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Evaluation effectiveness and safety of Hyperbaric and Isobaric Bupivacaine for spinal anesthesia for noncesarean delivery surgery: A Systematic Review and Meta-Analysis

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Abstract

Background and aim: In the present study, we tried to provide comprehensive results by evaluating the results of studies and summarizing the best evidence, the effectiveness of hyperbaric bupivacaine compared to isobaric Bupivacaine for spinal anesthesia. The findings may help anesthesiologists choose the best formulation for spinal anesthesia. Therefore the aim of present Systematic Review and Meta-Analysis was evaluation effectiveness and safety of Hyperbaric and Isobaric Bupivacaine for spinal anesthesia for noncesarean delivery surgery.

Method: From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform a systematic literature between 2001 andJanuary 2021. Risk ratiowith 95% confidence interval (CI), fixed effect model and Mantel-Haenszel methodwere calculated. The Meta analysis have been evaluated with the statistical software Stata/MP v.16 (The fastest version of Stata).

Result:A total of 314potentially relevant titles and abstracts were found during the electronic search. Finally, fourstudies required for this systematic review. Meta-analysis showed, there was no statistically significant difference between two groups about incidence of hypotension(RR, 0.09 95% CI -0.75, 0.93. P=0.96). Duration of the motor block was longer in HB group(MD, 30.53 min 95% CI 20.79, 40.26. P=0.00) and the duration of sensory block was significantly higher with the IB vs HB with significant inverse correlation(MD, -40.07 min 95% CI -47.84, -32.30. P=0.00).

Conclusion:due to the low quality of the existing studies, sufficient evidence could not be provided and results should be treated with caution.

Keywords: Hyperbaric bupivacaine, Isobaric Bupivacaine, spinal anesthesia

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Introduction

According to reports, about 300 million surgeries are performed worldwide each year, about 15 million of which are performed under spinal anesthesia(1,2). One of the most common aminoacyl local anesthetic for spinal anesthesia is Bupivacaine hydrochloride(3). Isobaric bupivacaine (IB) and hyperbaric bupivacaine (HB) are two forms of Bupivacaine hydrochloride that have the same density as cerebrospinal fluid and heavier cerebrospinal fluid density, respectively. Differences in density lead to different diffusion patterns and Determine their effectiveness, spread and side effects (4-6).The use of HB or IB is at the discretion of the anesthesiologist. However, there are differences of opinion as to which one to use(7). Previous studies have shown that a comprehensive and clear guide to selection is not specified and few guides are available to anesthesiologists(8, 9).The study reported that compared to the use of HB, IB for spinal anesthesia, the HB failure rate was lower than that of IB, in contrast, blood pressure is lower with IB(10).Other studies have reported higher rates of hypotension using HB (11-13).The results of some studies have shown that in the comparison of HB and HI, a decrease in blood pressure has been observed in the use of HB (14-17).Contradictory evidence has been reported for block onset time, block regression, motor block, and maximum dermatomal spread (16, 18, 19).In the present study, we tried to provide comprehensive results by evaluating the results of studies and summarizing the best evidence, the effectiveness of HB compared to IB for spinal anesthesia. The findings may help anesthesiologists choose the best formulation for spinal anesthesia. Therefore the aim of present Systematic Review and Meta-Analysis was evaluation effectiveness and safety of Hyperbaric and Isobaric Bupivacaine for spinal anesthesia for noncesarean delivery surgery.

Methods

Search strategy

From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform a systematic literature over the last ten years between February2001 and January 2021. The reason for choosing studies in the last twenty years is to be able to provide sufficient evidence in this area and use newer studies.Therefore, a software program (Endnote X8) has been utilized for managing the electronic titles. Searches were performed with mesh terms:
("Hyperbaric Oxygenation"[Mesh]) OR "Bupivacaine"[Mesh]) OR "3-hydroxybupivacaine" [Supplementary Concept]) OR ("Anesthetics, Local"[Mesh] OR "Anesthetics, Local" [Pharmacological Action] OR "Anesthesia, Local"[Mesh])) OR ("Bupivacaine/adverse effects"[Mesh] OR "Bupivacaine/toxicity"[Mesh])) AND "Anesthesia, Spinal"[Mesh]) AND "Anesthesia, Spinal"[Majr]) AND "Adult"[Mesh]) AND "surgery" [Subheading]) AND "Urology"[Mesh]) OR "Orthopedics"[Mesh]) OR "Gynecology"[Mesh]) OR "Abdomen"[Mesh].
Other databases were searched using the following keywords, spinal anesthesia AND aminoacyl local anesthetic OR Bupivacaine hydrochloride OR Hyperbaric Bupivacaine OR Isobaric Bupivacaine AND non-cesarean delivery surgery OR Urology OR Orthopedics OR lower limb OR lower extremity OR knee scope OR Gynecology OR Lower body surface surgery OR lower limb OR General OR abdominal OR Lower abdominal AND adult.
This systematic review has been conducted on the basis of the key consideration of the PRISMA Statement–Perfumed Reporting Items for the Systematic Review and Meta-analysis(20), and PICO strategy (Table1).

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Selection criteria

Inclusion criteria

1. Randomized controlled trials studies, controlled clinical trials
2. Adult patients >18 years
3. Spinal anesthesia
4- Bupivacaine with glucose 80 mg/mL
5. English language

Exclusion criteria

1Prospective and retrospective cohort studies, cross-sectional, In vitro studies, reviews, case-Control Studies, case report and animal studies
2- Patients undergoing emergency surgery
3- Patients undergoing cesarean
4- Opioids or mixtures of local anesthetics
5- Different dosages of local anesthetics
6. Incomplete or inconsistent data for the purpose of the present study.

Table1. PICO strategy

PICO strategy	Description
P	Population: adult patients under non-cesarean delivery surgery
I	Intervention:Hyperbaric for spinal anesthesia
C	Comparison: Isobaric Bupivacainefor spinal anesthesia
O	Outcome: general anesthetic, incidence of hypotension, Duration of anesthesia and Onset time of block

Study selection, Data Extraction and method of analysis

The data have been extracted from the research included with regard to the study, years, study design, and sample Size, type of surgery, bupivacaine dose,spinal needles, positioning during spinal anesthesia and final Position.

Cochrane Collaboration's tool (21) used to assessed quality of the studies that included in present meta-analysis. The scale scores for low risk was 1 and for High and unclear risk was 0, Scale scores range from 0 to 6 and higher score means higher quality.

For Data extraction, two reviewers blind and independently extracted data from abstract and full text of studies that included.Prior to the screening, kappa statistics was carried out in order to verify the agreement level between the reviewers. The kappa values were higher than 0.80.

Risk ratio with 95% confidence interval (CI), fixed effect model and Mantel-Haenszel method, mean differencewith 95% confidence interval (CI), fixed effect model and Invers-variance were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. I^2 values above 50% signified moderate-to-high heterogeneity. The Meta analysis have been evaluated with the statistical software Stata/MP v.16 (The fastest version of Stata).

Results

According to the purpose of the study, in the initial search with keywords, 314 articles were found. In the first step of selecting studies 311 studies were selected to review the abstracts. Then, studies that did not meet the inclusion criteria were excluded from the study (285 article).

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In the second step, the full text of 26 studies was reviewed, in this step 22 article were excluded and finally four studies were selected (Figure1).

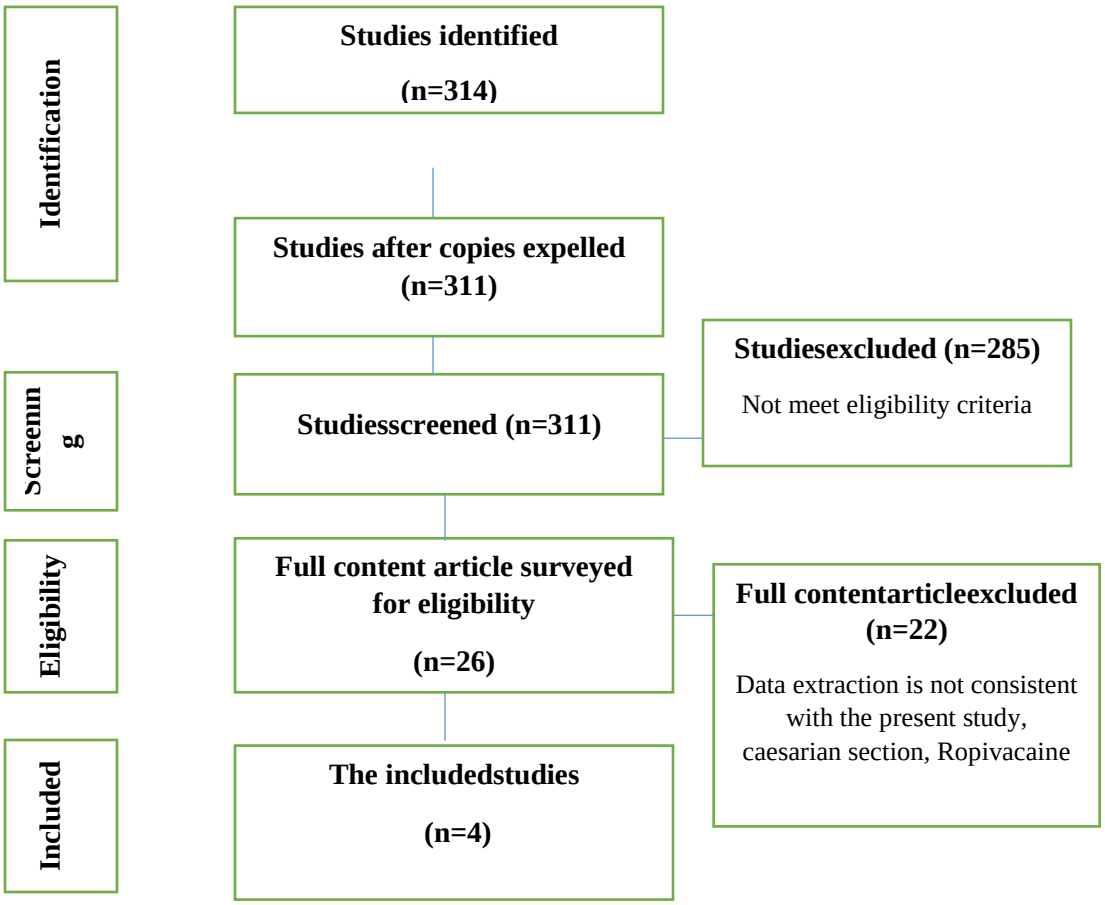

Figure 1. Study Attrition

Characteristics

Four studies (Randomized controlled trial) have been included in present article. The number of patients in a total was 280. The range of bupivacaine dose was between 5-15 mg. All spinal anesthetics were performed either in three studies a sitting position and in one study lateral position, final position in all studies was either supine (Table2).

Bias assessment

According to Cochrane Collaboration's tool, two studies had a total score of 2/6, one study had a total score of 3/6 and one study had a total score of 1/6. This result showed high risk of bias in three studies and moderate risk of bias in one study, none of the studiesshowed low risk of bias (Table3).

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Table2. Studies selected for systematic review and meta-analysis.

Study. Years	Study design	Types of surgical procedures	Sample size	Bupivacaine Dose	Spinal needles	positioning during spinal anesthesia	final position
Kour et al.,2018 (22)	RCT	Laparoscopic Cholecystectomy	60	1.5 ml	25 G Quincke	Sitting	Supine
Toptas et al., 2014 (23)	RCT	Lower abdominal, urology, lower extremity	60	15 mg	25 G Quincke	Sitting	Supine
Solakovic et al., 2010 (24)	RCT	Orthopedics (lower limb), Gynecology Urology	60	15 mg	25 G Quincke	Sitting	Supine
Imbelloni et al.,2007 (25)	RCT	Orthopedic	100	5 mg	27 GQuincke	Lateral	Supine

Table3. Risk of bias assessment (Low (+), unclear (?), high (-))

study	Random sequence generation	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective reporting	Total score
Kour et al.,2018 (22)	+	?	-	-	+	+	3
Toptas et al., 2014 (23)	+	?	?	-	+	?	2
Solakovic et al., 2010 (24)	?	?	-	-	+	?	1
Imbelloni et al.,2007 (25)	+	?	-	+	?	?	2

Conversion to the general anesthetic

Risk ratio of Conversion to the general anesthetic was 0.00 (RR, 0.00 95% CI -2.75, 2.75. P=1.00)among two studies and heterogeneity found (I^2<0%; P =1.00). This result showed there was no statistically significant difference between two groups (Figure2).

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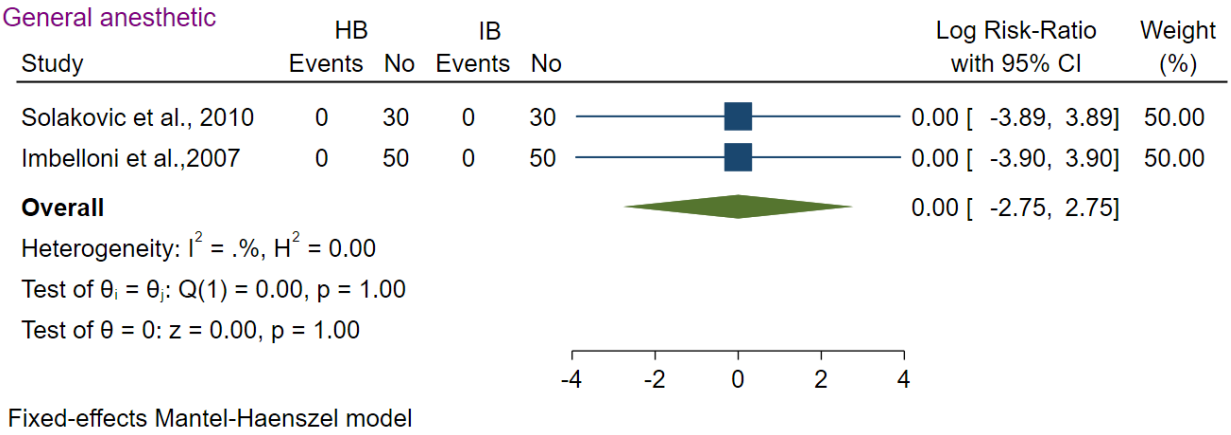

Figure2. Forest plot showed risk ratio of conversion to the general anesthetic between Hyperbaric and Isobaric Bupivacaine

Incidence of hypotension

The subgroup Meta-analysis of incidence of hypotension was 0.09 (RR, 0.09 95% CI -0.75, 0.93. P=0.96)among three studies and heterogeneity found (I^2<0%; P =1.00). This result showed there was no statistically significant difference between two groups (Figure3).

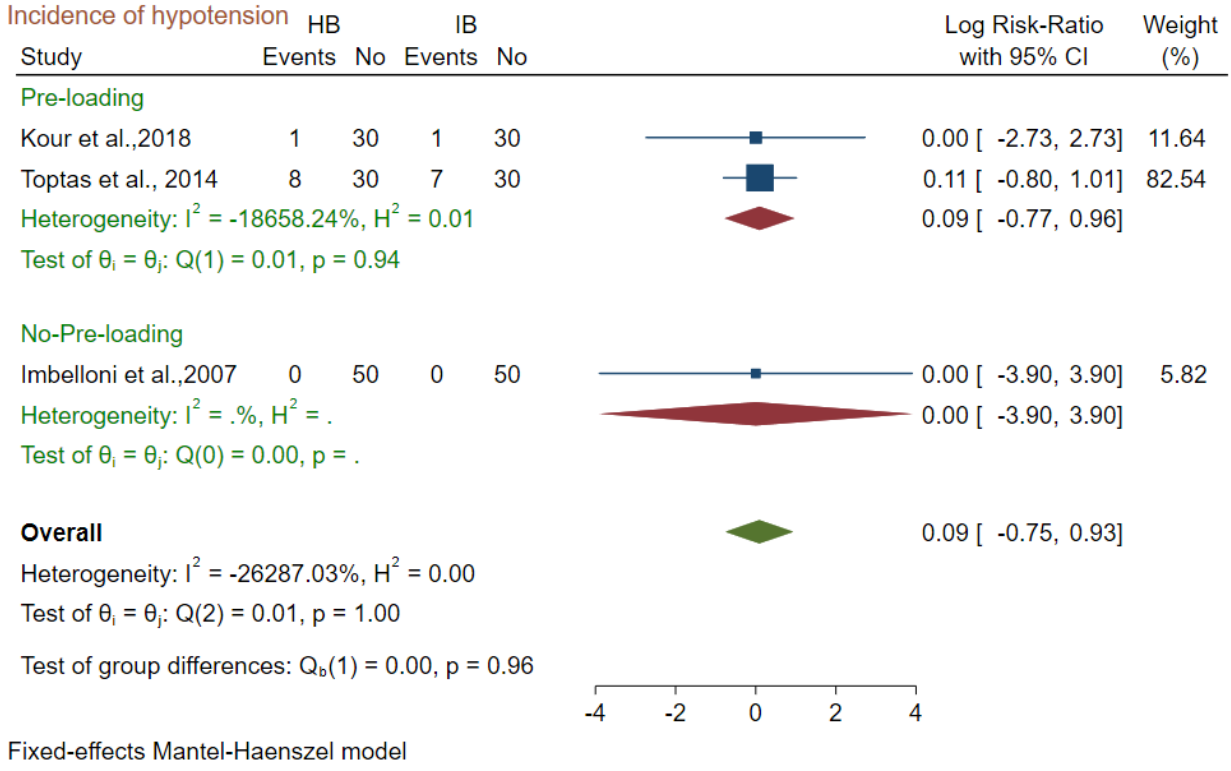

Figure3. Forest plot showed risk ratio of Incidence of hypotension between Hyperbaric and Isobaric Bupivacaine

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Onset Time for the Motor Block

One study Kour et al.,2018 (22) reported onset Time for the Motor Block, the outcome showed time to reach the maximum motor blockade was significantly longer in isobaric group (6.8 min) than hyperbaric group (2.13 min).

Duration of motor block

Mean difference of duration of motor block was 30.53 min (MD, 30.53 min 95% CI 20.79,40.26. P=0.00)among two studies and heterogeneity found (I2<0%; P =0.87). This result showed there wasstatistically significant difference between two groups (Figure2). TheDuration of motor block was significantly higher with the HB vs IB, duration of the motor block was longer in HB group (Figure4).

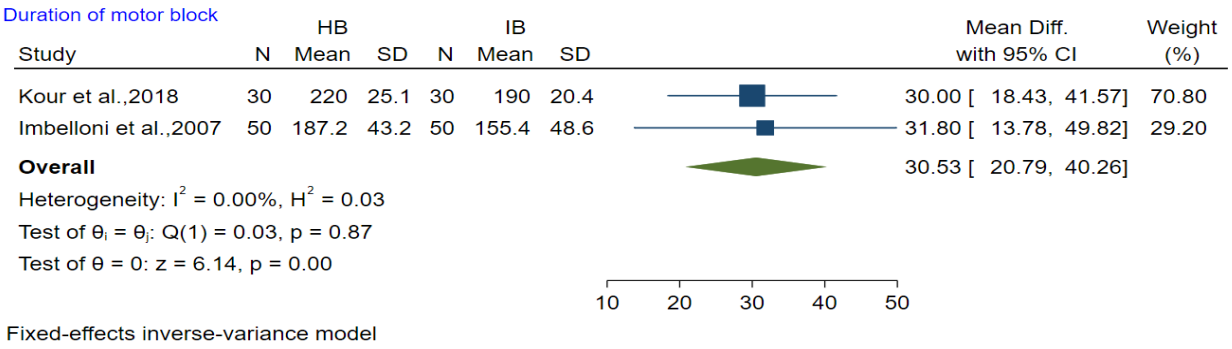

Figure4. Forest plot showed mean differences of duration of motor block between Hyperbaric and Isobaric Bupivacaine

Duration of Sensory Block

Mean difference of duration of Sensory Block was -40.07 min (MD, -40.07 min 95% CI -47.84, -32.30. P=0.00)among two studies and heterogeneity found (I2<0%; P =0.52). This result showed there wasstatistically significant difference between two groups (Figure2). The duration of sensory block was significantly higher with the IB vs HB with significant inverse correlation (P=0.00) (Figure5).

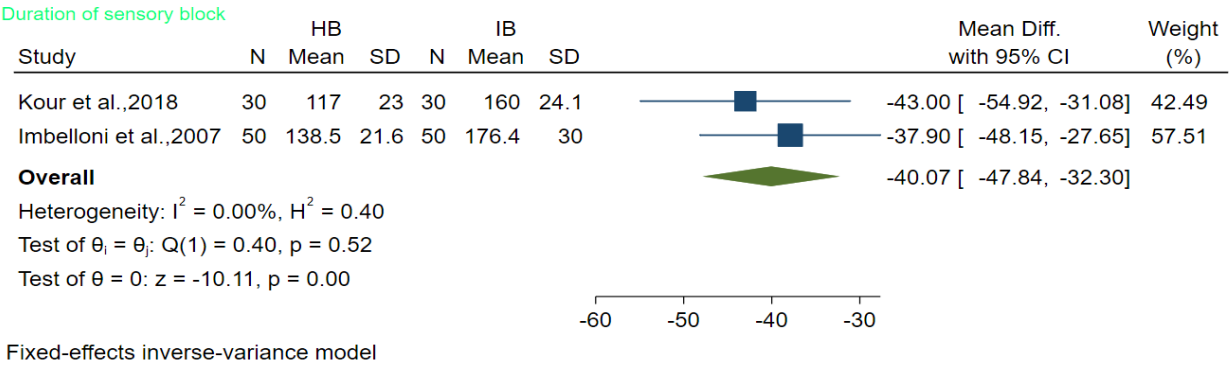

Figure5. Forest plot showed mean differences of duration of Sensory Block between Hyperbaric and Isobaric Bupivacaine

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Discussion

Present systematic review and meta-analysis of two studies (120 patients) showed no evidence of a difference between hyperbaric and isobaric bupivacaine in the rates of conversion to general anesthesia. Two studies reported this section (24), (25). In addition, the relatively small sample populations within the included studies may suggest that the results should be treated with caution, as future larger studies may modify these findings. Previous meta-analysisshowed that no significant difference between the two drug formulations (RR, 0.60; p=0.62)(12), which are consistent with the results of the present study. Meta-analysis by Sng et al.,2018 (9)determine the effectiveness and safety of hyperbaric bupivacaine compared with isobaric bupivacaine administered during spinal anaesthesia for elective caesarean section, the outcome showed consistent with the present study, despite the anatomical, physiological, and pharmacological differences of the population. Todeterminethe side effects such as hypotension, meta-analysis showed that there was no statistically significant difference of incidence of hypotensionbetween IB and HB.No difference was observedbetween the groups with respect to hypotension in three studies that included (22), (23), (25). Sng et al., 2018(9)did not observe any differences between IB and HB regarding incidence of hypotension, also another study showed similar results(12). In present Meta-analysis a longer durationof motor block was observed for HB compared to IB (30.53 min). In the previous meta-analysis study(12), a longer duration was reported for IB compared to HB, there is a difference between the results of the two studies that could be due to the results of the studies that were analyzed.In Kour et al., 2018 (22) study the duration of motor block was significantly higher with hyperbaric (220 min) vs 90 min in isobaric. The results of the meta-analysis in relation to the evaluation of the duration of sensory block were significantly higher with the isobaric solution, these results were consistent with the previous meta-analysis.In Sng et al., 2018 (9) study, the time taken was considerably shorter for HB, this difference may be due to the study population.Nevertheless, the small sample size involving these outcomes suggest that these results should be treated with caution. Russell et al., (26) showed longer duration of motor block with IB and other study showed longer sensory duration with IB(27).Clinical findings are important for anesthesiologists to choose the appropriate formulation that would allow the sufficiently prolonged duration of action.Studies conducted between 2001 and 2021 in relation to the purpose of the present study were few and most studies were of low quality, a study with low risk of bias was not found. The methodology of the studies was very poor and the results of the studies could not be fully relied on. Also, the method of generating a random sequence of studies was not well done, although all studies were RCT but only one study was of mediocre quality. Therefore, the results of the present study do not provide sufficient and strong evidence, on the other hand, the sample size of the study was small that cannot be fully cited in this population. Further studies with better and more complete methodology, more sample size, follow-up period for complications are needed to provide strong evidence.There is no convincing evidence to support HB or IB in terms of effectiveness or side effects.The decision can be based on the needs of the surgical procedure, especially regarding the onset time and duration of the block.This study had other limitations that could be noted: Opioids are commonly used to improve the quality of anesthesia or to prolong analgesia. Although studies have shown that opiates don’t have a significant effect on time to onset of sensory block, time to maximum level of sensory block, duration of sensory block, time to onset of motor block and duration of motor block. The studies reviewed in the present study, due to such low incidence rates, were low and did not have sufficient power to detect failure rates or even adverse events. In addition, a limited number of recent experiments in this area are available, and older

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experiments have not reported important methodological details, such as randomization, blinding, and evaluation of complete outcome data. The methods used to measure motor duration or sensory block or SA regression were between different studies. We think this can contribute significantly to the observed inconsistencies.

Conclusion

From Meta-analysis of the present study, no statistically significant differenceobserved between HB and IB about incidence of hypotension. The duration of motor block was significantly higher with HB, and duration of sensory block was significantly higher with the IB (high risk of bias).The present study had several limitations that have been mentioned before, but the most important limitations were the low quality of the studies and the small sample size, due to the low quality of the existing studies, sufficient evidence could not be provided. Future studies should be well designed to provide better results and aid in clinical decision making. The results of the present study should be used with caution due to the low quality of studies and high risk of bias, further studies are needed to provide better evidence.

References

1. Avidan M, Myles P. Auditing the national audit projects: impact and implementation. British journal of anaesthesia. 2018;121(1):107-11.
2. Nawabi A, Sullivan P, De Ruyter M, Pichoff A, King CD, Nawabi P. Surgical approach for kidney transplantation under spinal anesthesia. Journal of Surgical Case Reports. 2020;2020(12):rjaa538.
3. Ngo AL, Urits I, Yilmaz M, Fortier L, Anya A, Oh JH, et al. Postherpetic neuralgia: current evidence on the topical film-forming spray with bupivacaine hydrochloride and a review of available treatment strategies. Advances in therapy. 2020;37(5):2003-16.
4. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesthesia & Analgesia. 1985;64(7):715-30.
5. Olawin AM, Das JM. Spinal anesthesia. StatPearls [Internet]. 2019.
6. Martin-Flores M. Epidural and spinal anesthesia. Vet Clin North Am Small Anim Pract. 2019;49(6):1095-108.
7. Papesca JT. Effects of Neuraxial Anesthesia on Readiness for Ambulation Following Total Knee Arthroplasty: Regis College; 2020.
8. Sng BL, Siddiqui FJ, Leong WL, Assam PN, Chan ES, Tan KH, et al. Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section. Cochrane Database of Systematic Reviews. 2016(9).
9. Sng B, Han N, Leong W, Sultana R, Siddiqui F, Assam P, et al. Hyperbaric vs. isobaric bupivacaine for spinal anaesthesia for elective caesarean section: a Cochrane systematic review. Anaesthesia. 2018;73(4):499-511.
10. Vernhiet J, Cheruy D, Maindivide J, Vabre M, Clément C, Dartigues J, editors. Spinal anesthesia with bupivacaine. Comparative study of 2 hyperbaric and isobaric solutions. Annales francaises d'anesthesie et de reanimation; 1984.
11. Chambers W, Edstrom H, Scott D. Effect of baricity on spinal anaesthesia with bupivacaine. British journal of anaesthesia. 1981;53(3):279-82.

12. Uppal V, Retter S, Shanthanna H, Prabhakar C, McKeen DM. Hyperbaric versus isobaric bupivacaine for spinal anesthesia: systematic review and meta-analysis for adult patients undergoing noncesarean delivery surgery. Anesthesia & Analgesia. 2017;125(5):1627-37.
13. Solakovic N. Comparison of hemodynamic effects of hyperbaric and isobaric bupivacaine in spinal anesthesia. Medical Archives. 2010;64(1):11.
14. Muralidhar V, Kaul H. Comparative evaluation of spinal anaesthesia with four different bupivacaine (0.5%) solutions with varying glucose concentrations. J Anaesthesiol Clin Pharmacol. 1999;15:165-8.
15. Okazaki S, Ogata K, Kawaguchi E, Samuno T, Ogawara R, Yasumoto M, et al. Subarachnoid anesthesia with hyperbaric bupivacaine. Masui The Japanese journal of anesthesiology. 1989;38(7):923-6.
16. Uppal V, Shanthanna H, Prabhakar C, McKeen DM. Intrathecal hyperbaric versus isobaric bupivacaine for adult non-caesarean-section surgery: systematic review protocol. BMJ open. 2016;6(5):e010885.
17. Şahin AS, Ay N, Salihoğlu E, Sandal B, Derbent A. Should we use hypobaric bupivacaine in spinal anesthesia for eras patients undergoing total hip arthroplasty. Türkiye Klinikleri Tip Bilimleri Dergisi. 2019;39(1):1-8.
18. Badalov P, Çelebi H, Menteş B. Comparison of spinal anesthesia with isobaric 0.5% bupivacaine in the prone or jackknife position with hyperbaric 0.5% bupivacaine in the sitting position for anorectal surgery. Gazi Medical Journal. 2005;16(4).
19. Alston R. Spinal anaesthesia with 0.5% bupivacaine 3 ml: comparison of plain and hyperbaric solutions administered to seated patients. British journal of anaesthesia. 1988;61(4):385-9.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Chinese edition). Journal of Chinese Integrative Medicine. 2009;7(9):889-96.
21. Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A, et al. Cochrane bias methods group; cochrane statistical methods group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ. 2011;343(7829):d5928.
22. Kour L, Gupta KC, Mehta N, Mehta KS. Laparoscopic cholecystectomy under low thoracic combined spinal epidural anaesthesia: a comparative study between isobaric and hyperbaric bupivacaine. JMDS. 2018;17:01-4.
23. Toptaş M, Uzman S, İşitemiz İ, Yanaral TU, Akkoc I, Bican G. A comparison of the effects of hyperbaric and isobaric bupivacaine spinal anesthesia on hemodynamics and heart rate variability. Turkish journal of medical sciences. 2014;44(2):224-31.
24. Solakovic N. Level of sensory block and baricity of bupivacaine 0.5% in spinal anesthesia. Medical Archives. 2010;64(3):158.
25. Imbelloni LE, Beato L, Gouveia MA, Cordeiro JA. Low dose isobaric, hyperbaric, or hypobaric bupivacaine for unilateral spinal anesthesia. Revista brasileira de anestesiologia. 2007;57(3):261-70.
26. Russell I, Holmqvist E. Subarachnoid analgesia for caesarean section: a double-blind comparison of plain and hyperbaric 0.5% bupivacaine. British Journal of Anaesthesia. 1987;59(3):347-53.
27. Vichitvejpaisal P, Svastdi-Xuto O, Udompunturux S. A comparative study of isobaric and hyperbaric solution of bupivacaine for spinal anaesthesia in caesarean section. Journal-Medical Association Of Thailand. 1992;75:278-282.