Review

Efficacy of hyoscine in pain management during hysteroscopy: a systematic review and meta-analysis
Marchand et al. SR of hyoscine in hysteroscopy

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Abstract

Introduction: We conducted a systematic review and meta-analysis of relevant clinical trials from 6 different full-text scientific journal archives in order to assess the efficacy of hyoscine for the management of pain during in-office hysteroscopy procedures.

Methods: We searched Cochrane CENTRAL, Clinicaltrials.Gov, MEDLINE, PubMed, SCOPUS and the Web of Science site for all clinical trials that matched our selected search criteria. We then performed a full assessment of bias using the tools provided by the Cochrane Group. We included the following outcomes: visual analogue scale (VAS) score for postoperative pain, postoperative need for analgesia, and procedure time. In the case of homogeneous data, we performed our analysis using a fixed effects system, and we used the random effects system whenever analyzing heterogeneous data.

Results: We included three clinical trials. We found that the actual mean difference (MD), when calculated, of the VAS pain score showed no significant difference between either group (MD= -0.28 [-1.08, 0.52]), (P = 0.49). Regarding the need for postoperative analgesia, the overall mean difference showed no significant difference between hyoscine or the placebo (MD= 0.43 [0.16, 1.14]), (P = 0.09). The combined effect estimate failed to show any difference of statistical significance between hyoscine and placebo regarding procedure time (MD= -0.66 [-2.77, 1.44]) (P = 0.54).

Conclusion: Contrary to previously published data, our meta-analysis using the latest available RCTs fails to show hyoscine as being effective in reducing pain or the need for other forms of anesthesia in office hysteroscopy.

Keywords: Office hysteroscopy, hyoscine; office surgery, ERAS protocol, ERAS hysteroscopy

Introduction

Hysteroscopy is often considered the most accurate tool in the diagnosis of disorders of the endometrial cavity (1,2). Office hysteroscopy (OH), carries most of the benefits of hysteroscopy performed under general anesthesia in the operating room, with multiple other advantages. As a result, in the opinion of many surgeons, OH represents the cornerstone for both diagnosis and treatment of many gynecological conditions, such as submucosal polyps or leiomyoma (3). OH is also of importance in the diagnosis and management of other pathologies such as recurrent miscarriage and infertility (4). Prior to the advent of hysteroscopy, the management of intrauterine pathology was based largely on blind curettage of the uterus (5). This gave some important information, however Dilatation and curettage (D&C) is limited by an impared ability to recognize focal lesions, which can result in a higher percentage of false negative results (5). D&C also requires a higher degree of anesthesia to tolerate, usually being performed under general or spinal anesthesia (5).

Conventional hysteroscopy performed for diagnostic purposes depends largely on the usage of specula and may require dilation of the cervix (6). In recent years, the use of cervical dilators has been widely replaced by the introduction of smaller “mini-hysteroscopes,” which limit the need for cervical dilation prior to the procedure (7). Despite these advances, intraoperative pain remains a major problem limiting the use of hysteroscopy. In many circumstances it can be very challenging for the hysteroscopist to perform

hysteroscopy without the use of an anesthetic (8). Introducing even a small hysteroscope into the uterine cavity through the cervical canal may produce severe discomfort and pain, especially in sensitive patients (9). The use of sedation, local anesthesia, and cervical ripening agents, such as vaginal misoprostol have all been utilized in attempts to reduce this pain (10).

Hyoscine-n-butyl bromide (HBB) is a peripheral anticholinergic and does not readily cross the blood-brain barrier (11,12). Its mechanism of action is to block the nerve impulses that originate in the parasympathetic ganglia within the abdomen (13). Through blocking the muscarinic receptor, it exerts a spasmolytic action on muscle tissues of the biliary, gastrointestinal and genital organs, with smooth muscles being most affected (13,14). Many authors have theorized that the mechanism of action by which HBB decreases pain might be the blockage of these impulses, which may prevent uterine spasms (14).

There is not a plethora of randomized controlled trials addressing the effectiveness of the different premedications administered for control of pain OH. A previous meta-analysis failed to find any evidence of the benefit of administration of opioids during OH, when administered orally (15). Another study, this time an RCT, showed that certain anti-inflammatory medications were effective in reducing pain associated with OH, but this was complicated by the addition of a second variable - the usage of smaller (5 mm) hysteroscopes (16).

In order to contribute to the knowledge base in this topic, we aimed to conduct a meta-analysis to estimate the effect of HBB in reducing the postoperative VAS score for pain and the need for postoperative analgesia in women undergoing office hysteroscopy. We endeavored to use the latest available RCTs to produce the highest quality data possible.

Material and Methods

In performing this meta-analysis, we used strict adherence to the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) (17) guidelines and conducted every step in this study in accordance with all recommendation found in the "Cochrane Handbook for Systematic Reviews of Interventions" (18).

Literature search

We searched six databases: Web of Science, SCOPUS, Cochrane CENTRAL, ClinicalTrials.Gov, MEDLINE, and PubMed, from inception until January 2021. We followed this search strategy with no restriction on time or languages ;((Hyoscine-N-Butyl Bromide OR Hyoscine OR Scopolamine OR Buscopan) AND Hysteroscopy).

Eligibility Criteria

We included studies according to five criteria: 1.) **Patient Population:** patients receiving outpatient hysteroscopy, (ii) **Intervention:** hyoscine-N-Butyl Bromide administration regardless of the dose and the mode of administration, (iii) **Comparator:** placebo, (iv) **Primary Outcomes:** recorded visual analog pain scale score and postoperative score as well as usage of postoperative analgesia. (Secondary outcome was the total duration of the procedure measured in minutes. (v) **Included Study Types:** only those clinical trials with randomization (RCTs) were included. Exclusion criteria included: (1) any non-randomized controlled clinical trials, (2) studies that did not report data for our selected outcomes, (3) trials without the full text available, (4) trials with only a single arm.

Screening Process

After we retrieved the results from our search, the data was entered into our meta analysis software (Endnote X8.0.1 Build 1044), where duplicates were removed automatically. The first step of our screening was to screen the title and abstract, and this was followed by our authors screening the entire text. We used two different authors to screen the articles for selection of those that were ultimately included in our analysis. Any disagreement was solved by a third author.

Extraction and Analysis of Data

Following the completion of our screening, data was extracted from the selected studies. The selected data was classified into three categories: (a) the demographic data for each of the patients in the selected studies. This included age, weight, height, body mass index, number of previous cesarean sections, and history of pelvic pain. (b) the indication for the performed hysteroscopy. (c) Data of interest. This included the postoperative visual analog scale score, whether or not postoperative analgesia was required, and the elapse procedure time in minutes. That data that was required for completing a full assessment of the risk of bias according to Cochrane's risk of bias tools was also extracted in addition to the categories listed above (19).

Analysis of Data

We used Review Manager Software (version RevMan 5.4.1) to perform our analysis and the Inverse variance method was used. The mean difference (MD) as well as standard deviations were used to express continuous data with a relative 95% confidence interval (CI). We expressed dichotomous outcomes using percentage and total relative to a 95% CI. In order to measure inconsistency between the studies we employed both the I-square test (I2), and the Chi-square test to measure P-value. Any outcomes with $I^2 > 50\%$, $P<0.1$ were considered to be heterogeneous, while outcomes with $I^2 < 50\%$, $P>0.1$ were considered homogeneous. This is in accordance with guidelines from the Cochrane Handbook (20). Data that was homogenous was analyzed using a fixed-effects model, while heterogeneous data was analyzed using a random-effects model.

Quality Assessment

Quality assessment was performed in accordance with the "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE) guidelines. We included only RCTs and excluded all other observational evidence. We used Cochrane's risk of bias tool to perform the risk of bias (ROB) assessment for the included RCTS (21). The characteristics assessed by the Cochrane risk of bias tool include: a) proper randomization, b) proper blinding of the study participants into each group, c) proper blinding of participants only (single-blinding), blinding of both personnel and participants (double-blinding), or the lack of any blinding at all, d) Bias attributed to attrition, c) Bias attributed to selection, 6) Proper blinding of the outcome assessor (whether blinded or not), and 7) Other biases. The total risk of bias for these studies was assessed and graded as good.

Results

Summary of Studies Included in Our Analysis

A PRISMA flow diagram of our literature search can be found as figure 1. In this study, we performed an analysis of 291 patients from three studies(16,22,23). A total of 144 patients were allocated to receive hyoscine, and 147 patients were in the placebo group. The mean age of the participant in the treatment group was 38.1± 8.7 years, and that of the control group was 39.3±7.8. The mean body mass index of patients receiving hyoscine was 26.9±6, while that of the control group was 27±5. Table 1 shows a detailed

summary of the included participants, their demographic data, as well as what percentage had previous cesarean deliveries. Additionally, table 2 illustrates the indications of office hysteroscopy.

Results of Risk of Bias Assessment

The result of our assessments of the risk of bias in the included studies yielded an overall low risk of bias according to Cochrane's tool (24). Regarding bias from improper randomization, all studies were judged to be at low risk of bias from randomization. As for bias from allocation concealment, two of the studies (16,22) reported adequate allocation concealment, and therefore they were considered a low risk of bias. One study (23) did not report enough data about allocation concealment thus was considered to be an unclear risk of bias. Regarding the blinding of the participants and personnel, all of the included studies were double-blinded. We judged all studies to be at a low risk of bias from failing to blind the outcome assessment, except Souza et al. (23) which did not report sufficient details. As a result that study was considered an unclear risk of bias. As for attrition bias, all of the studies were judged to be at low risk of bias, except Souza et al (23) which was found to be at high risk of bias secondary to a lack of reporting sufficient details about the described outcomes. All of the remaining domains of the Cochrane tool were all at a low risk of bias. A summarized illustration including the data from the risk of bias in all of the included trials can be found in figure 2.

Analysis of all Outcomes

1. Postoperative VAS score:

All studies (291 participants) reported the postoperative VAS score for pain. Of these, 144 patients were in the hyoscine group, and 147 patients were in the control group. The overall mean difference (MD) of the VAS score showed that there was no significant difference between either group (MD= -0.28 [-1.08, 0.52]), (P = 0.49). Pooled analysis was homogeneous (P = 0.24); I^2 = 29% as shown in figure 3.

2. Need for Postoperative analgesia:

The need for postoperative analgesia was reported by all studies. The overall mean difference favored neither the hyoscine nor the placebo (MD= 0.43 [0.16, 1.14]), (P = 0.09) .Pooled analysis was heterogeneous (P = 0.01; I^2 = 76%) as shown in figure 4A. We solved the heterogeneity by the exclusion of Souza et al (23) (P = 0.69); I^2 = 0% . The pooled analysis after exclusion favored the hyoscine group significantly (MD= 0.26 [0.16, 0.43]) (P < 0. 01). Figure 4B shows the recalculated results of the analysis after one study was excluded.

3. Procedure time:

Two studies (16,22) reported the procedure time. The combined effect estimate did not show any statistically significant difference between hyoscine and placebo (MD= -0.66 [-2.77, 1.44]) (P = 0.54). Pooled analysis was heterogeneous (P = 0.01); I^2 = 83% as shown in figure 5. Heterogeneity could not be solved by the exclusion of one study.

Discussion

Previously published clinical trials reported contradictory results, Abbas et al (16) and Karasu et al (22) showed that hyoscine significantly reduces postoperative analgesia in patients undergoing hysteroscopy, while Souza et al (23) reported no significant difference. This could be explained by the fact that Souza et al used half the dose (10mg) compared with Abbas et al and Karasu et al,

which used 20mg. Regarding procedure time, Abbas et al (16) found that hyoscine reduces the procedure time by 1.65 minutes. On the other hand, Karasu et al (22) showed that the procedure time is nearly the same between both arms. As for the pain score, previous clinical trials reported no significant efficacy of hyoscine in reducing pain (16,22,23). Our meta-analysis failed to find any significant difference between hyoscine and placebo as far as procedure time, VAS pain score, and the need for postoperative analgesia.

As a common procedure carried out in many outpatient clinics, office hysteroscopy has a major role in diagnosing many gynecological abnormalities such as abnormal uterine bleeding, congenital anomalies of the uterus, removal of intrauterine devices and endometrial polyps, and visualization of intrauterine adhesions (1,25,26). The procedure is safe, quick, is of low cost, and does not usually require general or regional anesthesia (27,28). Office hysteroscopy has few side effects reported by patients, of which pain is the most common (29,30). The prevailing explanation as to why pain might arise from the procedure is that cervical dilatation and uterine distension cause more pain to the patient than normal vaginal manipulation (31).

Hyoscine is theorized to reduce pain by inducing cervical ripening and secreting pro-inflammatory cytokines and prostaglandins (32). It has also been tried as an analgesic for pain management after several gynecological procedures, with varying results. Jareethum et al (11) investigated the efficacy of hyoscine in women undergoing saline infusion sonography and found no significant effect of the drug on pain reduction. Moro et al (33) administered hyoscine to patients with infertility undergoing hysterosalpingo-contrast sonography and also found no significant effect. Although many pharmacological and non-pharmacological interventions have been used to reduce pain associated with hysteroscopy (34,35), hyoscine remains uncommonly used and with varying efficacy.

Duan et al (36) showed that carboprost methylate suppository given vaginal before hysteroscopy is an effective method for reducing pain prior to office hysteroscopy. Tagliaferri et al showed that saline solution as well as carbon dioxide can be used as acceptable media for performing OH; the study found that carbon dioxide has more advantages in reduction of pain perception (37). Compared with oral diclofenac potassium, hyoscine is not as effective as diclofenac potassium and may have more adverse effects. Abbas AM et al. found that oral diclofenac potassium administration administration before diagnostic hysteroscopy reduces pain with subsequent easier and shorter procedure duration (16). A recent meta-analysis revealed that misoprostol may be an effective medication for managing pain associated with the procedure (38).

Major strength points of our analysis include the overall low risk of bias among included trials and the homogeneity of data of the outcomes. We also included RCTs only to ensure high-quality evidence according to GRADE. Although we included all possible RCTs on this topic, the major limitation of this study is still the low sample size and a low number of published clinical trials; therefore, we still recommend more trials to combine hyoscine with other medications or at different doses to obtain more robust data.

Conclusion

In conclusion, based on the evidence available from all available RCTs at this point, we see no evidence supporting the use of hyoscine in office hysteroscopy at this time.

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Table 1 - Detailed summary of the included participants

Study ID	Age, years (mean ± SD)		BMI Kg/m2 (mean ± SD)		C-section, n (%)/(mean ± SD)		Chronic pelvic pain, n (%)		Weight Kg, (mean ± SD)		Height cm,(mean ± SD)	
	HBB	**PL**	**HBB**	**PL**	**HBB**	**PL**	**HBB**	**PL**	**HBB**	**PL**	**HBB**	**PL**
Abbas 2019	29.81± 6.41	30.65± 6.91	24.68± 2.12	23.95± 2.41	9(20.9)	10(23.3)	6(14)	5(11.6)	NR	NR	NR	NR
Karasu 2020	36.2± 7.1	37.1± 6.3	26.1± 5.7	25.9± 5.7	5(16.5)	5(16.50)	NR	NR	69.3± 13	66.1± 14.1	163.4± 6.7	159.7± 4.9
Souza 2020	48.4± 12.6	50.3± 10.4	30.1± 10.4	31.2± 6.9	0.6± 0.9	0.6± 0.8	15(6.90)	14(6.4)	75.6± 16.6	79.3± 17.9	159± 6	160±8

Data are reported as mean ± SD or n (%) unless otherwise specified. NR: not reported, HBB: Hyoscine-Butamyl Bromide, PL: Placebo, BMI: body-mass index

Table 2 - Indications for Office Hysteroscopy

Study ID	**Abnormal uterine bleeding**		**Recurrent miscarriage**		**infertility**	
	HBB	**PL**	**HBB**	**PL**	**HBB**	PL
	Frequency (%)	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**	Frequency (%)
Abbas 2019	6(14)	9(20.9)	4(9.3)	6(14)	33(76.7)	28(65.1)
Karasu 2020	NR	NR	NR	NR	NR	NR
Souza 2020	50(23)	52(24)	2(0.9)	2(0.9)	10(4.6)	5(2.4)

Data are reported as frequency (%) NR: not reported, HBB: Hyoscine-Butamyl Bromide, PL: Placebo.

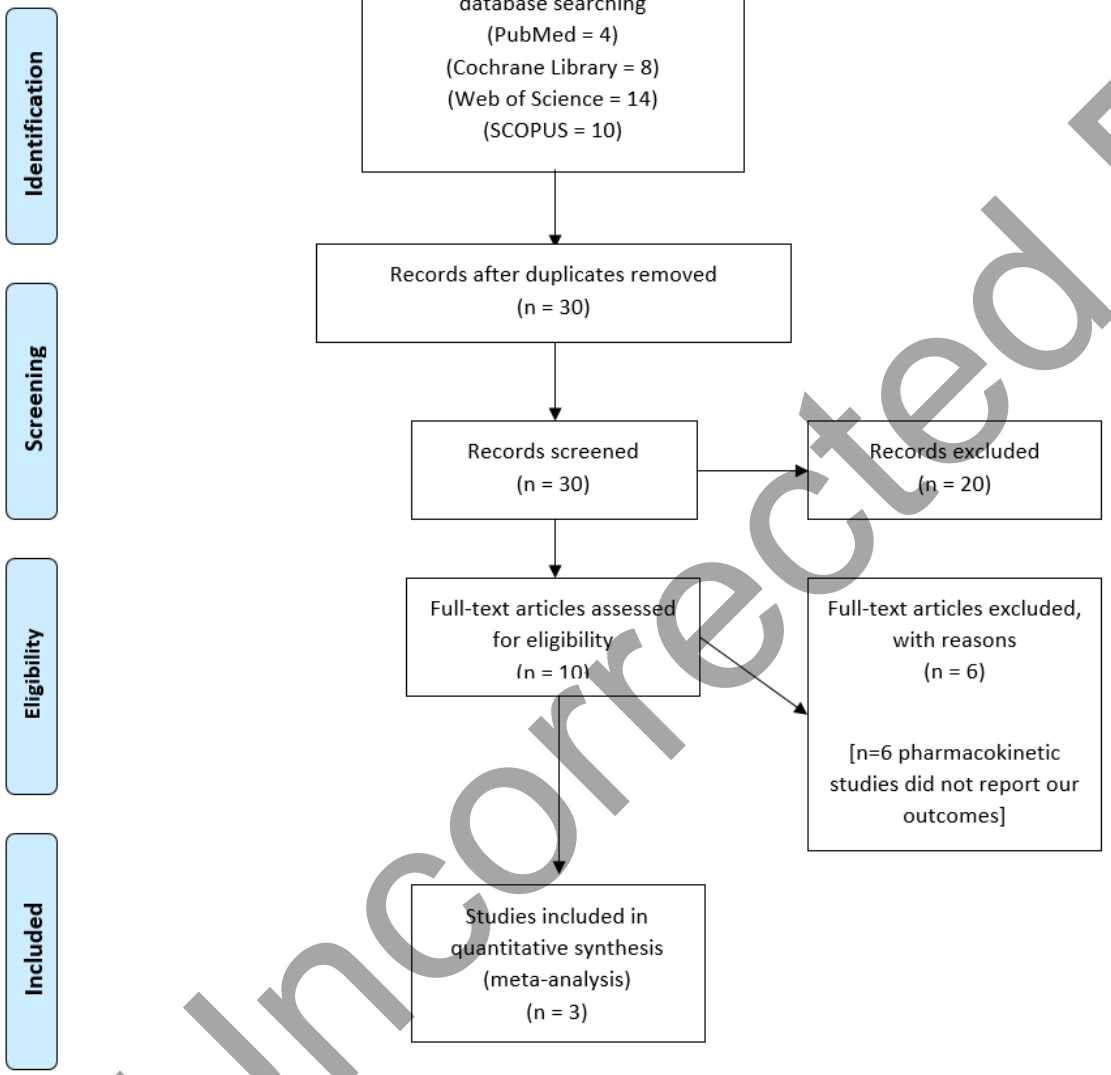

Figure 1. PRISMA flow diagram of our literature search

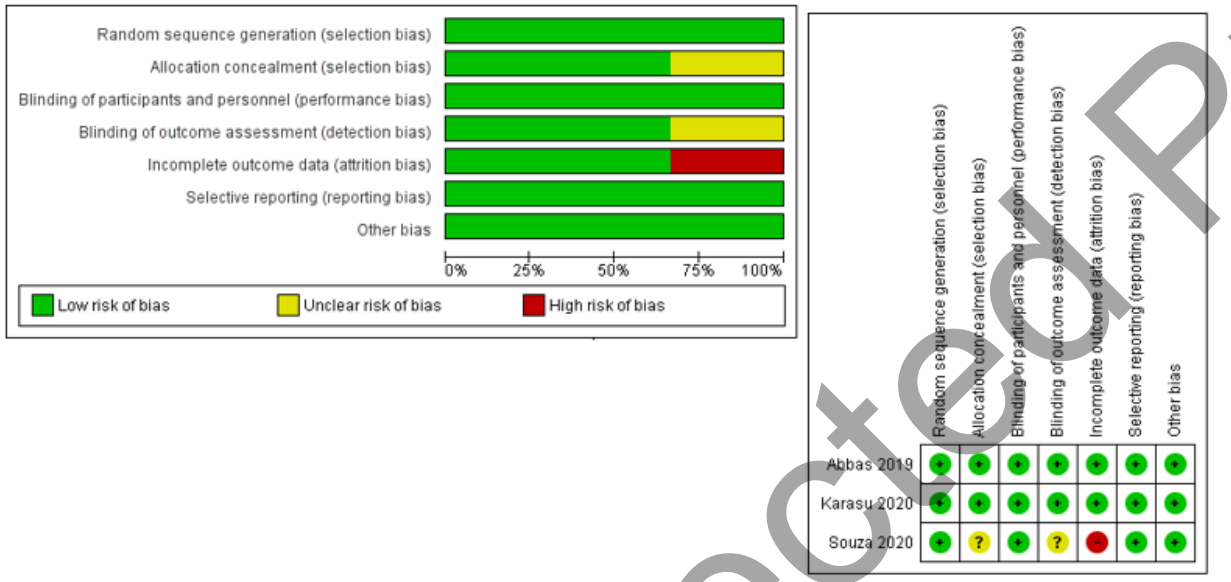

Figure 2. Summary and a graph of risk of bias of the included studies

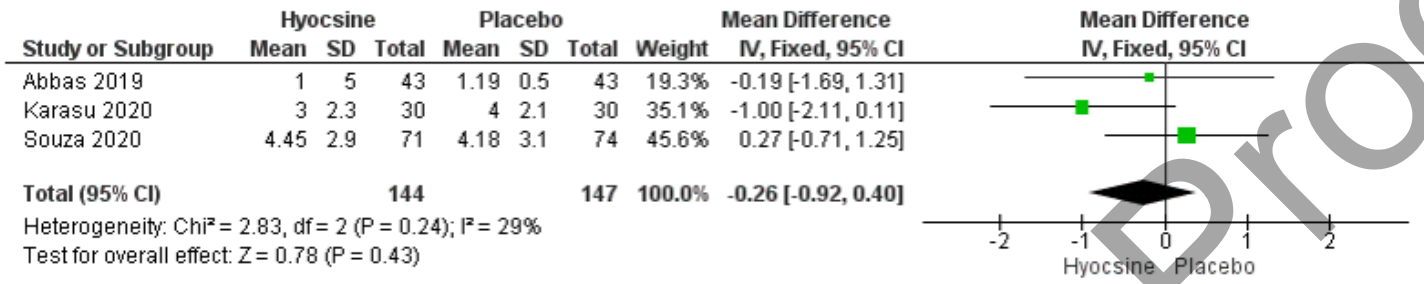

Figure 3. Forest plot for the analysis of VAS score for pain

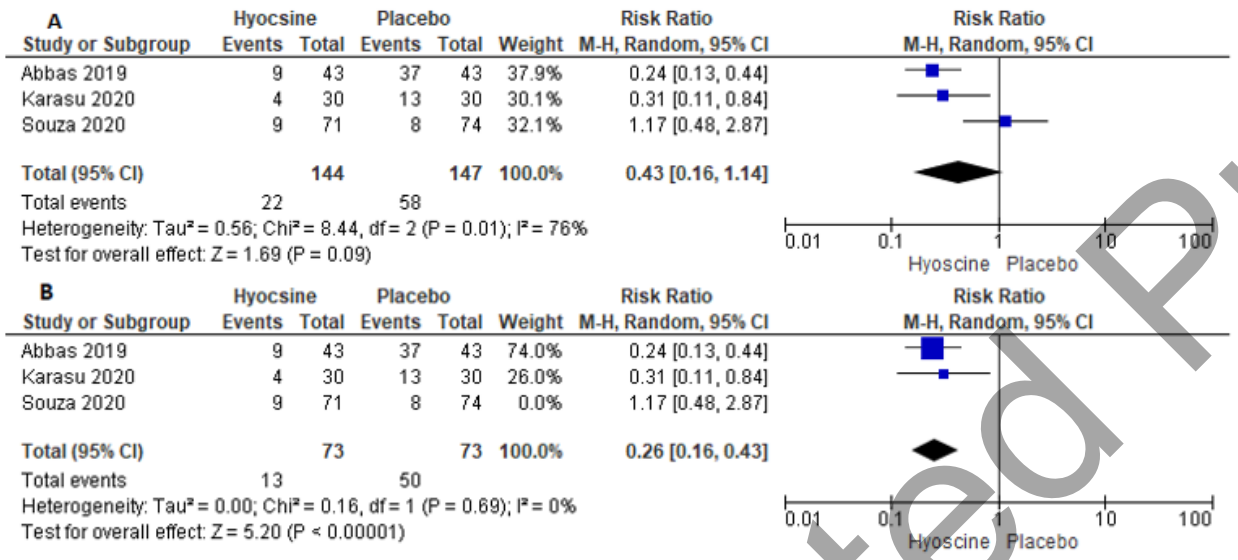

Figure 4a, b: 4a shows a forest plot for the analysis of the need for postoperative analgesia, and 4b shows the same forest plot after removing Souza et al. to solve for heterogeneity

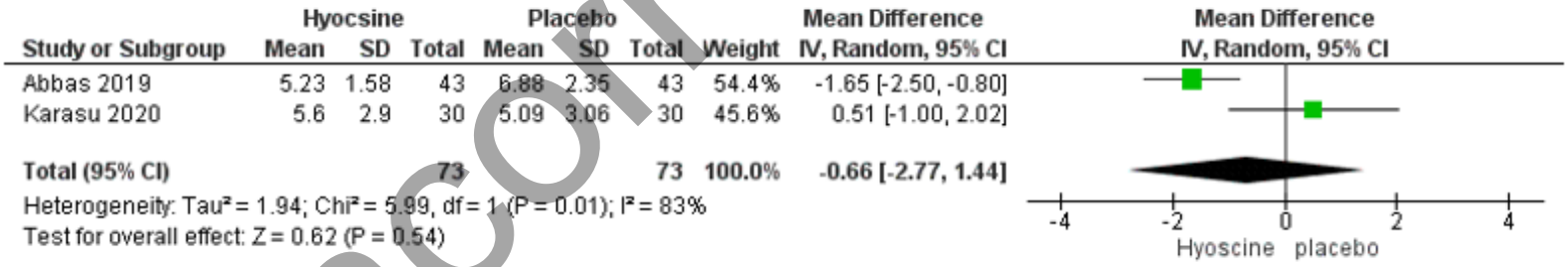

Figure 5. Forest plot for the analysis of procedure time