoprostol is effective during transabdominal myomectomy.
	Bilat. Ut. A. ligation		30					11.35 ±0.89					438.43 ±124.8		
Celik et al., 2003	Misoprostol	Double-blind RCT	13	OM	31.7 ±4.4	28.3 ±1.3	15.7 ±2.6	12.6 ±0.5		79 %	20 %	15.07 ±0.28	472 ±77	15.38%	Misoprostol is effective during transabdominal.
	Placebo		12		32.2 ± 2.9	28.5 ± 1	15.5 ± 2.8	12.3 ± 0.4		81%	18%	15.2 ±2.5	621 ±121	30.77%	
Abdel-Hafeez et al., 2015	Rectal Misoprostol	Double-blind RCT	25	OM	40.7 ± 5.1	28.9 ± 4.4	14 ± 1.7	11.4 ± 1		68 %	32%	14.9 ±3.9	574 ±194.8	24 %	Rectal misoprostol is a simple, applicable method for reducing intraoperative blood loss.
	Placebo		25		40.7 ± 5.5	27.2 ± 5	14.3 ± 2.2	11.4 ± 1.2		68%	32%	15.9 ±4.1	874 ±171.5	36 %	
Afolabi et al., 2018	Misoprostol	Open-label RCT	40	OM	36.4 ± 5.97		19.5 ± 6.93		33.78 ± 2.7	97.5%	87.5 %		931.89 ±602.13	2.5 %	Misoprostol is as effective as Tourniquet.
	Tourniquet		40				20.05 ± 6.98		34.56 ± 0.53	97.5%	82.5 %		848.4 ±588.6	5 %	
Saha et al., 2016	Vasopressin	Single-blind RCT	24	OM	33.4 ± 4.22		14.1 ± 1.72	10.5 ± 0.50	31.8 ± 1.44	50%	12.5%		356.5 ±58.4	8.33%	Intramyometrial vasopressin injection was more effective than Tourniquet.
	Tourniquet		24		33.5 ± 4.23		13.8 ± 1.76	10.5 ± 0.47	31.7± 1.51	54.2%	12.5 %		467.9 ±74.5	20.83%	
Ginsburg et al., 1993	Vasopressin	Open-label RCT	11	OM	36 ± 1				34.0 ± 1.3	100%		461 ±177		10 %	There were no evident differences between vasopressin and Tourniquet.
	Tourniquet		10		36 ±2				35.5 ± 1.2	100%		379 ±95		30 %	
Frederick et al., 2013	Vasopressin + misoprostol	Double-blind RCT	25	OM			22 (8, 36)	12.1 ±1.2			8.4 ±3.8	334 ±96.7		0.00%	Perivascular vasopressin plus misoprostol caused a significant reduction in blood loss compared with perivascular vasopressin alone.
	Vasopressin		25				16 (10, 22)	11.7 ±0.8			7.2 ±4.0	7.2 ±4.0	623 ±101.6	25 %	

Fletcher et al., 1996	Vasopressin	Double-blind RCT	26	OM	33.2 ±5.3		16.5 ±4.0	11.9 ±1.4				6.6 ±4.4	287.3 ±195	3.85%	Vasopressin prevents blood loss better than using the tourniquet during myomectomy.
	Tourniquet		26		35.2 ±3.9		16.6 ±3.81	12.2 ±1.1				9.4 ±6.1	512 ±400	19.23%	
Shady et al., 2018	TXA	Double-blind RCT	35	OM	35.54 ± 4.03	25.69 ± 2.21	20.63 ± 3.65	10.56 ± 0.77				12.66 ±3.96	658.43 ±204	17.14%	Intravenous and Topical TXA application is a safe and reliable method.
	Placebo		35		35.8 ± 4.7	25.43 ± 2.22	20.91 ± 3.67	10.57 ± 0.81				12.77 ±4.12	982.68 ±118.36	54.29%	
Shaaban et al., 2016	TXA	Open-label RCT	66	OM	35.03 ±5.43	28.28 ±2.06		10.77 ± 0.75	33.20 ± 2.37			9.96 ±1.48	346.67 ±92.9	19.7%	The TXA reduces blood loss during and after myomectomy for patients with multiple uterine fibroids.
	Placebo		66		34.60 ±5.06	28.59 ±2.07		10.73 ± 0.62	32.8 ± 2.07			10.48 ±1.37	560.76 ±80.7	34.85%	
Caglar et al., 2007	TXA	Double-blind RCT	50	OM	34.2 ±5.5	24.3 ±3.5		11.4 ±2					804 ±482	6 %	No additional benefit of intravenous TXA was found.
	Placebo		50		36.5 ±4.4	26.2 ±3.8		12 ±1.6	36 ±5	100%			1047 ±617	6 %	
Agostini et al., 2005	Oxytocin	Double-blind RCT	47	OM or HM	40 ±5.2			12 ±1.3	37 ±4	100%			508 ±585	14.89%	Oxytocin did not reduce perioperative blood loss.
	Placebo		47		39 ±4.3			11.95 ±1.82					451 ±363	4.26%	
Abdou et al., 2023	Oxytocin	Double-blind RCT	60	OM	31.08 ±4.22	26.87 ±6.2		10.8 ±0.77	32.38 ±2.31					21.7%	Tranexamic acid + ethamsylate and oxytocin had no significant effect in reducing intraoperative blood loss compared to placebo.
	Tranexamic acid + ethamsylate		60		31.33 ±3.82	27.18 ±5.88		10.81 ±0.83	32.41 ±2.51					15 %	
	Placebo		60		29.52 ±4.37	27.17 ±5.83		10.9 ±0.84	32.79 ±2.58					20 %	
Abdul et al., 2019	Tranexamic acid + tourniquet	Double-blind RCT	40	OM		29.31 ±4.72		11.4 ±0.94	34.3 ±2.4					45 %	Tranexamic acid + the tourniquet is better than a tourniquet alone in reducing intraoperative blood loss
	Tourniquet +placebo		40			27.88 ±6.13		11.34 ±1.28	34.18 ±3.47					30 %	
Alhalaby et al., 2021	Misoprostol	RCT	25	OM	32.88 ±3.73	25.60 ±4.11		0.77 ±0.11	37.20 ±2.60						Vaginal misoprostol is effective in lowering blood loss during abdominal myomectomy
	Placebo		25		34.64 ±4.10	27.60 ±4.30		11.70 ±0.12	37.73 ±2.40						
Çetin et al., 2019	Oxytocin	Double-blind RCT	50	OM	36.66 ±5.47	25.54 ±3.53	14.20 ±3.43	11.5 ±1.59	35.85 ±4.69			8.06 ±3.34		4 %	Intraoperative administration of oxytocin appears to be safe and effective.
	Placebo		50		36.72 ±4.69	25.74 ±2.99	15.16 ±4.12	11.87 ±1.51	36.5 ±3.92			8.20 ±3.78		16 %	

Ghanaei et al., 2021	lidocaine + epinephrine	Double-blind RCT	30	OM	42.6 ±5.95	26.92 ±5.61		11.7 ±1.26							lidocaine + epinephrine administration appears to be safe and effective in reducing intraoperative blood loss.
	Placebo		30		42.6 ±7.15	27.15 ±4.53		11.55 ±1.33							
Hashmi et al., 2021	Misoprostol	Double-blind RCT	50	OM	32.16 ±9.44	26.07 ±10.44		13.64 ±8.55						4 %	preoperative use of misoprostol is effective and saves in reducing blood loss.
	Placebo		50		32.48 ±7.44	26.55 ±9.44		13.55 ±8.55						6 %	
Isah et al., 2020	Vasopressin	Double-blind RCT	62	OM	33.9 ±4.1		21.8 ±3.7							12.9%	Intra-myometrial injection of vasopressin had a significant effect in reducing intraoperative blood loss.
	Placebo		63		32.8 ±3.4		21 ±4.2							42.9 %	
Nnagbo et al., 2023	Misoprostol + tourniquet	Open-label RCT	63	OM		27.32 ±4.27	23.26 ±5.69	11.4 ±0.86							the use of misoprostol + tourniquet significantly reduced intraoperative blood loss.
	Tourniquet		63			26.40 ±3.79	23.73 ±7.04	11.5 ±1.12							
Sharami et al., 2020	Misoprostol	Double-blind RCT	47	OM	39.34 ±6.38	25.82 ±2.89		11.42 ±1.10	34.27 ±3.30					8.5 %	preoperative use of misoprostol is effective in reducing intraoperative blood loss.
	Placebo		47		38.00 ±4.89	25.99 ±3.26		11.31 ±1.23	33.89 ±3.77					10.6 %	
Taher et al., 2021	Carbetocin	Double-blind RCT	69	OM	44.4 ±3.2	26.7 ±3.6	15.9 ±1.8	11.8 ±0.8				14.51 ±1.26		11.6 %	Preoperative intravenous carbetocin is effective in reducing intraoperative blood loss.
	Placebo		69		44.01 ±3.4	26.5 ±3.9	16.4 ±2.2	11.5 ±0.5				14.61 ±1.28		24.6 %	
Ahmed et al., 2020	Oxytocin	RCT	67	OM	32.3 ±3.5	24. 9±2.3	18.5 ±1.7	11.8 ±0.9	33.7 ±3.2	100%	0	3.8 ±0.6		9 %	Intraoperative oxytocin infusion may be effective and save in lowering intraoperative blood loss.
	Placebo		67		32.4 ±3.7	25.1 ±2.3	18.3 ±1.9	11.7 ±1.0	33.5 ±3.8	100%	0	4.0 ±0.7		22.4 %	
Ahmed et al., 2020 _2	Oxytocin	Single-blind RCT	30	OM	37.10 ±4.35		18.33 ±4.52	11.53 ±0.61						10 %	Intraoperative oxytocin infusion may be effective and save in lowering intraoperative blood loss.
	Placebo		30		36.67 ±3.70		16.67 ±3.53	11.44 ±0.51						36.6 %	
Ali et al., 2019	Misoprostol	Double-blind RCT	18	OM	33.4 ±6.3			12.3 ±1.2	38.0 ±5.2					38.9 %	Pericervical tourniquet is more effective than pre-operative vaginal misoprostol in reducing both intra-operative and post-operative blood loss.
	Uterine tourniquet		18		30.8 ±5.8			11.9 ±1.1	36.2 ±3.2					5.6 %	

Al-Morsi et al., 2021	Tranexamic acid +ethamsylate	RCT	30	OM	37.90 ±7.19	25.24 ±4.05		10.89 ±0.98	32.66 ±2.95	50%	50%			0.00%	Tranexamic acid andethamsylate are more effective than oxytocin in reducing the need for blood transfusion.
	Oxytocin		30		39.76 ±4.75	26.78 ±2.84		10.85 ±0.41	32.18 ±1.23	60%	40%			20 %	
	Placebo		30		38.66 ±5.22	25.74±3.13		10.92 ±0.41	31.54 ±1.21	53.3%	46.70%			26.7 %	
Asraa et al., 2021	Tourniquet	RCT	30	OM	36.7 ±4.6	23.9 ±3.2	13.2 ±1.2	11.8 ±0.9	36.1 ±2.3	53.3%	66.70%		375.0 ±96.3	6.7 %	Pericervical tourniquet is more effective than pre-operative misoprostol in reducing intra-operative.
	Misoprostol		30		37.8 ±3.8	23.9 ±2.1	13.3 ±1.4	11.8 ±1.0	36.0 ±2.1	46.7%	80.00%		440.0 ±78.1	26.7 %	
Dele et al., 2022	Tranexamic acid +tourniquet	Double-blind RCT	66	OM	34.4 ±3.6	28.4 ±2.1	23.9 ±6.4	11.0 ±0.9					415.4 ±173.2		Intravenous tranexamic with pericervical tourniquet is effective in reducing blood loss during abdominal myomectomy.
	Placebo		65		35.9 ±5.5	28.7 ±2.0	23.3 ±5.4	11.0 ±0.9					807.5 ±366.6		
El Maraghy et al., 2023	Misoprostol	RCT	20	OM	33.9 ±5.2	23.09 ±2.6		12.3 ±1.1					294.25 ±169.01	0.00%	Preoperative misoprostol may be a method of lowering intraoperative blood loss.
	Placebo		20		30.6 ±5.5	23.8 ±3.7		11.9 ±1.02					447.5 ±213.89	5 %	
Gamal et al., 2023	Carbetocin	RCT	55	OM				10.74 ±0.76	32.18 ±2.22						Uterine artery tourniquet is more effective than carbetocin in lowering blood loss during abdominal myomectomy.
	Tourniquet		55					10.83 ±0.77	32.47 ±2.29						
Lotfy et al., 2020	Tranexamic acid	RCT	66	OM	38.03 ±5.04	27.86 ±3.24		11.19 ±0.98	33.53 ±2.39				535.15 ±80.30		Carbetocin efficacy in reducing blood loss is higher than tranexamic acid.
	Carbetocin		66		36.97 ±4.16	28.03 ±3.17		11.41 ±1.01	33.80 ±2.47				399.27 ±28.94		
Mansour et al., 2021	Tourniquet	Double-blind RCT	36	OM	30.8 ±5.8			11.9 ±1.1	36.2 ±3.2					50 %	Pericervical uterine artery tourniquet is more effective than trans-rectal Misoprostol in reducing intraoperative blood loss.
	Misoprostol		36		33.4 ±6.3			12.3 ±1.2	38.0 ±5.2					61.1%	

Mohamed et al., 2021	Carbetocin	RCT	40	OM	45.67 ±3.85	25.2 ±1.86		11.05 ±0.70	37.15 ±1.84	72.5%	0.00%				Intramyometrial carbetocin injection is more effective than rectal misoprostol in minimizing blood loss during abdominal myomectomy.
	Misoprostol		40		43.27 ±4.16	25.42 ±1.57		10.82 ±0.72	36.83 ±1.05	80%	0.00%				
	Placebo		40		44.52 ±3.85	26.5 ±1.85		11.01 ±0.6	36.9 ±2.2	75%	0.00%				
Mousad et al., 2022	Carbetocin	Single-blind RCT	30	OM	37.10 ±4.35		18.33 ±4.52	11.53 ±0.61						10 %	Carbetocin injection is an effective method of reducing intraoperative blood loss.
	Placebo		30		36.67 ±3.70		16.67 ±3.53	11.44 ±0.51						36.6 %	
Nasr Al-Deen et al., 2020	Oxytocin	Double-blind RCT	30	OM	35.4 ±4.5	24.9 ±2.1	16.7 ±1.1	10.1 ±1.6	40.7 ±2.2					3.3 %	Oxytocin infusion may be an effective method to reduce blood loss.
	Placebo		30		34.3 ±3.9	25.6 ±1.7	16.3 ±1.2	10.8 ±1.3	41.5 ±1.9					20 %	
Niaz et al., 2022	Oxytocin	RCT	54	OM	40.481 ±1.84									7.4 %	Intraoperative oxytocin infusion may be an effective and safe method to minimize intraoperative blood loss.
	Placebo		54		40.425 ±2.8									25.9 %	
Elgendy et al., 2021	Vasopressin	Open-label RCT	30	OM	33.37 ±5.57			10.87 ±1.1	31.38 ±1.59				115.53 ±23.17	0.00%	Intramyometrial injection of vasopressin may have an effective role in decreasing blood loss and subsequent need for blood transfusion.
	Placebo		30		33.4 ±5.08			11.13 ±1.06	31.78 ±4.51				826.67 ±185.94	30 %	
El Sharkwy et al., 2016	Misoprostol + vasopressin	RCT	52	OM	41.2 ±4.1	31 ±3.7	16.0 ±2.5	10.8 ±1.5				9.5. ±2.6	254.1 ±185.4	9.7 %	The usage of preoperative misoprostol and perivascular vasopressin together is a highly efficient way to reduce blood loss during abdominal myomectomy.
	Tourniquet		52		40.6 ±3.6	32 ±3.1	14.7 ±2.9	11.9 ±1.6				8.7 ±3.8	375.7 ±292.3	32.7 %	
Vahdat et al., 2015	Misoprostol	Double-blind RCT	32	OM	35.75 ±5.45	28.37 ±2.99		10.59 ±1.11						15.6 %	Preoperative sublingual misoprostol is effective in reducing intraoperative blood loss during abdominal myomectomy.
	Placebo		32		35.69 ±6.75	28.64 ±3.14		10.11 ±1.27						25 %	
Sallam et al., 2018	Carbetocin	Double-blind RCT	43	OM	34.84 ±4.41	25.58 ±2		10.73 ±0.85						18.6 %	Pre-operative intravenous Carbetocin is an effective method to reduce intraoperative blood loss during abdominal myomectomy.
	Placebo		43		34.49 ±4.39	25.43 ±2.06		10.69 ±0.89						69.8 %	

Rashed et al., 2014	Misoprostol	Double-blind RCT	20	OM	30.60 ±2.72	28.10 ±0.83		12.43 ±0.66	36.53 ±1.95					0.00%	Preoperative rectal misoprostol is an effective method for reducing blood loss during myomectomy.
	Placebo		20		31.75 ±2.45	28.31 ±0.78		12.37 ±0.75	35.89 ±2.11					10 %	
Mohamed et al., 2018	Misoprostol	Double-blind RCT	25	OM	36.64 ±3.7	25.7 ±1.8	9.66 ±2.64	11.8 ±0.85	36.6 ±2.1	76%	20.00%			4 %	Preoperative rectal misoprostol may be effective in reducing blood loss in patients undergoing myomectomy.
	Placebo		25		36.7 ±2.8	25.6 ±1.8	10.24 ±3.4	11.5 ±0.77	36.6 ±2.1	88%	12.00%			16%	
Gharabaghi et al., 2017	Misoprostol	Double-blind RCT	35	OM	37.7 ±5.3	26.4 ±2.9	12.1 ±3.5	12.3 ±1.4	37 ±4.4			91.6 ±35.2		3.2%	Preoperative vaginal misoprostol may be an effective method for reducing blood loss during myomectomy.
	Oxytocin		35		38.4 ±4.6	25.7 ±3.4	10.7 ±2.2	12.7 ±1.2	38 ±3.9			88.4 ±29.7		9.7%	
Gad Allah et al., 2015	Carbetocin	Single-blind RCT	20	OM	33.75 ±6.61			10.96 ±0.56	35.91 ±2.59					5 %	Intramyometrial carbetocin injection is effective in lowering blood loss in women undergoing myomectomy.
	Tourniquet		20		34.8 ±4.33			11.14 ±0.68	34.42 ±3.17					15 %	
Badawy et al., 2017	Vasopressin	Double-blind RCT	20	OM	39.4 ±5.7	31.72 ±4.15		10.93 ±0.83						0.00%	Intra-myometrial octreotide acetate injection effectively reduces blood loss during myomectomy, but local vasopressin is still more effective.
	Octreotide acetate		20		37.9 ±7.45	30.32 ±4.04		10.91 ±0.72						5 %	
	Placebo		20		37.2 ±7.04	30.92 ±3.69		11.23 ±0.84						45 %	
Amin et al., 2017	Oxytocin	Single-blind RCT	70	OM	28.60 ±4.61	26.0 ±2.76		12.3 ±1.2	28.86 ±1.23	60%	40.00%			31.4 %	A peri-cervical tourniquet reduces blood loss more effectively than oxytocin infusion during myomectomy.
	Tourniquet		70		26.80 ±6.98	24.0 ±3.93		11.9 ±1.1	32.34 ±2.92	48.6%	51.40%			5.7%	
Abouzeid et al., 2018	Bupivacaine +epinephrine	RCT	20	OM	43.30 ±6.94			13.37 ±1.13		100%	0.00%			0.00%	Intramyometrial injection of bupivacaine plus epinephrine is highly effective in reducing blood loss.
	Tourniquet		20		34.45 ±2.72			13.10 ±0.97		100%	0.00%			0.00%	
	Placebo		20		36.25 ±2.86			12.70 ±1.19		100%	0.00%			10 %	

Minimally-Invasive Myomectomy															
Zullo et al., 2004	Bupivacaine + Epinephrine	Double-blind RCT	30	LM	28.2 ±3.1	24.2 ±2.5							143.9 ±48.1	0.00%	The injection of bupivacaine plus epinephrine during laparoscopic myomectomy is effective.
	Placebo		30		27.1 ±2.9	23.9 ±2.3							212.5 ±51	0.00%	
Lee et al., 2016	Ascorbic acid	Double-blind RCT	24	LM	42 ±6.38	23.1 ±3.12		12.6 ±1.58		25 %	66.7 %	6.6 ±1.62	193.3 ±204.9	4.17%	The intravenous ascorbic acid infusion did not reduce intraoperative blood loss.
	Placebo		22		41.1 ±5.69	22.6 ±2.5		11.8 ±1.94		41 %	50%	6.7 ±1.75	159.5 ±193.9	18.18%	
Kalogiannidis et al., 2011	Misoprostol	Open-label RCT	30	LM	37.2 ±6.5								126 ±41	0.00%	Misoprostol significantly reduces intraoperative blood loss.
	Placebo		34		34.8 ±4.6								217 ±74	0.00%	
Wang et al., 2007	Oxytocin	Open-label RCT	30	LM	38.1 ±6.8					100 %		7.6 ±2.2	269.5 ±225.8	6.67%	Oxytocin infusion may decrease operative blood loss.
	Placebo		30		35.8 ±6.1					100 %		7.5 ±1.9	445 ±268.6	36.67%	
Assaf et al., 1993	Ornipressin	Open-label RCT	21	LM	33.4 6 2.23								220.6 ±50		Vasoconstricting agents make laparoscopy more convenient for the surgeon.
	Placebo		17										370.2 ±40		
Wong et al., 2014	Vasopressin	Double-blind RCT	20	LM	45 (25–52)						100 %		15.25 ±12.5		Transcervical intralesional vasopressin injection reduces intraoperative blood loss.
	Vasopressin		19		45 (30–52)						100 %		47.75 ±37.25		
Srivastava et al., 2018	Vasopressin + misoprostol	Single-blind RCT	30	LM	30.3 ± 3.3		15.5 ± 4.3	12.3 ± 1.2	11.11 ±1.02			8.8 ± 2.7	196 ±96.7	0.00%	The addition of rectal misoprostol to intramyometrial vasopressin led to a significant reduction in blood loss.
	Vasopressin		30		29.6 ± 4.9		16.7 ± 3.4	11.9 ± 1.0	10.73 ±0.99			9.2 ± 2.6	206 ±101.6	3.33%	
Rasheedy et al., 2020	Tranexamic acid	Double-blind RCT	40	HM	37.63 ±5.33	30.8 ±2.21		11.11 ±1.02		0.00%	0.00%			0.00%	Intrauterine instillation of TXA effectively minimizes the decrease in postoperative hemoglobin.
	Placebo		40		37.17 ±5.41	31.1 ±2.2		10.73 ±0.99		0.00%	0.00%			0.00%	
Soliman et al., 2021	Vasopressin	Double-blind RCT	97	LM	37.30 ±4.70			12.23 ±1.45		48.45%	15.46%			15.46%	Intramyometrial vasopressin injection is effective in lowering blood loss during laparoscopic myomectomy.
	Placebo		97		36.68 ±4.13			11.90 ±1.37		51.54%	8.25%			29.89%	

Jafari-Shobeiri et al., 2019	Tranexamic acid	Single-blind RCT	46	HM	47.91 ±9.14			12.31 ±1.36	36.62 ±3.74	0.00%	0.00%	19.05 ±8.22			Tranexamic acid is an effective method to reduce intraoperative bleeding during hysteroscopic myomectomy.
	Oxytocin		46		45.61 ±8.74			12.31 ±1.20	36.44 ±3.22	0.00%	0.00%	19.45 ±11.01			
Mohamed et al., 2019	Tranexamic acid	RCT	30	HM	38.67 ±5.69					0.00%	0.00%			0.00%	Oxytocin and tranexamic acid both work equally well to minimize blood loss and the need for transfusions during hysteroscopic myomectomy.
	Oxytocin		30		39.13 ±3.82					0.00%	0.00%			0.00%	
Mousa et al., 2012	Tranexamic acid	Double-blind RCT	23	HM	34.08 ± 6.43	26.27 ±3.28		11.95 ± 0.78						21.70%	Oxytocin usage is associated with a better hematological profile and less need for blood transfusion than tranexamic acid.
	Oxytocin		24		35.24 ± 5.17	26.21 ± 2.99		11.81 ± 0.74						4.10%	
Hudecek et al., 2016	Epinephrine	RCT	100	LM	34.3 ± 5.6	29.4 ± 6.2	39.76 ± 2.20			100 %	100 %		57.3 ± 22.9		The usage of epinephrine during laparoscopic Myomectomy is an effective and safe method to reduce blood loss.
	Placebo		90		32.3 ± 5.3	28.5 ±6.5	39.8 ± 2.33			100 %	100 %		142.9 ± 105.6		

OM: Open myomectomy; LM: Laparoscopic myomectomy; HM hysteroscopic myomectomy; Bilat.Ut. A. ligation: Bilateral uterine artery ligation; TXA: Tranexamic acid; RCT: Randomized controlled trial. * p <0.05

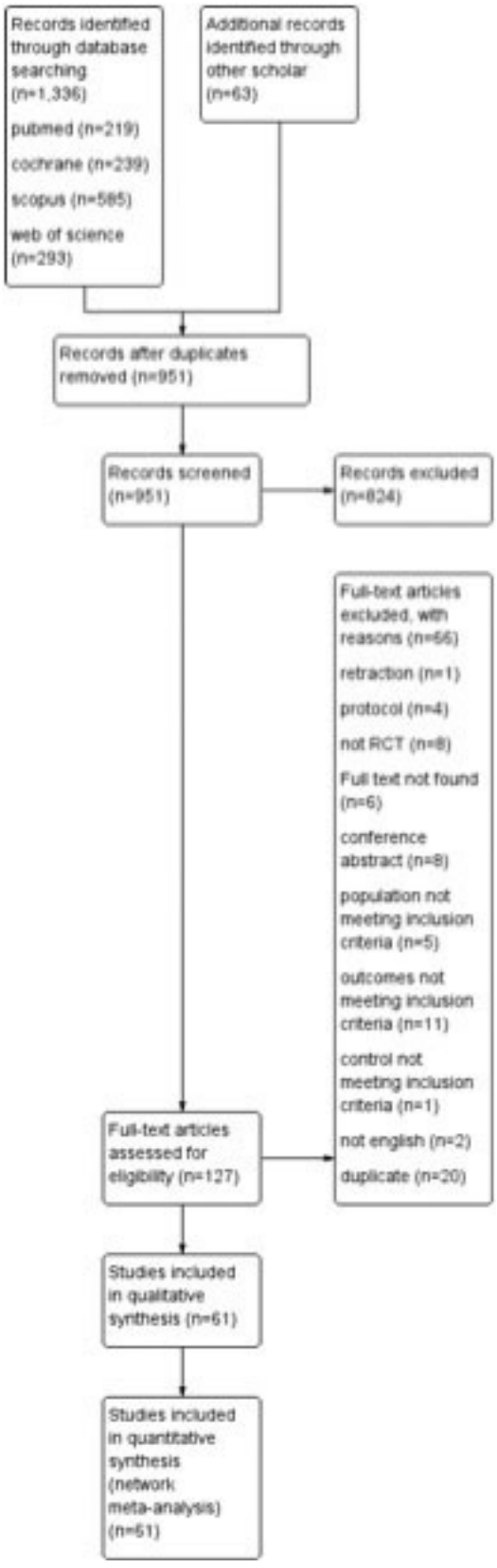
Supplemental table 3: summary of the results of NMA, comparing Placebo with other different drugs

	Number of studies	The best treatment	95% CI	Hetero-geneity
Open Myomectomy				
Intraoperative blood loss	44	Vasopressin + Misoprostol	MD: -714.57 95%CI: [-929.98 , -499.17]	I^2= 95.9% P<0.0001
Need for transfusion	39	Vasopressin + Misoprostol	RR: 0.08 95%CI: [0.03 , 0.22]	I^2= 27.7% P= 0.076
Postoperative HB	44	Bupivacaine + Epinephrine	MD: 2.16 95%CI: [1.21 , 3.11]	I^2= 77.4% P<0.0001
Postoperative HCT	26	Tourniquet	MD: 4.66 95%CI: [2.91 , 6.41]	I^2= 91.6% P<0.0001
Postoperative hospital stay	20	Tourniquet	MD: -0.59 95%CI: [-0.77 , -0.41]	I^2= 52% P= 0.0067
Postoperative fever	11	Vasopressin	RR: 0.36 95%CI: [0.09 , 1.4]	I^2= 0 P= 0.78
Other complications	16	Misoprostol + Tourniquet	RR: 0.15 95%CI: [0.03 , 0.72]	I^2= 0 P= 0.94
Minimal invasive myomectomy				
Intraoperative blood loss	9	Oxytocin	MD: -175.5 95%CI: [-313.13 , -37.87]	I^2= 90.3% P= 0.0014
Need for transfusion	11	Oxytocin	RR: 0.18 95%CI: [0.04 , 0.75]	I^2= 0 P= 1
Postoperative HB	6	Oxytocin	MD: 1.4 95%CI: [0.08 , 2.72]	I^2= 84.5% P= 0.0016
Postoperative fever	2	Oxytocin	RR: 0.33 95%CI: [0.01 , 7.86]	P --
Other complications	4	Tranexamic acid	RR: 0.14 95%CI: [0.01 , 2.68]	Q=0 df = 0 P --

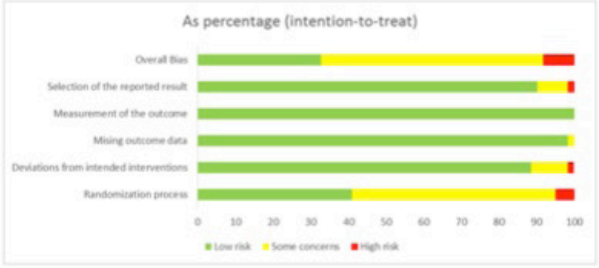
Supplemental table 3 presents the summary of the NMA of comparing placebo with different pharmacological treatments

HCT; Hematocrit and HB; Haemoglobin, RR; Relative risk, MD; Mean Difference, and CI; Confidence interval

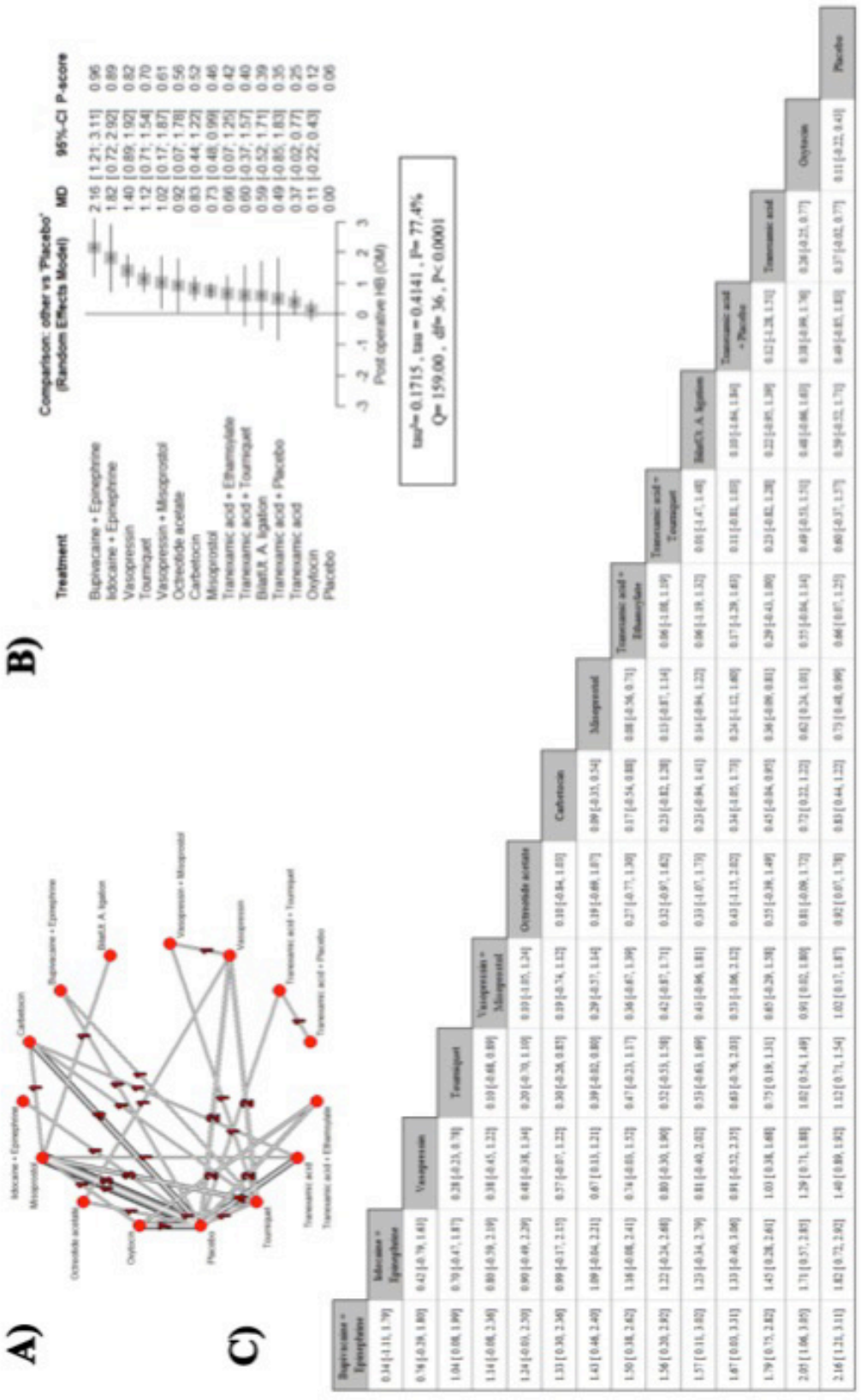
Supplemental figure 1: PRISMA flow diagram



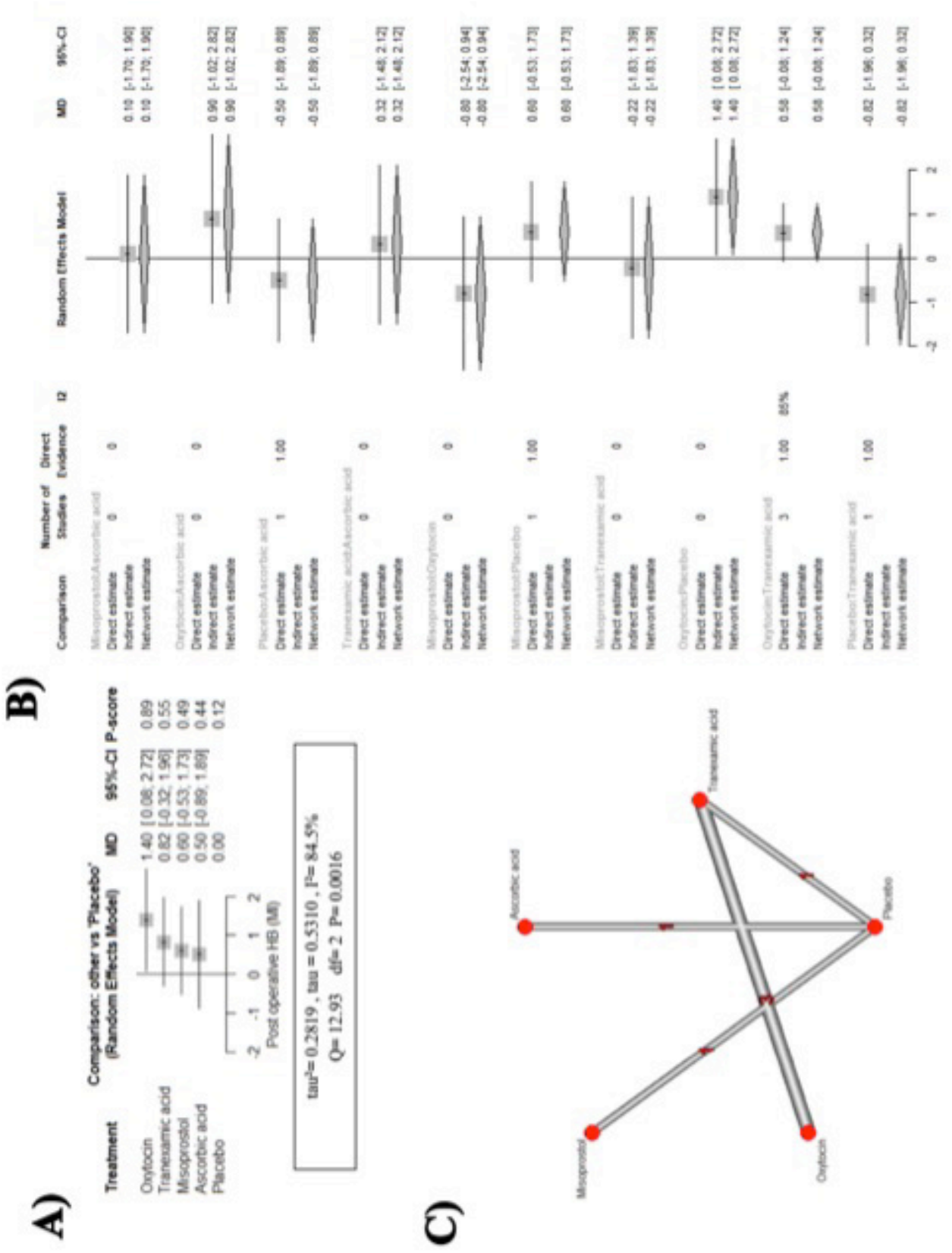
Supplemental figure 2: ROB assessment



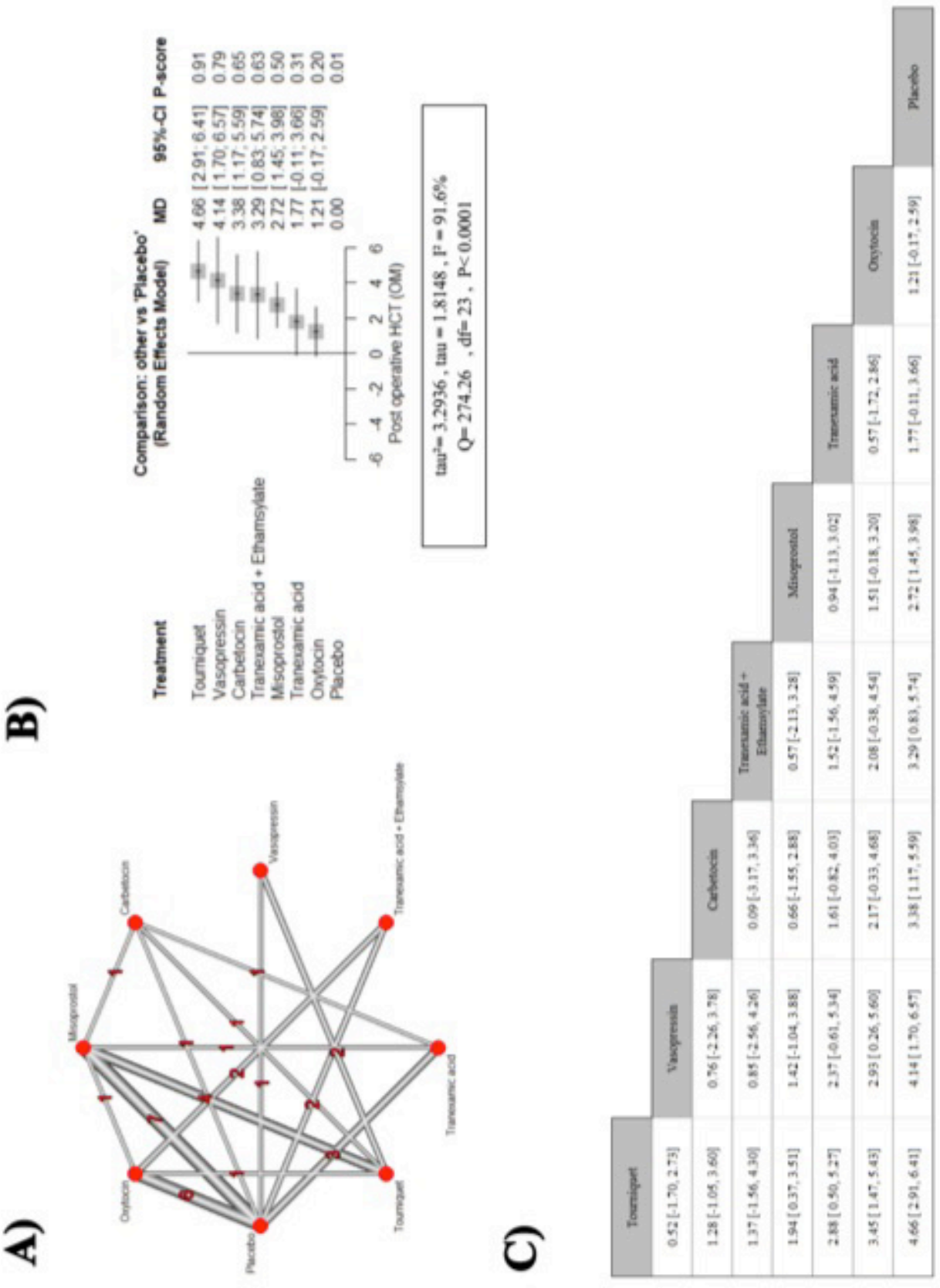
Supplemental figure 3: Postoperative HB value OM



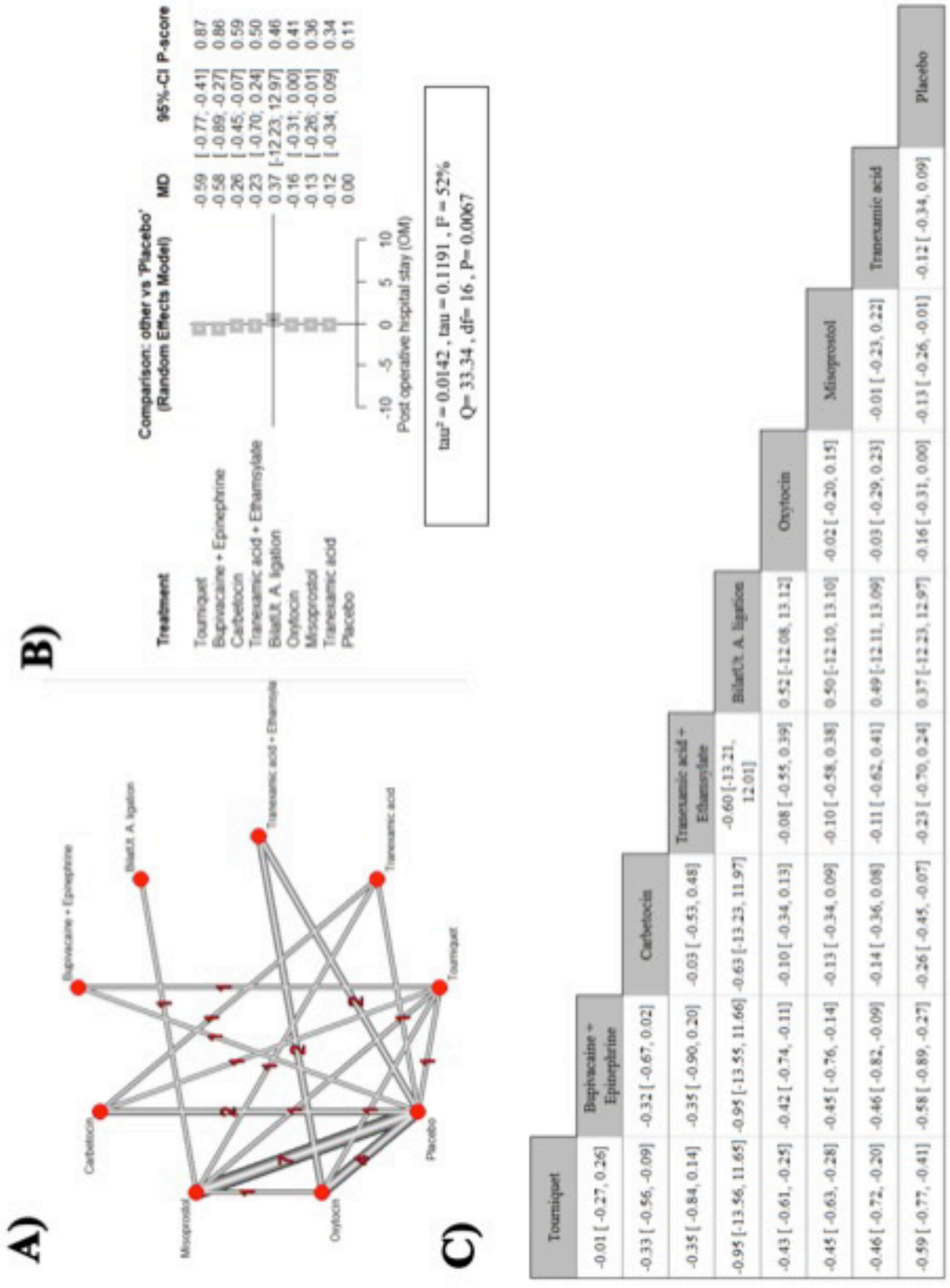
Supplemental figure 4: Postoperative HB value MI myomectomy



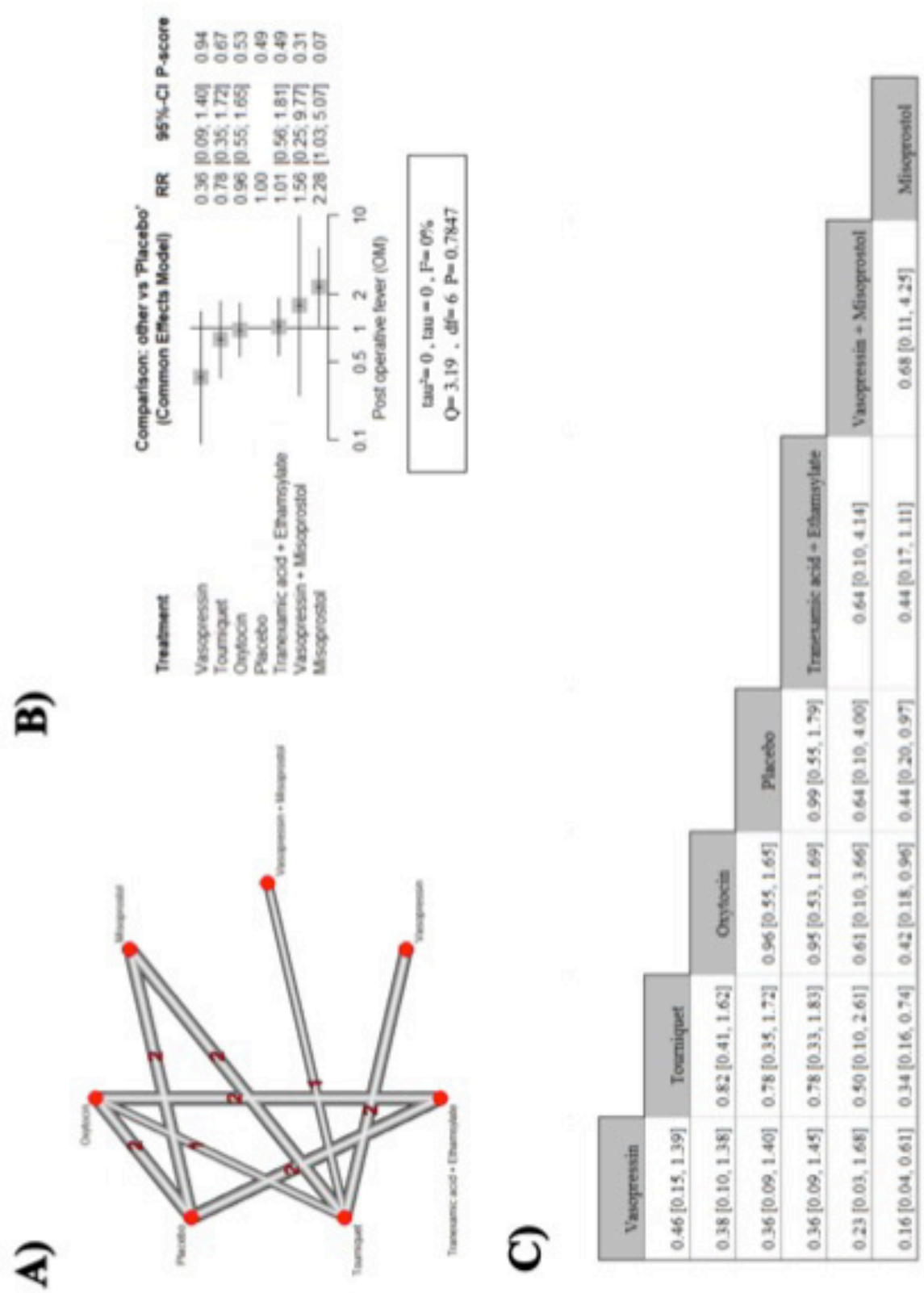
Supplemental figure 5: Postoperative HCT value OM



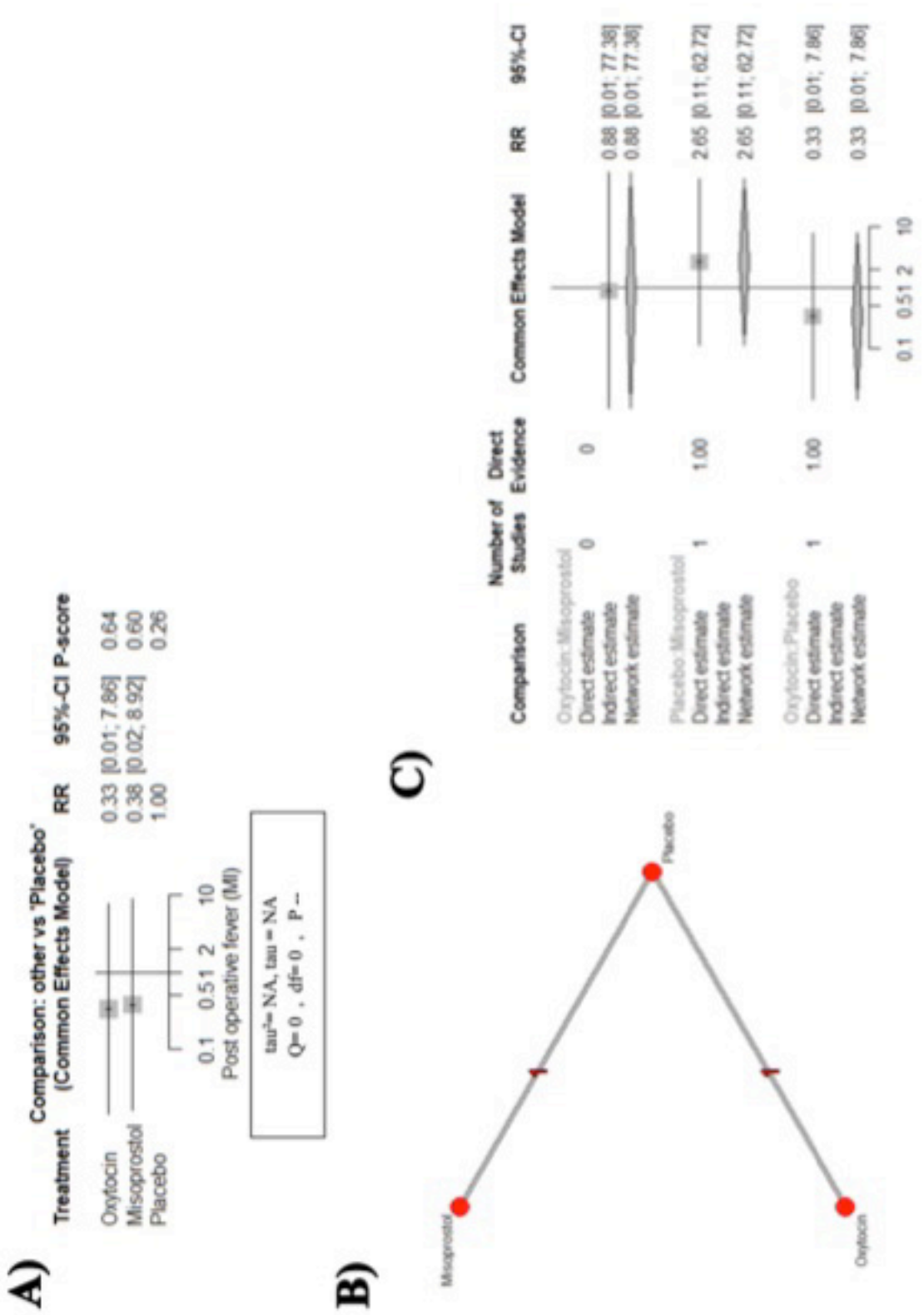
Supplemental figure 6: Postoperative hospital stay OM



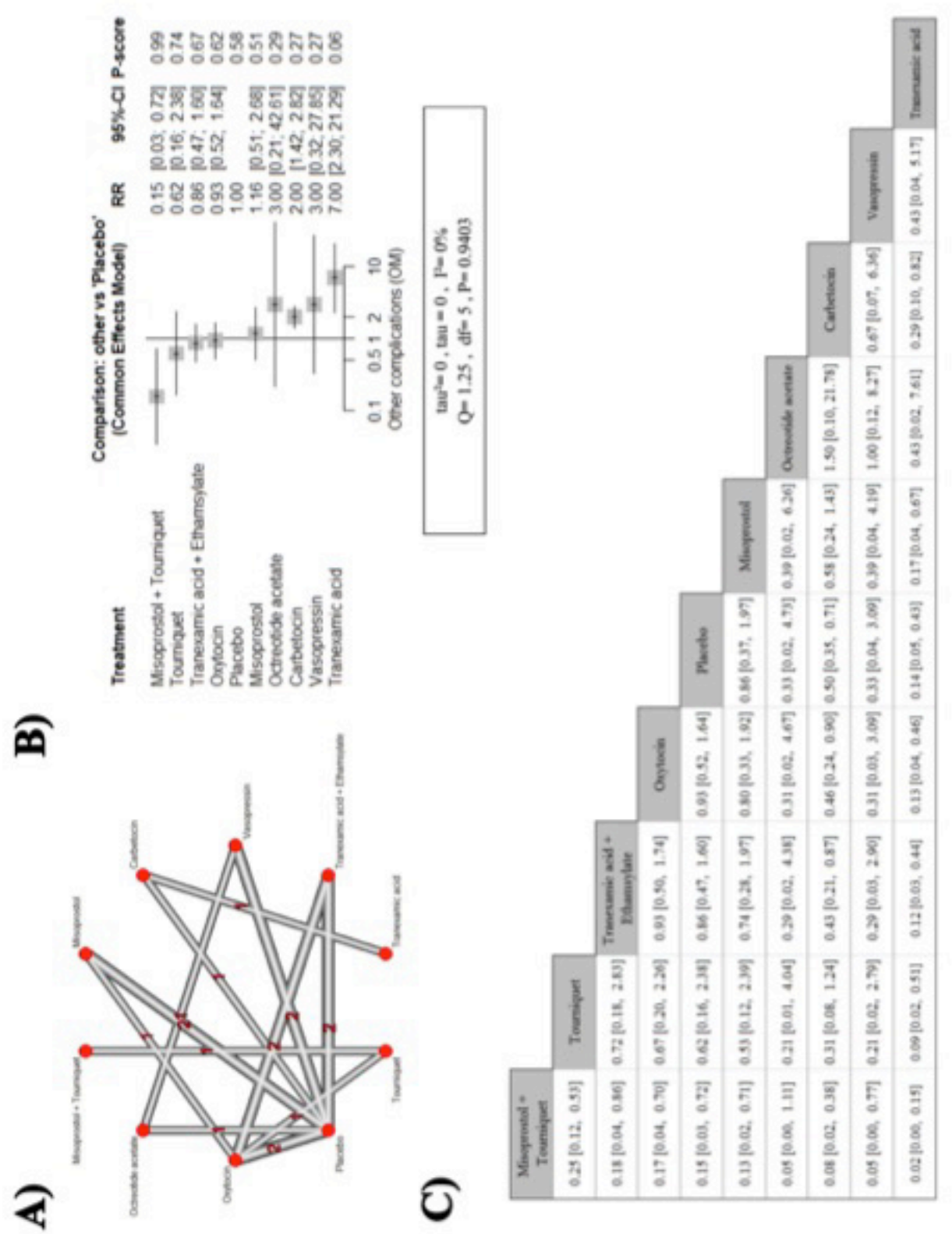
Supplemental figure 7: Postoperative fever OM



Supplemental figure 8: Postoperative fever MI myomectomy

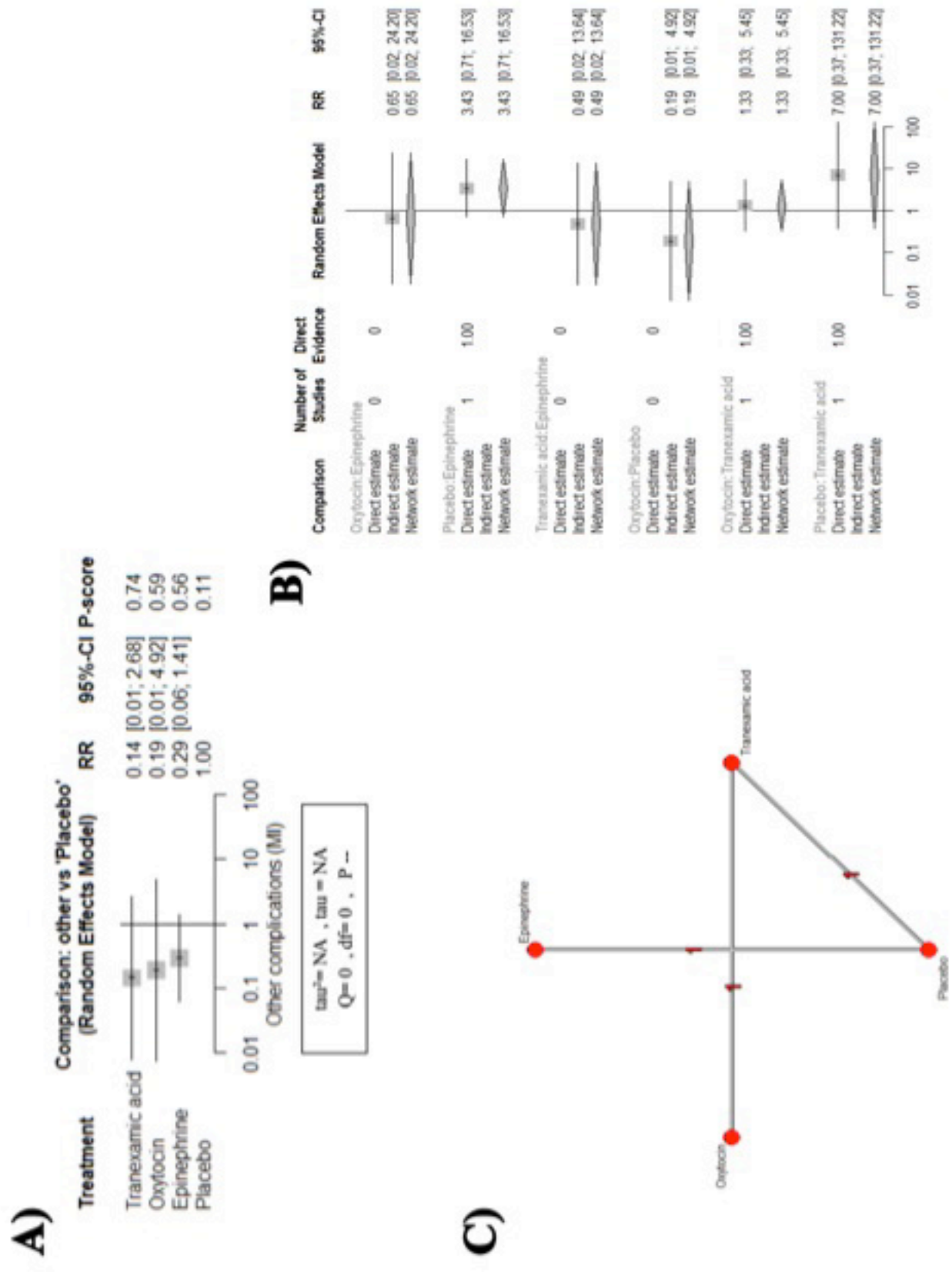


Supplemental figure 9: Postoperative other complications OM



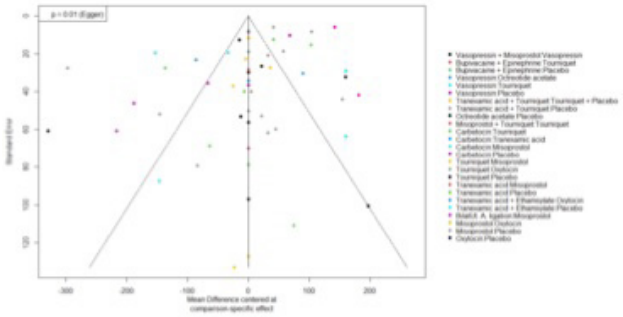
	Misoprostol + Tourniquet	Tourniquet	Tranexamic acid + Ethamsylate	Oxytocin	Placebo	Misoprostol	Octreotide acetate	Carbetocin	Vasopressin	Tranexamic acid
Misoprostol + Tourniquet		0.25 [0.12, 0.53]	0.18 [0.04, 0.86]	0.17 [0.04, 0.70]	0.15 [0.03, 0.72]	0.13 [0.02, 0.71]	0.05 [0.00, 1.11]	0.08 [0.02, 0.38]	0.05 [0.00, 0.77]	0.02 [0.00, 0.15]
Tourniquet	0.72 [0.18, 2.83]		0.93 [0.50, 1.74]	0.67 [0.20, 2.26]	0.62 [0.16, 2.38]	0.53 [0.12, 2.39]	0.21 [0.01, 4.04]	0.31 [0.08, 1.24]	0.21 [0.02, 2.79]	0.09 [0.02, 0.51]
Tranexamic acid + Ethamsylate	0.86 [0.47, 1.60]	0.74 [0.28, 1.97]	0.39 [0.02, 4.38]	0.43 [0.21, 0.87]	0.29 [0.03, 2.90]	0.12 [0.03, 0.44]				
Oxytocin	0.93 [0.52, 1.64]	0.80 [0.33, 1.92]	0.31 [0.02, 4.67]	0.46 [0.24, 0.90]	0.31 [0.03, 3.09]	0.13 [0.04, 0.46]	0.14 [0.05, 0.43]			
Placebo	0.86 [0.37, 1.97]	0.33 [0.02, 4.79]	0.50 [0.35, 0.71]	0.33 [0.04, 3.09]	0.14 [0.05, 0.43]					
Misoprostol	0.39 [0.02, 6.26]	0.58 [0.24, 1.43]	0.39 [0.04, 4.19]	0.17 [0.04, 0.67]						
Octreotide acetate	1.50 [0.10, 21.78]	1.00 [0.12, 8.27]	0.43 [0.02, 7.61]							
Carbetocin	0.67 [0.07, 6.34]	0.29 [0.10, 0.82]								
Vasopressin	0.43 [0.04, 5.17]									
Tranexamic acid										

Supplemental figure 10: Postoperative other complications MI myomectomy

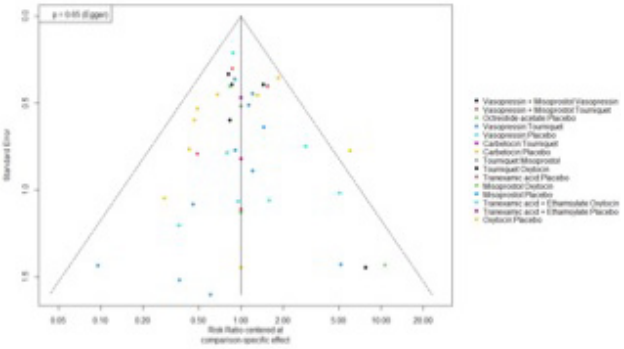


Supplemental figure 11: Publication bias of different outcomes

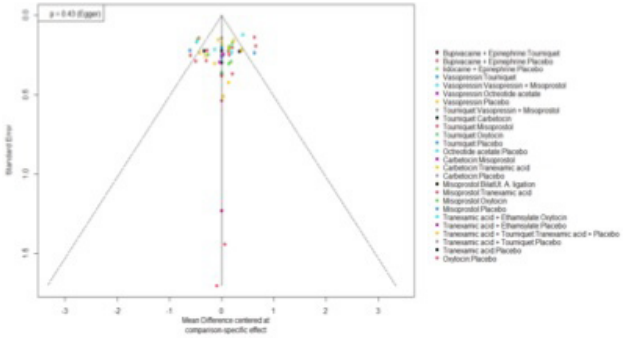
A)



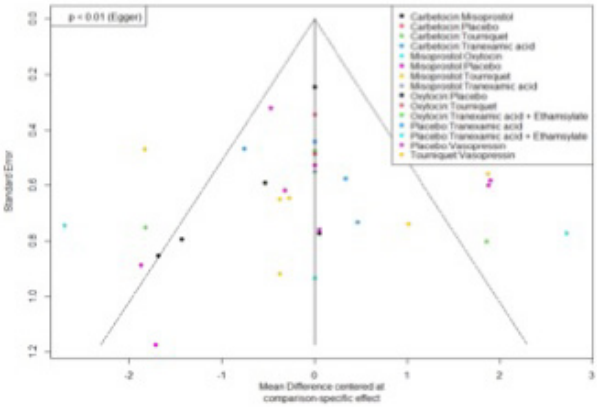
B)



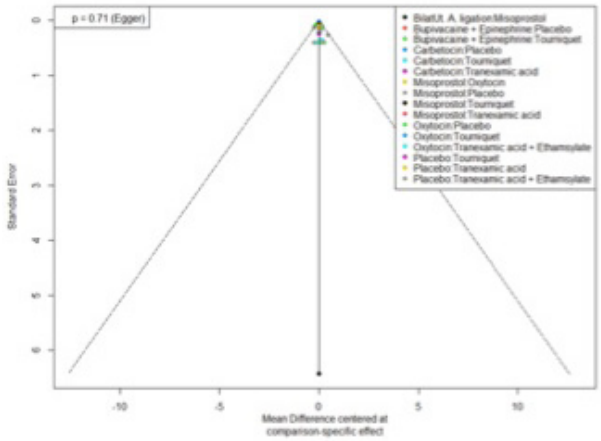
C)



D)



E)



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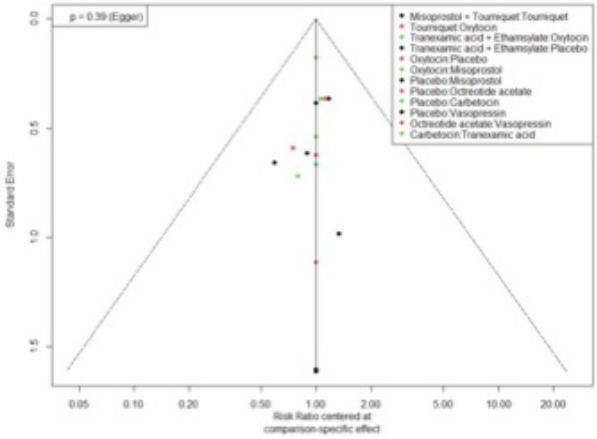

Funnel plot of different outcomes:

A) Intraoperative blood loss OM,
B) Need for blood transfusion OM,
C) Postoperative HB OM,
D) Postoperative HCT OM,
E) Postoperative hospital stay OM,
F) Other complications OM