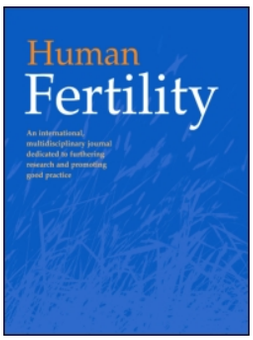

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REVIEW ARTICLE

The effect of hyoscine-N-butylbromide on pain perception during and after hysterosalpingography in infertile women: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

This paper reports a systematic review and meta-analysis of the effectiveness of hyoscine-N-butylbromide (HBB) administration in hysterosalpingography (HSG). Four electronic databases were searched for randomised controlled trials (RCTs) that compared HBB versus placebo or no intervention in infertile women undergoing HSG. Pain during and after HSG and different adverse events including nausea, vomiting, and dizziness were evaluated. Three RCTs with 335 patients were included. The analysis showed HBB was significantly effective in reducing pain during and after HSG (MD = −0.76 mm, 95% CI [−1.35, −0.17], $p = 0.01$) and (MD = −0.81 mm, 95% CI [−1.07, −0.56], $p < 0.001$), respectively. There were no significant differences in adverse events between HBB and control groups. The methodological evidence quality was high as evaluated by GRADEpro. In conclusion, this review provides good evidence that prior administration of HBB is effective in reducing induced pain during and after HSG with tolerable side effects.

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KEYWORDS
Hyoscine butylbromide; HBB; hysterosalpingography; HSG; pain

Introduction

Infertility is a recognisable concern affecting many young adults. It is defined as a failure of conception after 12 months (6 months if > 35 years) of frequent unprotected sexual intercourse (Handelzalts et al., 2016). Infertility can be due to pathology in the man or woman or in both partners. Female infertility accounts for 40–50% of the total cases (Pournourali et al., 2016) with tubal pathology accounting for 30–40% of the causes of infertility in females (Steinkeler et al., 2009). Different techniques are utilised to evaluate fallopian tube abnormalities including contrast enhanced saline infused sonography, hysterosalpingography (HSG), and diagnostic laparoscopy with chromopertubation (Hajishafiha et al., 2009).

HSG is used to evaluate the female genital tract after the injection of radio-opaque dye through the cervical canal. HSG is often the initial investigation used to assess tubal patency as it is less invasive, simple, inexpensive, and has a high sensitivity of 85–100% in the detection of tubal occlusion (Simpson et al., 2006). Although it is a valuable procedural test, pain is very common with this procedure (Unlu et al., 2015) mainly due to distension of the uterus during dye injection, which in turn enhances prostaglandin secretion and eventually results in uterine cramps (Wilkes et al., 2006).

Many drugs have been assessed for pain alleviation in HSG including oral, topical, intrauterine, and intravenous analgesics (Elson & Ridley, 2000; Hassa et al., 2014). However, no consensus has been reached regarding the ideal method for pain relief in HSG. Hyoscine-N-butylbromide (HBB) is an anti-spasmodic medication administrated for alleviation of abdominal

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Supplemental data for this article can be accessed here.

cramps in endoscopy, biliary colic, and renal colic (Holdgate & Oh, 2005; Tytgat, 2008). It acts mainly through the inhibition of synaptic cholinergic transmission and prevents neural impulse conduction in pelvic-abdominal parasympathetic ganglia (Sekhavat et al., 2012).

A recent study reported that HBB administration was associated with a significant decline in pain during and after HSG in comparison to placebo (Jitchanwichai & Soonthornpun, 2019). In contrast, Abbas et al. (2018) concluded there was no benefit from HBB administration in pain reduction during and after HSG. The aim of the present study was to conduct a systematic review and meta-analysis of published trials to provide the best evidence-based recommendations for the use of HBB in relieving pain during HSG.

Material and methods

The systematic review and meta-analysis were performed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). The PRISMA statement guidelines were followed during the preparation of this study (Moher et al., 2009).

Literature search

We performed a comprehensive search of four electronic databases during June 2020 (PubMed, Cochrane Library, Scopus, and ISI Web of Science) for all studies using the following strategy: (Hyoscine OR Scopolamine OR Hyoscine Butylbromide OR Hyoscine Butyl Bromide OR Buscopan OR Hyoscine-N-Butylbromide OR HBB) AND (Hysterosalpingography OR HSG). Two investigators (RAA & AMA) performed this search strategy. There were no restrictions with regard to the language of the study or the year of publication. The search strategies for each database and their results are shown in supplementary file no.1.

Eligibility criteria

Randomised controlled trials (RCTs) were included that met the following inclusion criteria:

(I) population: infertile women on whom it was intended to perform HSG; (II) intervention: HBB; (III) comparator: placebo or no intervention; (IV) outcome parameters: pain during and after the procedure and different adverse events including nausea, vomiting, and dizziness in both groups; and (V) study design: randomised controlled trials (RCTs). We excluded different studies for the following reasons: (I) abstracts only were available, (II) studies were non-randomised, (III) studies were in vitro or on animals. Screening for study eligibility was conducted in a two stepwise manner (title/abstract screening and full-text screening) by two authors (MAS & SMYE).

Data extraction

Data were extracted to include the following: list of authors, year of publication, sample size, study location and baseline characteristics of patients. HSG in the included studies was performed as follows: patients sat in a lithotomy position then a sterile speculum was placed by the radiologist into the vagina and povidone-iodine was used to clean the cervix. The anterior cervical lip was grasped by a tenaculum, and insertion of the metal cannula was done into the cervical canal followed by injection of water-soluble contrast medium into the uterine cavity. The assistant physicians obtained the radiographical images after visualising the dye filling the whole uterus. In addition, primary outcomes were extracted; pain scores both during and after HSG and secondary outcomes which were different adverse events including nausea, vomiting, and dizziness. Pain assessment during HSG was after dye injection. Pain was assessed within 15–30 min of the procedure using a Visual analog scale (VAS).

Risk of bias assessment

The methodological quality of the studies was evaluated using the Cochrane risk of bias assessment tool (Higgins et al., 2019) which tool includes the following domains: random sequence generation, allocation concealment, performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), attrition bias, reporting bias, and other potential sources of bias. The authors' judgement of bias was categorised as "low risk," "high risk," or "unclear risk." Differences between the authors were considered and a consensus reached.

In addition, the methodological quality of evidence among the studies was assessed using the GRADEpro software which provides fundamental details regarding the effectiveness magnitude of the interventions, the sum of the available data on main outcomes and the quality of evidence.

Data synthesis

Dichotomous data were pooled as a risk ratio (RR) and continuous data were pooled as mean difference (MD) with the corresponding 95% confidence intervals (CIs) using the Mental-Haenszel method. Statistical analysis was performed using RevMan software. We assessed the statistical heterogeneity between the studies by visual inspection of the forest plots using I-squared (I^2) statistics; values of $\geq$50% were indicative of high heterogeneity. In cases of a non-significant heterogeneity the fixed-effect model was used, and the random-effect model in cases of significant heterogeneity. We performed a sensitivity analysis to determine the contribution of each study to the pooled estimate by excluding one trial at a time and recalculating the pooled mean difference for the remaining studies.

Publication bias

We were unable to assess the publication bias using Egger's test due to the small number of studies (<10) (Egger et al., 1997; Terrin et al., 2003).

Results

Characteristics of studies included

The search strategy resulted in 32 studies. After title and abstract screening, eight articles were eligible for full-text screening. Five studies were excluded in which one was irrelevant and the other four did not meet the inclusion criteria. Three studies matched the criteria and were included in the final analysis. The PRISMA flow diagram for study selection is shown in Figure 1.

Three RCTs (Abbas et al., 2018; Jitchanwichai & Soonthornpun, 2019; Safi et al., 2019) with a total number of 335 patients were included. The baseline characteristics of the studies included are shown in Table 1.

Risk of bias assessment

The summary of the risk of bias assessment is shown in Figure 2. The quality of RCTs was based on the Cochrane risk of bias assessment tool. All studies were

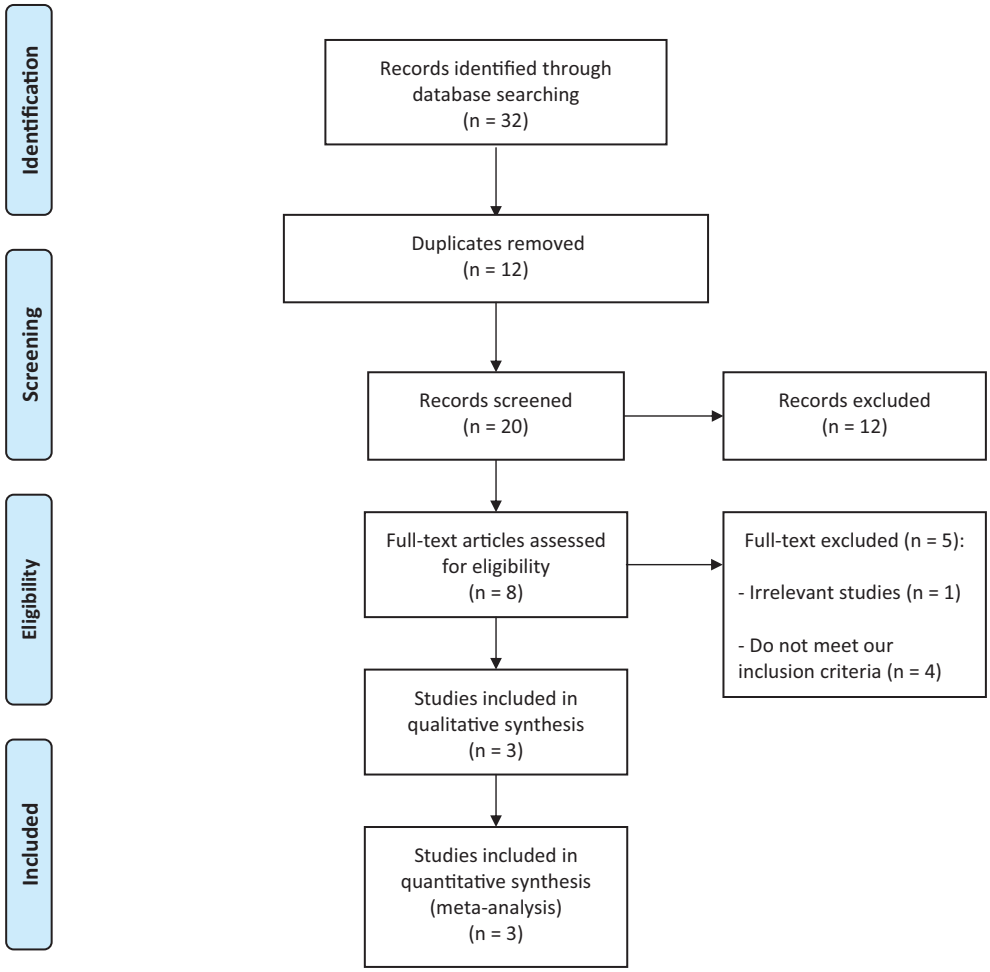

Figure 1. PRISMA flow diagram for study selection.

Table 1. Baseline characteristics of the included studies.

Study	Study arms	Study location	Sample size	Age (years), mean ± SD	Type of infertility		Mean duration of infertility (years), mean ± SD	History of dysmenorrhoea, *n* (%)	History of chronic pelvic pain, *n* (%)
					Primary, *n* (%)	Secondary, n (%)			
Abbas et al., 2018	Hyoscine Group	Egypt	47	28.15 ± 6.66	20 (42.6)	23 (48.9)	4.02 ± 2.32	7 (14.9)	1 (2.1)
	Control Group (Placebo)		47	28.45 ± 6.34	27 (57.4)	24 (51.1)	3.7 ± 2.34	11 (23.4)	2 (2.4)
Safi et al., 2019	Hyoscine Group	Iran	30	31.46 ± 5.54	30 (60)	20 (40)	25.32 ± 30.19	23 (46)	2 (4)
	Control Group (No treatment)		39	29.40 ± 5.25	30 (60)	20 (40)	27.26 ± 32.84	18 (36)	7 (14)
Jitchanwichai & Soonthornpun (2019)	Hyoscine Group	Thailand	30	26.90 ± 4.64	54 (77.1)	16 (22.9)	3.9 ± 2.7	34 (48.6)	4 (5.7)
	Control Group (Placebo)		39	24.25 ± 4.15	53 (74.6)	18 (25.4)	4.0 ± 2.5	39 (54.9)	2 (2.8)

SD: standard deviation; HSG: hysterosalpingography.

Figure 2. Risk of bias summary.

reported as low risk of bias in all items except for one study (Safi et al., 2019) which contained insufficient information on blinding of the participants and personnel and blinding of the outcome assessment; thus this study was scored as high risk in these two items.

Outcomes

Pain during the procedure

HBB was effective in reducing pain during HSG compared to the control group (MD = −0.76 mm, 95% CI [−1.35, −0.17], $p = 0.01$) as shown in Figure 3. The pooled studies showed a high degree of heterogeneity ($p = 0.02$, $I^2 = 73\%$). This was removed after excluding one study (Jitchanwichai & Soonthornpun, 2019) ($p = 0.39$, $I^2 = 0\%$) and the results still showed the effectiveness of HBB in reducing pain (MD= −0.55 mm, 95% CI [−0.83, −0.26], $p = 0.0002$). The quality of the evidence was high, as determined by the GRADEpro software, as shown in Figure 4.

Post-procedure pain

HBB effectively reduced the pain after HSG compared to the control group (MD = −0.81 mm, 95% CI [−1.07, −0.56], $p < 0.001$) as shown in Figure 5. The pooled studies were homogeneous ($p = 0.85$, $I^2 = 0\%$). The

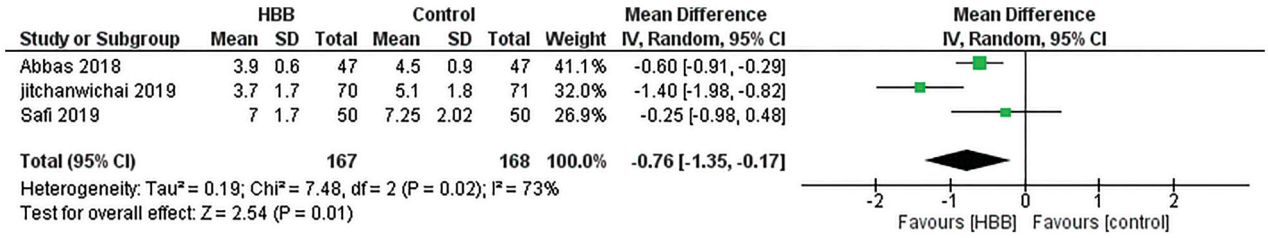

Figure 3. Forest plot of pain during procedure.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyoscine-N-butylbromide (HBB)	control	Relative (95% CI)	Absolute (95% CI)		
Pain during the procedure												
3	randomised trials	not serious	not serious	not serious	not serious	none	167	168	-	MD **0.76 mm lower** (1.35 lower to 0.17 lower)	⨁⨁⨁⨁ HIGH	
Pain after the procedure												
3	randomised trials	not serious	not serious	not serious	not serious	none	167	168	-	MD **0.81 mm lower** (1.07 lower to 0.56 lower)	⨁⨁⨁⨁ HIGH	
Nausea and vomiting												
3	randomised trials	not serious	not serious	not serious	not serious	none	17/97 (17.5%)	7/97 (7.2%)	**RR 3.60** (0.17 to 75.84)	**188 more per 1,000** (from 60 fewer to 1,000 more)	⨁⨁⨁⨁ HIGH	
Dizziness												
3	randomised trials	not serious	not serious	not serious	not serious	none	16/167 (9.6%)	14/168 (8.3%)	**RR 1.14** (0.60 to 2.16)	**12 more per 1,000** (from 33 fewer to 97 more)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Figure 4. GRADEpro analysis.

quality of evidence was high, as determined by the GRADEpro software, as shown in Figure 4.

Nausea and vomiting

There were no significant differences between both groups regarding nausea and vomiting (RR= 3.60, 95% CI [0.17, 75.84], $p = 0.41$) as shown in Figure 6. The pooled studies were heterogeneous ($p = 0.04$, $I^2 = 77\%$) which could not be resolved since two studies only reported this outcome. The quality of evidence was high, as evaluated by the GRADEpro software, as shown in Figure 4.

Dizziness

There was no significant difference between HBB and the control groups concerning dizziness as a side effect (RR= 1.14, 95% CI [0.60, 2.16], $p = 0.69$) as shown in Figure 7. The pooled studies were homogeneous ($p = 0.25$, $I^2 = 29\%$). The quality of evidence was high as determined by the GRADEpro software, as shown in Figure 4.

Discussion

In this meta-analysis, we found a significant reduction in pain in the HBB group both during and after HSG. No differences were found between HBB and the control groups in adverse events including nausea, vomiting, and dizziness.

Jitchanwichai and Soonthornpun (2019) concluded that HBB was associated with a significant reduction in pain during and after the HSG, confirming our findings. However, two RCTs did not report any beneficial effect of HBB in decreasing the induced pain during and after HSG (Abbas et al., 2018; Safi et al., 2019). Another larger RCT of 816 women evaluated the efficacy of HBB in reducing pain during hysterosalpingo-contrast sonography which has the same mechanism of pain as HSG (Moro et al., 2012). There were no differences in pain and discomfort scores between HBB and control groups (Moro et al., 2012).

The reports of Safi et al. (2019) and Jitchanwichai and Soonthornpun (2019) confirm our results since they found no significant differences regarding different adverse effects between HBB and control groups.

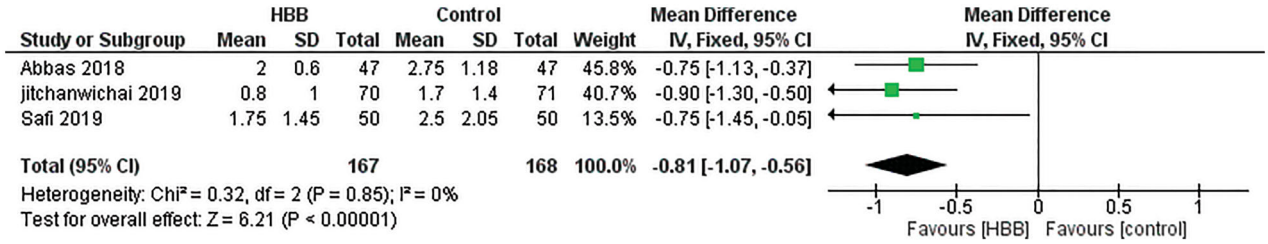

Figure 5. Forest plot of post-procedure pain.

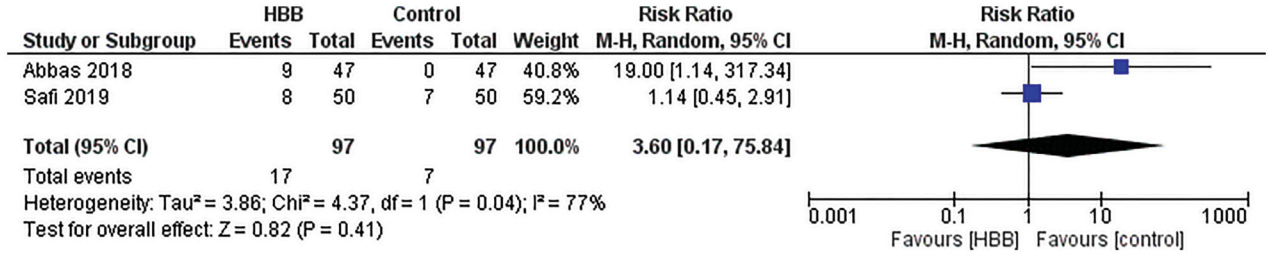

Figure 6. Forest plot of nausea and vomiting.

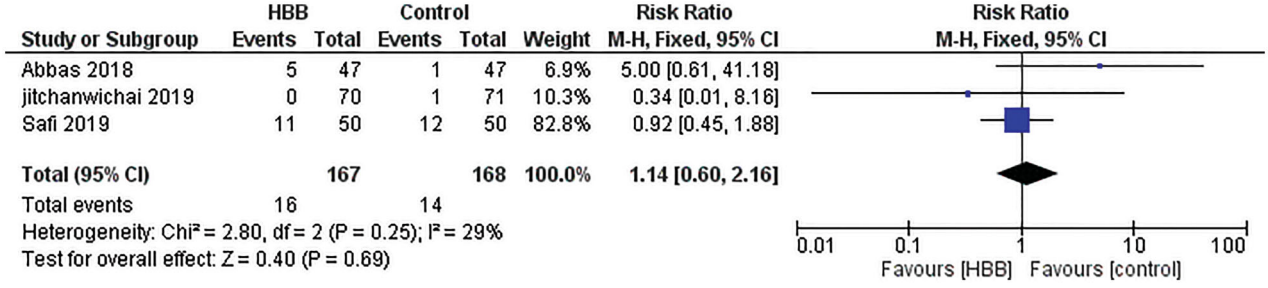

Figure 7. Forest plot of dizziness.

However, Abbas et al. (2018) found that HBB was significantly associated with more side effects especially in nausea and vomiting after HSG.

Most women state HSG to be very painful as a result of cervical traction, placement of cervical tenaculum, dye injection through the cervical cannula, and bilateral tubal spillage (Robinson et al., 2007). Some studies suggest that injection of the dye is responsible for most of the pain during HSG (Abbas et al., 2018; Robinson et al., 2007). Another study stated that the greatest pain was reported during cervical instrumentation (Liberty et al., 2007). The pain during HSG is transmitted through pelvic splanchnic nerves from the lower uterus and cervix and conducted through hypogastric nerves from the uterine fundus and body (Gupta et al., 2008).

HBB acts mainly by binding to the muscarinic receptors on smooth muscle cells in different organs and is considered to belong to the family of the anticholinergic drugs (Tytgat, 2007). Thus, spasmolytic and relaxing influences on smooth muscle cells can be achieved by HBB. HBB is used to treat abdominal pain resulting from cramping by muscarinic receptors blockage and HBB can attach to nicotinic receptors and act as a ganglionic blocker (Tytgat, 2007).

With regard to patient satisfaction, Abbas et al. (2018) reported that HBB had no benefits in improving satisfaction after performing HSG. Moreover, an RCT performed by Jareethum et al. (2011) used HBB during saline infusion sonohysterography and assessed satisfaction and pain scores using VAS after the procedure. However they reported no benefit from HBB administration in satisfaction and pain prevention after the procedure (Jareethum et al., 2011). It should be noted that satisfaction is influenced by different factors including the gender of the doctor, doctor-patient relationship, and counselling before beginning HSG.

Interestingly, Jitchanwichai and Soonthornpun (2019) established that HBB administration prior to HSG could decrease the rates of proximal tubal obstruction and false occlusion since it is a spasmolytic agent that can lead to uterine and tubal muscle relaxation and relieve the cornual spasm greatly.

In a Cochrane review, Hindocha et al. (2015) assessed the effectiveness of different pain medications used in HSG. They reported that intravenous opioids, topical anaesthesia, and local anaesthesia injection were effective in pain reduction during the procedure compared to placebo or no treatment. In addition, they found oral opioid and non-opioid analgesics were not beneficial in pain relief during and 30 minutes after the procedure. However, a survey by Duffy et al. (2008) found that administration of non-opioid analgesics (acetylsalicylic acid, acetaminophen, and fenoprofen) were commonly used by clinicians for pain prevention during HSG.

In addition, Liberty et al. (2007) applied lidocaine-prilocaine cream to the cervical uteri before performing HSG and found a significant reduction in procedure-related pain. Robinson et al. (2007) examined the intracervical block for pain reduction in HSG and found that patients can endure pain during tenaculum traction and placement with intracervical block during the procedure. However, reduction in pain was not found during contrast injection into the uterus which different studies considered to be the most painful stage of HSG (Robinson et al., 2007).

Our findings are limited by the small number of studies ($n = 3$), the small sample size, and the reported heterogeneity in some outcomes which may have been due to differences in doses and routes of HBB administration. Another limitation was subjectivity in the assessment of the induced pain.

We recommend further RCTs with the same study design as previously but with a larger sample size. We also recommend conducting other trials that compare HBB to different agents for pain relief during HSG.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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