Lidocaine vs. Other Local Anesthetics in the Development of Transient Neurologic Symptoms (TNS) Following Spinal Anesthesia: A Meta-Analysis of Randomized Controlled Trials

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Abstract: The use of lidocaine in spinal anesthesia may increase the risk of transient neurological symptoms (TNS) according to previous meta-analyses. However, the previous meta-analyses lacked data on some other local anesthetics and thus, more evaluations are still needed to compare the risk of lidocaine on the development of TNS. The objective of this study was to compare the risk of TNS according to lidocaine versus other local anesthetics in patients undergoing spinal anesthesia. A total of 39 randomized controlled trials with 4733 patients were analyzed. The incidence of TNS was 10.8% in the lidocaine group and was 2.2% in the control groups (risk ratio (RR) 4.12, 95% confidence interval (CI) 3.13 to 5.43, p < 0.001). In subgroup analysis, lidocaine increased the incidence of TNS compared with other local anesthetics except mepivacaine, ropivacaine or sameridine. The risk of TNS was higher in the hyperbaric (p < 0.001) or isobaric lidocaine (p < 0.001) group compared with the control group, but there were no differences found between the two groups when hypobaric lidocaine was administered (p = 1.00). This study confirmed that lidocaine for spinal anesthesia still causes TNS more frequently than most other local anesthetics, especially when hyperbaric or isobaric lidocaine was used.

Keywords: Lidocaine; Anesthesia; spinal; Postoperative Complications

1. Introduction

Lidocaine is an attractive regional anesthetic for ambulatory surgery. It offers a rapid onset and fast recovery of both motor and sensory block [1]. However, when compared with other local anesthetics, the use of lidocaine in spinal anesthesia has been known to be associated with increased risk of transient neurological symptoms (TNS) [2,3], hindering its application in ambulatory spinal anesthesia. Other local anesthetics including mepivacaine, low-dose bupivacaine, procaine, articaine, levobupivacaine, ropivacaine and 2-chloroprocaine have been suggested as replacement drugs.

TNS generally occurs in patients with single injection spinal anesthesia within the first 24 hours [2]. TNS consists of pain in the lower extremities without abnormalities in neurologic and radiologic examination [2]. In previous systematic reviews and meta-analyses [2,3], lidocaine has a significantly higher relative risk of developing TNS compared with most other local anesthetics, but the previous meta-analyses lacked data on ropivacaine, levobupivacaine, and chloroprocaine; thus, more evaluations are still needed to confirm favorable results for these aforementioned local anesthetics.
In the last decade, many randomized controlled trials (RCTs) comparing between the incidence of TNS after lidocaine and other local anesthetics have been conducted. More subsequent studies evaluating the effect of lidocaine on the risk of TNS have been published [2,3]. Furthermore, among them, many studies reported no patients suffering from TNS after spinal anesthesia with lidocaine [4–18]. Therefore, it is still controversial on the safety of lidocaine for spinal anesthesia during ambulatory surgery in terms of TNS. The objective of this systematic review and meta-analysis is to compare the incidence of TNS between lidocaine and other local anesthetics and to evaluate the frequency of TNS with various types of local anesthetics in adult surgical patients after spinal anesthesia.

2. Materials and Methods

2.1. Literature Search

This systematic review and meta-analysis was conducted according to the Preferred Items for Systematic Reviews and Meta Analyses (PRISMA) statements guideline [19]. A predefined protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019137819). RCTs comparing lidocaine versus other local anesthetics during spinal anesthesia were searched on the following databases: PubMed, EMBASE, CENTRAL, CINAHL, Scopus, Web of Science and KoreaMed. The final search was performed on March 31st, 2019. Search strategies were established with MeSH terms and keywords, including “spinal anesthesia”, “lidocaine”, or “lignocaine”. Each finding was combined with the Boolean operator, such as “AND”, “OR”. Detailed search strategies for each database were described in Table S1. The title, abstract, and authors of all retrieved articles were extracted and collected, regardless of the publication year, language or region.

2.2. Study Selection

C.-H.K. and H.-J.S. independently accessed the titles and abstracts of the articles to screen for relevant studies. Subsequently, full-texts of relevant articles were obtained via hand-search, library service or contacting the authors. C.-H.K. and J.-H.R. read the full text to select studies that were appropriate for this meta-analysis. The inclusion criteria were (1) randomized controlled trials, (2) surgical patients under spinal anesthesia, (3) lidocaine use for spinal anesthesia in at least in one group, and (4) use of other local anesthetic for spinal anesthesia in the control group. The exclusion criteria were: (1) abstract, protocol, conference poster or review; and (2) The study which did not report the incidence of TNS. S.-H.H. participated on selection if any disagreement existed.

2.3. Data Extraction

C.-H.K. and H.-J.S. independently investigated and collected the following data from final full-texts: author, publication year, language, sample size, type of surgery, type of anesthesia, patient’s position during surgery, needle type, characteristics of lidocaine (concentration, baricity, dose, and adjuvants), characteristics of local anesthetics used in the control group (type, concentration, baricity, dose, and adjuvants) and the incidence of TNS.

2.4. Risk of Bias Assessment

C.-H.K. and J.-H.R. independently assessed the risk of bias of the included studies using the Cochran Risk of Bias tool [20]. It consists of seven items: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. Each item was graded as low, unclear or high. S.-H.H. settled any disagreements between the aforementioned assessors.

2.5. Data Synthesis and Statistical Analysis

Data synthesis and meta-analysis were performed using Revman 5.3 software (Cochrane Collaboration, Oxford, UK) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna,
Austria). Since the incidence of TNS was dichotomous variable, the authors calculated the risk ratio (RR) as a pooled estimate. The inverse variance method and random effect models were employed. A continuity correction of 0.5 was applied to zero total events trials [21]. The findings were presented as a forest plot with 95% confidence intervals. A subgroup analysis was conducted according to the local anesthetics which were used in the control group. Additional subgroup analyses were carried out to investigate any relationship between the incidence of TNS and baricity/concentration. The heterogeneity among the studies was evaluated by F statistic. F could be interpreted in the following manner: 0% to 40% might not be important; 50% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity [22]. A publication bias was assessed by construction of a funnel plot and the linear regression test. Sensitivity analysis (leave one study out) was conducted to confirm the robustness of the results.

3. Results

3.1. Descriptions of Trials

A total of 4515 articles were found on the initial database search. Among them, 2493 articles were removed due to duplication. Subsequently, 2202 articles and 168 articles were considered as irrelevant based on their title and abstract, respectively. The full-text of 123 articles were evaluated, and then, 84 articles were excluded due to the following reasons: no results about the incidence of TNS (n = 42); no other local anesthetics were used (n = 18); conference posters (n = 7); abstracts only (n = 4); protocols (n = 4); healthy subjects (n = 4); non-randomized studies of intervention (n = 2); different anesthetic techniques between groups (n = 1); mixed spinal anesthetics (n = 1); and a brief report (n = 1). Therefore, a total of 39 RCTs were included in the final analysis (Figure 1) [4–18,23–46].

![Flow diagram of the included and excluded studies](image)

**Figure 1.** Flow diagram of the included and excluded studies. A total of 4515 articles were found during the literature search. Among them, 2493 articles were duplicated retrievals. A total of 2202 articles and 168 articles were obviously irrelevant studies. We excluded 84 articles due to various reasons. Finally, 39 articles were included in the final analysis. Abbreviations: TNS = transient neurological symptoms, LA = local anesthetics, RCT = randomized controlled trial.
Table 1. Baseline characteristics of the included randomized trials (n = 39).

| Author          | Year | Language | Anesthesia | Type of Operation                          | Number of Groups | Local Anesthetics (Control Group) | Needle | Position during Surgery | Follow-up Periods |
|-----------------|------|----------|------------|-------------------------------------------|------------------|-----------------------------------|--------|------------------------|-------------------|
| Ali             | 2015 | English  | SAa        | Knee arthroscopy                          | 2                | Bupivacaine                       | 25G Quincke | Supine                | 24,72,168 h       |
| Aouad           | 2001 | English  | SAa        | Cesarean section                          | 2                | Bupivacaine                       | 25G Whitacre | Supine                | 24,48,72 h        |
| Beilin          | 2003 | English  | CSEb       | Cervical cerclage                         | 2                | Bupivacaine                       | 25G Sprotte  | Lithotomy             | 24 h              |
| Breebaart       | 2003 | English  | SAa        | Knee arthroscopy                          | 3                | Levobupivacaine                   | 27G Whitacre | Supine                | 48 h              |
| Breebaart       | 2014 | English  | SAa        | Knee arthroscopy                          | 4                | Chloroprocaine                    | 27G Whitacre | Supine                | 168 h             |
| Casati          | 2007 | English  | SAa        | Knee arthroscopy                          | 2                | Chloroprocaine                    | 25G Whitacre | Not described         | 24,168 h          |
| de Santiago     | 2009 | English  | SAa        | Tubal sterilization                       | 2                | Levobupivacaine                   | 27G Whitacre | Trendelenburg         | 168 h             |
| de Santiago     | 2010 | Spanish  | SAa        | Anorectal surgery                         | 2                | Levobupivacaine                   | 27G Whitacre | Jackknife             | 72,168 h          |
| de Weert        | 2000 | English  | SAa        | Short surgery of the lower body           | 2                | Prilocaine                        | 25G pencil-point | Supine                | 24 h              |
| Etezadi         | 2013 | English  | SAa        | Varicocele, surgical fixation of lower extremities, transurethral resection of prostate, transurethral lithotripsy, herniorrhaphy | 4                | Bupivacaine                       | 25G Sprotte or Quincke | Supine or lithotomy | 8, 16, 24, 32, 40, 48, 72 h |
| Fanelli         | 2009 | English  | SAa        | Knee arthroscopy                          | 2                | Ropivacaine                       | 25G Whitacre | Supine                | 24,168 h          |
| Gozdemir        | 2010 | English  | SAa        | Varicoce vein, inguinal hernia, appendectomy | 2                | Levobupivacaine                   | 25G Quincke  | Supine                | 48,168 h          |
| Gozdemir        | 2016 | English  | SAa        | Varicocele vein, inguinal hernia, appendectomy | 4                | Levobupivacaine                   | 27G pencil-point | Not described         | 24,48,72 h        |
| Hampl           | 1995 | English  | SAa        | Short gynecological procedure             | 3                | Bupivacaine                       | 25G pencil-point | Lithotomy             | 24 h              |
| Author | Year | Language | Type | Procedure | Local Anesthetic | Needle | Position | Duration |
|--------|------|----------|------|-----------|-----------------|--------|----------|----------|
| Hampl  | 1998 | English  | SA*  | Short gynecological procedure | G1: Prilocaine, G2: Bupivacaine | 25G pencil-point | Lithotomy | 24 h |
| Hodgson| 2000 | English  | SA*  | Knee arthroscopy | Procaine | 24 or 25G pencil-point | Supine | 72 h |
| Imbelloni| 2010 | English  | SA*  | Anorectal surgery, inguinal hernia, femoral hernia, knee arthroscopy, removal of osteosynthetic material, fractures in the lower extremities, incision of infraumbilical abscess | Bupivacaine | 27G Quincke | Jackknife | Until 30th day |
| Keld   | 2000 | English  | SA*  | General, gynecological, or other surgery | Bupivacaine | 25G pencil-point | Supine | 24, 72 h |
| Khant  | 2017 | English  | SA*  | Urologic surgery | Bupivacaine | 26G Quincke | Supine or lithotomy | Not described |
| Kyokong| 2001 | English  | SA*  | Cesarean section, general, gynecological, or other surgery | Bupivacaine | 27G Quincke | Supine or lithotomy | 24 h |
| Le Truong| 2001| English  | SA*  | Orthopedic, urologic, gynecologic, vascular, general surgery, inguinal hernia, surgery below the umbilicus | Prilocaine | 25G Whitacre | Supine | 48 h |
| Liguori| 1998 | English  | SA*  | Knee arthroscopy | Prilocaine | 25G Whitacre | Not described | 48h |
| Maliachi| 1999| Portuguese| SA*  | Femur surgery | Prilocaine | 25G Whitacre | Not described | 72–120 h |
| Martin | 2005 | English  | SA*  | Postpartum tubal ligation | Prilocaine | 25G pencil-point | Supine | 24 h |
| Martinez| 1998| English  | SA*  | Orthopedic, urologic, gynecologic, vascular, general surgery, inguinal hernia, surgery below the umbilicus | Mepivacaine | 25,26,27,29G Quincke | Supine or lithotomy | 24 h |
| Mulroy | 1999 | English  | SA*  | Urology surgery | Prilocaine | 25G Whitacre | Not described | 24 h |
| Orozco | 2006 | Spanish  | SA*  | Anterior cruciate ligament repair | Mepivacaine | 27G Pencan | Supine | 24, 48, 72 h |
| Pawlowski| 2012| English  | CSE* | Postpartum tubal ligation | Bupivacaine | 25G Whitacre | Supine | 24, 48 h |
| Study          | Sample size | LDC | Control | LDC | Control |
|---------------|-------------|-----|---------|-----|---------|
| Pollock 1996  | English     | SA | Knee arthroscopy or inguinal hernia | 3   | Bupivacaine | 22 or 25G Quincke or Whitacre |
| Pradhan Punj 2010 English | SA | Cesarean section pelvic surgery | 2   | Bupivacaine | 26G Quincke |
| Punj 2010 English | SA | Cesarean section pelvic surgery | 4   | Bupivacaine | 24G Quincke |
| Salazar 2001 English | SA | Minor surgery of lower extremities | 2   | Mepivacaine | 26 or 27G Quincke |
| Salmela 1998 English | SA | Urologic surgery, varicose vein, hemorrhoidectomy, hernia | 3   | G1: Mepivacaine G2: Bupivacaine | 27G Quincke or Whitacre |
| Teunkens 2016 English | SA | Knee arthroscopy | 3   | G1: Chloroprocaine G2: Bupivacaine | 27G Whitacre |
| Vaghadia 2012 English | SA | Transurethral resection of prostate | 2   | Chloroprocaine | 25 or 27G Whitacre |
| Yea 1998 Korean | SA | Surgery of lower body | 2   | Mepivacaine | 25G Quincke |

Abbreviations: *SA = spinal anesthesia; b CSE = combined spinal-epidural anesthesia.

Table 2: Concentration, baricity, doses and adjuvants of study drugs (n = 39).

| Study          | Sample size | LDC | Control |
|---------------|-------------|-----|---------|
|               |             | LDC | Control | LDC | Control |
|               |             | Concentration | Baricity | Dose | Added |
|               |             | Type | Concentration | Baricity | Dose | Added |
|               |             | G1: Levobupivacaine G2: Ropivacaine | 1% | Isobaric | 10 mg | - |
|               |             | G1: Mepivacaine G2: Bupivacaine | 0.375% | Hyperbaric | 3 mg | FTN b 10μg |
|               |             | G1: Chloroprocaine G2: Bupivacaine | 0.75% | Hyperbaric | 12 mg | - |
|               |             | G1: Bupivacaine G2: Bupivacaine | 0.175% | Hyperbaric | 5.25 mg | FTN b 20μg |
|               |             | G1: Levobupivacaine G2: Ropivacaine | 1% | Isobaric | 40 mg | - |
|               |             | G1: Mepivacaine G2: Bupivacaine | 0.33% | Hyperbaric | 10 mg | FTN b 10μg |
|               |             | G1: Chloroprocaine G2: Bupivacaine | 0.5% | Hyperbaric | 4 mg | - |
|               |             | G1: Mepivacaine G2: Bupivacaine | 0.1% | Hyperbaric | 3 mg | FTN b 10μg |
| Study            | G1 | G2 | G3 | Dose | Local Anesthetic                  | Concentration | Needle Type | Dose | Local Anesthetic                  | Concentration | Needle Type | Dose | Local Anesthetic                  | Concentration |
|------------------|----|----|----|------|-----------------------------------|---------------|-------------|------|-----------------------------------|---------------|-------------|------|-----------------------------------|---------------|
| de Santiago 2010 | 30 | 30 | 0.6% | Hypobaric | 18 mg | Levobupivacaine | 0.5% | Hypobaric | 3 mg | Levobupivacaine | 0.5% | Hypobaric | 10 mg | -                              |
| de Weert 2000    | 35 | 34 | 2%   | Isobaric  | 80 mg | Prilocaine | 2% | Isobaric | 80 mg | Prilocaine | 2% | Isobaric | 12.5–15 mg | -                  |
| Etezadi 2013     | 125 | 125 | 5%  | Hyperbaric | 75–100 mg | Bupivacaine | 0.5% | Isobaric | 10 mg | Bupivacaine | 0.5% | Isobaric | 20 mg | -                  |
| Fanelli 2009     | 15 | 15 | 1%   | Isobaric  | 50 mg | Ropivacaine | 0.5% | Isobaric | 10 mg | Ropivacaine | 0.5% | Isobaric | -              |                   |
| Gozdemir 2010    | 30 | 30 | 2%   | Isobaric  | 80 mg | Levobupivacaine | 0.5% | Isobaric | 20 mg | Levobupivacaine | 0.5% | Isobaric | -              |                   |
| Gozdemir 2016    | 100 | G1: 100 | G2: 100 | G3: 100 | 2% | Isobaric | 60 mg | -              | -              | Isobaric | 15 mg | -              |                   |
| Hampl 1995       | 15 | 16 | G1:5% (7.5% dextrose) | Hyperbaric | G1:75 mg | Bupivacaine | 0.5% | Hyperbaric | 7.5 mg | -              | -              | Hyperbaric | 10 mg | -                  |
| Hampl 1998       | 30 | G1: 30 | G2: 30 | 2% | Hyperbaric | 50 mg | -              | -              | Hyperbaric | 100 mg | -              | -                  |
| Hodgson 2000     | 35 | 35 | 2.5% | Hyperbaric | 50 mg | Procaine | 5% | Hyperbaric | 100 mg | Procaine | 5% | Hyperbaric | 12.5 mg | -                  |
| Imbelloni 2010   | 75 | 75 | 0.6% | Hypobaric | 18 mg | Bupivacaine | 0.15% | Hyperbaric | 4.5 mg | Bupivacaine | 0.5% | Hyperbaric | -              |                   |
| Keld 2000        | 35 | 34 | 5%   | Hyperbaric | 100 mg | -              | -              | Hyperbaric | 12.5 mg | -              | -                  |
| Khant 2017       | 498 | 492 | 3.125% | Not described | 25 mg | Bupivacaine | 0.5% | Not described | 5 mg | Bupivacaine | 0.5% | Not described | -              |                   |
| Kyokong 2001     | 71 | 71 | 5%   | Hyperbaric | 60 mg | Bupivacaine | 0.5% | Hyperbaric | 11 mg | Bupivacaine | 0.5% | Hyperbaric | -              |                   |
| Le Truong 2001   | 29 | 25 | 5%   | Hyperbaric | 100 mg | -              | -              | Hyperbaric | 100 mg | -              | -                  |
| Liguori 1998     | 27 | 30 | 2%   | Not described | 60 mg | Mepivacaine | 1.5% | Not described | 45 mg | Mepivacaine | 1.5% | Not described | -              |                   |
| Maliachi 1999    | 20 | 20 | 5%   | Not described | 1 mg/kg | -              | -              | Not described | 7–15 mg | -              | -                  |
| Author          | Year | Group 1 | Group 2 | Group 3 | Local Anesthetic | Concentration | Delivery Method | Dose | Control Treatment | Concentration | Delivery Method | Dose |
|-----------------|------|---------|---------|---------|------------------|---------------|-----------------|------|------------------|---------------|-----------------|------|
| Martin 2005     | 40   | 40      |         |         | Not described    | 45 mg         | Hyperbaric      | -    | Prilocaine       | 1.5%          | Hyperbaric      | -    |
| Martinez 1998   | 100  | 98      |         | G1: 23  | Hyperbaric       | 67.7 ± 8.7 mg | Hyperbaric      | 6.86±9.7 mg | Prilocaine       | 5%            | Hyperbaric      | 15 mg |
| Mulroy 1999     | 32   |         | G2: 23  | G3: 42  | Hyperbaric       | 100 mg        | -               | G2: 20 mg | Sameridine       | Not described | Isobaric        | 23 mg |
| Orozco 2006     | 109  | 97      |         |         | Not described    | Not described | Bupivacaine     | 0.5% | Not described    | Not described | Not described   |      |
| Ostgaard 2000   | 49   | 50      |         |         | Isobaric         | 80 mg         | -               | 80 mg | Prilocaine       | 2%            | Isobaric        | 80 mg |
| Philip 2001     | 29   | 28      |         |         | Hyperbaric       | 60–80 mg      | -               | Bupivacaine | 0.75% | Hyperbaric      | 10.5–12 mg    |      |
| Pollock 1996    | G1:51| G2:51   | G1: 2%  | G2: 2%  | Hyperbaric or isobaric | 60 or 75 mg | EPI or none | Bupivacaine | 0.75% | Hyperbaric      | 7.5 or 9 mg   |      |
| Pradhan 2010    | 41   | 38      |         |         | Hyperbaric       | 75 mg         | -               | Bupivacaine | 0.5% | Hyperbaric      | 12.5 mg       |      |
| Punj 2013       | G1:20| G2:20   | G1: 5%  | G2: 2.5%| Hyperbaric       | Not described | -               | Bupivacaine | G1: 0.5% | Hyperbaric      | G1: 10 mg     | G2: 5 mg   |
| Salazar 2001    | 40   | 40      |         |         | Isobaric         | 40–60 mg      | -               | Mepivacaine | 2%   | Isobaric        | 40–60 mg       |      |
| Salmela 1998    | 30   | G1:30   | G2: 30  |         | Hyperbaric       | 60–100 mg     | -               | G1: Mepivacaine | G1: 4% | Hyperbaric      | G1:40–80 mg   | G2: 17 mg |
| Teunkens 2016   | 28   | G1: 30  | G2: 34  |         | Isobaric         | 40 mg         | -               | Chloropropanine | G1: 1% | Hyperbaric      | G1: 40 mg     | G2: 7.5 mg |
| Vaghadia 2012   | 20   | 20      |         |         | Not described    | 35 mg         | FTN 12.5 µg    | Chloropropanine | 1.77% | Isobaric        | 40 mg         |      |
| Yea 1998        | 30   | 30      |         |         | Hyperbaric       | 75 mg         | -               | Mepivacaine   | 2%   | Hyperbaric      | 12.5 µg       |      |

Abbreviations: *LDC = Lidocaine; *FTN = Fentanyl; *MP = Morphine; *EPI = Epinephrine.
All these RCTs compared lidocaine with other local anesthetics (bupivacaine, prilocaine, mepivacaine, levobupivacaine, chloroprocaine, ropivacaine, procaine, articaine, or sameridine) and reported the incidence of TNS. We found that 28 RCTs had two groups [4–12,14,15,18,23,26,27,29,30,34–42,44,46] of lidocaine more than other local anesthetics, while 11 RCTs had multiple groups [13,16,17,24,25,28,31–33,43,45]. Five out of 11 RCTs have more than two lidocaine groups [16,24,28,33,43]. According to the Cochrane guidelines [22], all lidocaine groups were pooled into a single group. In another five RCTs, more than two other local anesthetics were used for spinal anesthesia [17,25,31,32,45]. In the remaining RCT [13], three doses of sameridine were used for spinal anesthesia and the results of three sameridine groups were combined. Patients who received general anesthesia due to insufficient spinal block were excluded from the final analysis because it was unclear whether local anesthetics were administered in the cerebrospinal fluid. Details of each trial are summarized in Table 1. The 5% hyperbaric lidocaine was most used, followed by 2% isobaric. The dose of lidocaine used in each trial varied from 10 to 100mg. Specific details, including concentration, baricity, doses and adjuvants of study drugs, are summarized in Table 2.

3.2. Methodology Quality and Risk of Bias

The methodology quality and risk of bias are summarized in Figure 2. In each study, all patients were randomized to receive intrathecal lidocaine or other local anesthetics; however, the randomization method was unclear in eight studies. Twenty one studies maintained allocation concealment, but the other studies failed to describe it clearly. The risk of performance bias was high in 9 studies and unclear in 20 studies. It might be important for anesthesiologists to be aware of drugs for patient safety and sufficient block when performing spinal anesthesia. Unlike performance bias, the risk of detection bias was low overall. The risk of attrition bias, reporting bias, and other biases were low in more than 75% of the studies evaluated. Reasons for each risk of bias are shown in Table S2.

Figure 2. Risk of bias summary and graph using the Cochrane Risk of Bias tool [20]. The randomization and allocation concealment were well performed in most studies, but the method was not described in several studies. The performance bias was unclear or high in most studies, whereas the detection bias was low overall. The risk of attrition bias, reporting bias and other biases were low in most studies. Abbreviations: + = low risk of bias, ? = unclear risk of bias, - = high risk of bias.

3.3. Outcome Synthesis

A total of 39 studies included 4733 patients; 2209 patients were allocated to the lidocaine group and 2524 patients to the control group. The incidence of TNS was 10.8% (238/2209) in the lidocaine group and was 2.2% (56/2524) in the control group. The risk of TNS after spinal anesthesia was significantly higher in the lidocaine group than in the control group (Risk ratio (RR) = 4.12, 95% confidence interval (CI) = 3.13 to 5.43, p < 0.001), with a low level of heterogeneity ($I^2 = 0\%$, $p = 0.61$) (Figure 3).
symmetrical funnel plot and linear regression test showed insignificant results for publication bias ($p = 0.206$) (Figure S1). Sensitivity analysis revealed the robustness of the results (Table S3). Omitting one study [28] decreased the RR to 3.51, but still maintained the significance.

### Table S3: Sensitivity Analysis of the Risk Ratio for the Incidence of TNS

| Study          | Events LDC | Events Other LA | Risk Ratio | RR  | 95% CI          | Weight |
|---------------|------------|-----------------|------------|-----|-----------------|--------|
| Ali 2015      | 25         | 25              | 1.00       | 3.51| (0.02, 48.49)   | 0.05   |
| Aoud 2001     | 100        | 100             | 1.00       | 4.91| (0.02, 49.91)   | 0.05   |
| Belkin 2003   | 29         | 0               | 5.17       | 10.20| (0.26, 103.20)  | 0.08   |
| Breebaart 2003| 330        | 60              | 13.89      | 26.31| (0.74, 260.31)  | 0.09   |
| Breebaart 2014| 500        | 50              | 3.00       | 7.19| (0.13, 71.91)   | 0.08   |
| Buckenmaier 2002| 37        | 35              | 0.95      | 2.46| (0.02, 46.44)   | 0.05   |
| Casali 2007   | 55         | 15              | 1.10      | 6.23| (0.66, 182.37)  | 1.00   |
| de Santiago 2009| 625     | 62              | 1.00      | 4.86| (0.02, 48.56)   | 0.05   |
| de Santiago 2010| 30         | 30              | 1.00      | 4.88| (0.02, 48.88)   | 0.05   |
| de Weerd 2000 | 75         | 34              | 1.15      | 7.38| (0.02, 48.88)   | 0.05   |
| Eftezad 2013  | 85         | 125             | 6.07      | 9.09| (3.65, 10.09)   | 0.29   |
| Fanelli 2009  | 65         | 15              | 13.00     | 21.43| (0.80, 211.43)  | 1.00   |
| Godsmir 2010  | 85         | 10              | 6.00      | 10.09| (1.07, 60.09)   | 1.00   |
| Godsmir 2016  | 27         | 100             | 4.50      | 2.59| (0.59, 7.81)    | 24.90  |
| Hamp 1995     | 95         | 28              | 11.00     | 67.17| (0.68, 177.03)  | 1.00   |
| Hamp 1998     | 95         | 30              | 16.00     | 29.15| (2.09, 135.55)  | 1.00   |
| Houle 2000    | 11         | 35              | 5.50      | 131.23| (0.31, 230.53)  | 3.70   |
| Imbattoli 2010| 07         | 75              | 1.00      | 4.97| (0.02, 49.71)   | 0.05   |
| Kell 2008     | 95         | 35              | 8.74      | 115.63| (1.17, 65.34)   | 1.00   |
| Kramer 2017   | 9          | 450             | 0.99      | 4.99| (0.02, 49.68)   | 0.05   |
| Kyokong 2001  | 07         | 71              | 1.00      | 4.97| (0.02, 49.71)   | 0.05   |
| Le Truong 2001| 8         | 29              | 14.69     | 82.24| (0.09, 242.26)  | 1.00   |
| Ligouri 1998  | 6          | 27              | 14.42     | 85.24| (0.05, 244.30)  | 0.09   |
| Malushi 2004  | 4          | 20              | 5.10      | 26.76| (0.26, 97.65)   | 0.05   |
| Martin 2005   | 4          | 40              | 1.00      | 4.91| (0.02, 49.19)   | 0.05   |
| Martinez 1998 | 4          | 98              | 4.06      | 40.57| (0.46, 35.87)   | 1.00   |
| Muir 1999     | 0          | 32              | 3.34      | 1.64| (0.07, 164.98)  | 0.05   |
| Orozco 2006   | 1          | 109             | 2.67      | 11.64| (0.61, 64.81)   | 1.00   |
| Ostgaard 2000 | 7          | 49              | 3.57      | 16.35| (0.76, 163.5)   | 3.30   |
| Pawlowski 2012| 0          | 41              | 0.93      | 4.52| (0.02, 45.62)   | 0.05   |
| Philip 2001   | 1          | 29              | 0.46      | 0.05| (0.00, 0.03)    | 0.05   |
| Pollock 1996  | 16         | 102             | 16.26     | 205.65| (1.00, 205.65)  | 1.00   |
| Prachan 2010  | 0          | 26              | 1.00      | 4.86| (0.02, 48.56)   | 0.05   |
| Puj 2013      | 0          | 40              | 1.00      | 4.91| (0.02, 49.19)   | 0.05   |
| Sakkari 2001  | 0          | 40              | 1.00      | 4.91| (0.02, 49.19)   | 0.05   |
| Samela 1998   | 6          | 30              | 1.00      | 4.26| (0.05, 26.96)   | 0.05   |
| Teunisse 2016 | 0          | 28              | 2.26      | 11.15| (0.05, 111.25)  | 0.09   |
| Vagheh 2012   | 4          | 20              | 6.00      | 52.16| (0.02, 52.16)   | 0.05   |
| Ye 1998       | 0          | 30              | 1.00      | 4.88| (0.02, 48.80)   | 0.05   |

In subgroup analysis as shown in Figure 4, lidocaine increased the incidence of TNS compared with most other local anesthetics, such as bupivacaine (RR = 4.79, 95% CI = 3.31 to 6.94, $p < 0.001$), levobupivacaine (RR = 5.1, 95% CI = 2.37 to 11.0, $p < 0.001$), prilocaine (RR = 4.94, 95% CI = 1.89 to 12.9, $p = 0.001$), chloroprocaine (RR = 5.24, 95% CI = 1.11 to 24.76, $p = 0.037$), procaine (RR = 6.74, 95% CI = 1.88 to 24.13, $p = 0.003$), and articaine (RR = 4.5, 95% CI = 1.94 to 10.42, $p < 0.001$). However, no significant difference was observed between the lidocaine group and the mepivacaine (RR = 0.82, 95% CI = 0.27 to 2.48, $p = 0.728$), ropivacaine (RR = 5.92, 95% CI = 0.99 to 35.47, $p = 0.052$) or sameridine group (RR = 3.34, 95% CI = 0.07 to 164.98, $p = 0.545$). A low level of heterogeneity was found in each subgroup analysis.
Figure 4. Forest plot for subgroup analysis. A subgroup analysis was conducted according to the local anesthetics which were used in the control group. The incidence of TNS was significantly higher in the lidocaine group than in the bupivacaine (p < 0.001), levobupivacaine (p < 0.001), prilocaine (p = 0.001), chloroprocaine (p = 0.037), procaine (p = 0.003) and articaine group (p < 0.001). However, there were no differences in the risk of TNS between the lidocaine group and mepivacaine (p = 0.728), ropivacaine (p = 0.052) and sameridine group (p = 0.545). Abbreviations: LDC = lidocaine, LA = local anesthetics, CI = confidence interval.

The relationship between the incidence of TNS and baricity or concentration is shown in Figure 5. Sixteen studies used hyperbaric lidocaine [5,6,11,13,15,16,18,28,32–36,39,42,45], 12 studies used isobaric [14,17,23–27,29–31,41,44], and 4 studies used hypobaric lidocaine for spinal anesthesia [4,7,26,33]. One study had two treatment groups that administered hyperbaric or isobaric lidocaine [43]. Since 6 studies failed to report the baricity of lidocaine [10,12,37,38,40,46], those RCTs were excluded from subgroup analysis. The risk of TNS was higher in the lidocaine group compared with the control group when hyperbaric (RR = 3.59, 95% CI = 2.03 to 6.33, p < 0.001) or isobaric lidocaine (RR = 4.45, 95% CI = 2.86 to 6.93, p < 0.001) was used. However, there were no differences between the two groups with respect to the risk of TNS when hypobaric lidocaine was administered (RR = 1.00, 95% CI = 0.14 to 6.99, p = 1.00). As shown in Table 2, the concentration used in each study varied from 0.3% to 5%. Two studies have multiple groups with different concentration [16,43]. Most studies used 2% or 5% lidocaine and subgroups were categorized into 3 groups: (1) 5%, (2) 2%≤5%, and (3) <2%. The incidence of TNS was significantly higher in the lidocaine group compared with the control group in all categories (5%: RR = 5.23, 95% CI = 3.40 to 8.05, p < 0.001; 2%≤5%: RR = 3.53, 95% CI = 2.03 to 6.12, p < 0.001; <2%: RR = 3.28, 95% CI = 1.24 to 8.71, p = 0.017).

Figure 5. Forest plot for subgroup analysis. Additional subgroup analyses were conducted according to the baricity or concentration of the lidocaine. The risk of TNS was significantly higher in hyperbaric
(p < 0.001), isobaric lidocaıne group (p < 0.001) compared to the control group. In terms of concentration, lidocaine showed a higher incidence of TNS regardless of concentrations compared to the control group (p < 0.05). Abbreviations: LDC = lidocaine, LA = local anesthetics, CI = confidence interval.

4. Discussion

The present meta-analysis confirmed that lidocaine used for spinal anesthesia still causes TNS more frequently than most other local anesthetics (bupivacaine, levobupivacaine, prilocaine, chloroprocaine, procaine, and articaine) except for mepivacaine, ropivacaine or sameridine. This is the first study that analyzed the role of baricity and concentration of lidocaine as potential risk factors for TNS, and the subgroup analysis showed that hyperbaric and isobaric lidocaine showed higher TNS rates than the others, and higher rates of TNS have been observed in all concentration categories of lidocaine.

The incidence of TNS of lidocaine was about 4 times higher than that of other local anesthetics in this study, which supported the result of the previous meta-analysis by Zaric et al. [2] which included 16 RCTs with a total of 1467 patients. Since then, many RCTs have been still conducted to compare the incidence of TNS between lidocaine and other local anesthetics. A recent meta-analysis including 24 studies with 2226 patients compared the risk of TNS by using direct and indirect comparison [3]. However, in this meta-analysis, more RCTs, including 39 studies with 4733 patients (more than twice) were analyzed and lidocaine was compared with more various local anesthetics. However, the risk ratio and prevalence of developing TNS of the current study was slightly lower than those of the previous studies; Zaric et al. (risk ratio 4.62, prevalence 14.2%) [2], Forget et al. (prevalence 18%) [3]. These difference can be explained in part by that many RCTs of the present meta-analysis reported no case of TNS in the lidocaine group [4–18], and a continuity correction of 0.5 was applied to these zero total events trials to prevent the overestimation of the risk of TNS [21]. Among other local anesthetics, chloroprocaine and mepivacaine have similar characteristics with lidocaine in terms of rapid onset time and short duration [47,48]. Subgroup analysis suggested that the incidence of TNS of chloroprocaine was lower than that of lidocaine. This finding significantly differs from the previous results [2,3]. However, the previous meta-analyses included only one or two RCTs comparing the effect of lidocaine and chloroprocaine. This study included four RCTs and no case of TNS in the chloroprocaine group was reported [17,24,26,46]. This would appear to indicate that chloroprocaine may be an attractive alternative to lidocaine for the short ambulatory surgery with fast onset and quick recovery time [48]. On the other hand, there was no difference in the incidence of TNS between lidocaine and mepivacaine, which was consistent with the result of the previous studies [2,3]. The idea that ropivacaine could decrease the development of TNS is still controversial. Although Zaric et al. [2] found that there was no difference in the risk of TNS between lidocaine and ropivacaine, Forget et al. [3] found that ropivacaine could decrease the risk of TNS than lidocaine. However, as expected, two studies included smaller number of studies and the latter study estimated pooled effect size by mostly indirect comparison. Surprisingly, the present study found more studies comparing the effect of lidocaine and ropivacaine, and estimated the pooled effect size by using a direct comparison.

Subgroup analysis suggested that no cases of TNS were found in the hypobaric lidocaine group whereas previous studies showed that the TNS of the lidocaine group occurred regardless of the baricity and concentration [49–51]. This result can be explained by low doses (10–20 mg) of hypobaric lidocaine group administered. Ben-David et al. [52] also reported that small doses of hypobaric lidocaine reduced the risk of TNS more than large doses of hypobaric lidocaine. However, this needs to be interpreted with caution since low doses of local anesthetics may be insufficient for adequate regional block [53]. Regarding the concentration of lidocaine, higher rates of TNS have been observed in all categories of concentration, which confirms the previous finding that altering the lidocaine concentration had no influence on the prevention of TNS [54].

This meta-analysis has a few limitations. First, various definitions of TNS were used in each study. Generally, TNS is defined as pain originating in the gluteal region and radiating to both lower
extremities [2]. Some studies included considered TNS as only pain [4], while several other studies regarded TNS as pain and abnormal sensation (hypoesthesia or dysesthesia) [26,30]. Moreover, the anatomical regions (back, thigh, buttock or lower extremity), involving TNS, varied in each study. Furthermore, some studies did not specify details and/or a definition of TNS [35,47]. This variance with respect to TNS may have created bias, influencing the exact frequency of TNS. Second, specific types of surgery and position may be considered as risk factors of TNS, such as knee arthroscopy and lithotomy position. In the present study, various types of surgery and surgical position were included, and this may induce a bias in the results. Subgroup analysis according to the surgical position may provide a better overview. However, surgical position is heterogeneous and is not defined in some trials and the subgroup analysis according to the position, which may induce inaccurate results with bias. Third, only one study compared lidocaine to articaine with 134 patients, which may not be enough to conclude that the frequency of TNS with articaine is less than with lidocaine. Similarly, one RCT compared sameridine with lidocaine with 140 patients and there were no cases of TNS in the sameridine group.

5. Conclusions

In conclusion, the risk of developing TNS after spinal anesthesia with lidocaine was significantly higher than with bupivacaine, levobupivacaine, prilocaine, chloroprocaine, procaine or articaine. In addition, hyperbaric and isobaric lidocaine showed higher TNS rates than other lidocaines.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Funnel plot of comparison, lidocaine vs. other local anesthetics, Table S1: Search strategy for each database, Table S2: Details for judgement for each risk of bias, Table S3: Sensitivity analysis of comparison.

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