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The Efficiency and Safety of Intrarectal Topical Anesthesia for Transrectal Ultrasound-Guided Prostate Biopsy: A Systematic Review and Meta-Analysis

Keywords

Anesthesia · Biopsy · Intrarectal topical anesthesia · Prostate cancer

Abstract

Objective: The study aims to review the current evidence to determine the efficiency and safety of intrarectal topical anesthesia (ITA) for transrectal ultrasound-guided prostate biopsy. **Materials and Methods:** A comprehensive search of the literature was performed using Medline, Embase and Cochrane central register of controlled trials. All randomized controlled trials (RCTs) comparing the efficacy and safety of periprostatic nerve block (PNB), ITA, and PNB combined with ITA were included. The mean pain scores after the biopsy procedure, the mean pain scores after the probe insertion and adverse events were evaluated. **Results:** Thirty-2 RCTs were identified in the meta-analysis. ITA could significantly reduce pain during probe insertion compared to control and placebo. The PNB group had less pain after the prostate biopsy than the ITA group. PNB combined with ITA could significantly reduce pain during the biopsy procedure compared to ITA alone. No significant differences were found in adverse events in ITA versus control, ITA versus placebo, and

ITA versus PNB. **Conclusions:** ITA could reduce pain after probe insertion and pain after biopsy although it was inferior to PNB in reducing pain during prostate biopsy. ITA combined with PNB was more effective than ITA alone. In addition, it was safe to perform ITA for prostate biopsy.

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Introduction

Transrectal ultrasound (TRUS) guided prostate biopsy is the most commonly used procedure for the diagnosis of prostate cancer since the mid-1980s and well tolerated [1]. However, 65–90% of patients complain of pain during this procedure [2]. Ten and extended 10+ core prostate biopsy techniques are recommended in order to increase the cancer detection rate [1]. As the number of biopsies is increasing, more pain is experienced by patients. When pain is severe, it may decrease the planned number of biopsies or even to interrupt the procedure,

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and eventually the cancer detection rate can be reduced. Pain could increase the complication and lead to the patient's discomfort [2]. In addition, the complication is related to the extent of cooperation exhibited by patients and operators. Therefore, it is important to perform prostate biopsy with optimal anesthesia.

The 2 most commonly used methods of anesthesia are intrarectal topical anesthesia (ITA) and periprostatic nerve block (PNB). ITA with anesthetic gel or cream was recommended as a desirable alternative and a noninvasive technique to alleviate pain during prostate biopsy [2]. Periprostatic infiltration of lidocaine is considered the most used and best method in pain control [2]. Thus, the question as to which method can be more effective in pain control during prostate biopsy is emerging.

In 2007, Tiong et al. [2] conducted the first systematic review comparing ITA and PNB. They found that PNB, but not ITA, was effective and safe in relieving pain from TRUS-guided biopsy [2]. However, limited evidence (only 25 studies) was identified and included in the study. Since then, a large number of new trials have been published about PNB and ITA in prostate biopsy. Additionally, there are more and more new data published that compared the efficacy and safety among ITA, PNB, and PNB combined with ITA.

Therefore, the present meta-analysis and systematic review were not only to update 2007 data but also to confirm the efficiency and safety of ITA versus PNB and PNB combined with ITA for TRUS-guided prostate biopsy.

Material and Methods

We searched the electronic databases Medline, Embase and Cochrane central register of controlled trials (CENTRAL) to identify all randomized controlled trial (RCT) about anesthesia methods to alleviate pain during TRUS-guided prostate biopsy. The last search was made on April 10, 2016. The following search terms were used to identify relevant studies: (anesthesia and analgesia or anesthesia, local or anesthesia, rectal) and (prostate biopsy or biopsy, prostate).

Our primary outcomes were the mean overall pain scores after the biopsy procedure, measured on a linear pain scale and their SD. The majority of included studies utilized a 10-point visual analog scale (0-no pain, 10-maximum pain). If 5-point or 100-point pain scale was used, the scores were converted to a 10-point pain scale to facilitate data analysis. The secondary outcomes were the mean pain scores after the probe insertion and adverse event after the prostate biopsy.

The relevant data were independently extracted by 2 of the authors. When data of interest were not presented in the study, we attempted to contact the authors first. If we failed to communicate with the authors, we converted the original data of intervention

and control group into CI, *t* statistics, *p* values or individual variances. Otherwise, we used the intervention-to-treat analysis to deal with the lost data.

Jadad scale was used to assess the methodological quality of the included RCT. Jadad score ranges between 0 and 5, and a higher score indicates better quality [3]. In addition, heterogeneity of the included RCTs was analyzed using the chi-square test on N-1 degree of freedom, with an alpha of 0.10 and with I^2 test. If $I^2 < 50\%$, the fixed-effect model was used. If $I^2 \geq 50\%$, the random-effect model was adopted. Adverse events were assessed using relative ratio (RR) with 95% CI. Mean overall pain scores were assessed using mean difference (MD) with its 95% CI. All of the analyses were performed by Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). Publication bias was evaluated with a funnel plot. Subgroup analysis was used to explore possible heterogeneity, for example, dividing into different doses and classes of the narcotic drug.

Results

Literature Flow

Four hundred twenty-nine studies were identified from the electronic database and hand search. After the study assessment, 32 studies were included in the present systematic review (Fig. 1). The study characteristics for the 32 studies are presented in Table 1. Baseline information was comparable in them.

Efficacy

ITA versus Control

Nine studies including a total of 854 patients investigated the mean overall pain after biopsy in ITA versus control. The heterogeneity was observed in pooled analysis ($p < 0.00001$; $I^2 = 88\%$) [4–12]. The MD of mean pain after biopsy in lidocaine gel and lidocaine-prilocaine cream was -0.57 (95% CI -1.22 to 0.88) and -1.49 (95% CI -2.62 to -0.36) respectively. The meta-analysis of 9 studies demonstrated a statistically significant difference in favor of ITA (random effect model; MD -0.99 ; 95% CI -1.68 to -0.29 ; $p = 0.005$; Fig. 2).

Four studies including a total of 314 patients investigated the mean pain after probe insertion in the ITA group and control group. The heterogeneity was observed in pooled analysis ($p < 0.00001$, $I^2 = 95\%$) [4, 5, 7, 9]. The MD of mean pain after probe insertion in lidocaine and lidocaine/prilocaine was -1.50 (95% CI -2.25 to -0.75) and -2.85 (95% CI -5.03 to -0.67) respectively. The meta-analysis of 4 studies observed that ITA was more effective than the control group in terms of mean pain after probe insertion (random effect model; MD -2.39 ; 95% CI -4.21 to -0.57 ; $p = 0.010$; Fig. 3).

Fig. 1. Data flowchart of meta-analysis. RCT, randomized control trial.

Fig. 2. Forest plot of the meta-analysis on topical anesthesia versus control after prostate biopsy.

ITA versus Placebo

Two studies including 400 patients compared the mean pain after probe insertion between the ITA group and the placebo group. The heterogeneity was not observed in pooled analysis ($p = 0.72$; $I^2 = 0\%$) [13, 14]. Me-

ta-analysis of 2 studies demonstrated a significant difference in favor of ITA (fixed effect model; MD -1.23; 95% CI -1.58 to -0.88; $p < 0.00001$; Fig. 4).

Twelve studies including 1,605 patients investigated the mean overall pain after biopsy in ITA versus pla-

Table 1. Characteristics and baseline of trials included in the meta-analysis

First author, year	Study design	Number of prostatic core	Treatment arms (number of patients)	Pain during probe insertion (mean $\pm$ SD)	Overall pain	Complication	Jadad score
Giannarini, 2009 [4]	RCT, B	10	5 mL perianal-intrarectal lidocaine-prilocaine (EMLA) gel and 10 mL 1% lidocaine PNB (68) 5 mL perianal-intrarectal lidocaine-prilocaine gel (67) 10 mL 1% lidocaine PNB (68) No anesthesia (67)	1.5 $\pm$ 0.94 1.41 $\pm$ 0.98 5.37 $\pm$ 1.33 5.31 $\pm$ 1.27	0.77 $\pm$ 0.81 1.27 $\pm$ 1.4 1.27 $\pm$ 1.19 4.33 $\pm$ 2.26	Hematuria, rectal bleeding, hemospermia	5
Gurbuz, 2010 [5]	RCT, B	10	No anesthesia (25) 5 mL of 1% lidocaine gel perianally (25) 10 mL of 1% lidocaine PNB (25) 5 mL EMLA intrarectally and perianally (25)	2.48 $\pm$ 1.73 2.81 $\pm$ 1.69 2.67 $\pm$ 0.92 2.5 $\pm$ 1.77	2.97 $\pm$ 2.02 1.65 $\pm$ 0.41 1.39 $\pm$ 0.67 2.58 $\pm$ 2.18	No major complications	5
Buckley, 2006 [6]	RCT, B	–	30 mL of 2% lidocaine gel intrarectally (60) 4 mL of 2% lidocaine at base and apex of prostate (60) 4 mL of 2% lidocaine at apex only (60) No anesthesia (60)	– – – –	3.1 $\pm$ 1.9 1.7 $\pm$ 1.7 2.0 $\pm$ 1.8 3.5 $\pm$ 1.9	No complication occurred	4
Stirling, 2002 [7]	RCT	>8	No anesthesia (50) 10 mL of 2% lidocaine gel intrarectally (50) 5 mL 1% lidocaine PNB (50)	3.7 $\pm$ 2.1 2.2 $\pm$ 1.7 3.0 $\pm$ 1.9	3.8 $\pm$ 1.8 3.1 $\pm$ 1.7 2.6 $\pm$ 1.8	–	1
Trucchi, 2005 [8]	RCT	10	No anesthesia (20) 10 mL 1% lidocaine gel intrarectally (20) 10 mL 1% carbocaine PNB (20)	– – –	5.5 $\pm$ 2.3 5.5 $\pm$ 2.7 0.5 $\pm$ 0.8	–	2
Kandirali, 2009 [9]	RCT	12	No anesthesia (20) 5 mL lidocaine-prilocaine gel perianally (20) 5 mL lidocaine-prilocaine gel intrarectally (20) Lidocaine-prilocaine gel perianally and intrarectally (20)	5.21 $\pm$ 2.30 2.86 $\pm$ 1.97 5.08 $\pm$ 2.10 2.67 $\pm$ 1.64	3.89 $\pm$ 1.50 2.11 $\pm$ 1.61 3.63 $\pm$ 1.38 1.92 $\pm$ 1.31	Hematuria, rectal bleeding	3
Galosi, 2005 [10]	RCT, B	–	5 mL of EMLA perianally (60) 10 mL of 2.5% lidocaine perianally (50) 5 mL of hydrophilic gel perianally (40) No anesthesia perianally (60)	– – – –	2.6 $\pm$ 1.4 3.8 $\pm$ 1.6 3.9 $\pm$ 1.8 3.6 $\pm$ 1.6	Hemospermia, slight hematuria, urinary retention	2
Issa, 2000 [11]	RCT, B	6	10 mL 2% lidocaine gel intrarectally (25) Control (25)	– –	2 5 ($p = 0.00001$)	–	4
Yurdakul, 2009 [12]	RCT	–	No anesthesia (25) 10 mL of 2% lidocaine gel intrarectally (25) 5 mL of 0.25% bupivacaine PNB + 10 mL of 2% lidocaine gel intrarectally (25) 5 mL of 0.25% ropivacaine PNB + 10 mL of 2% lidocaine gel intrarectally (25)	– – – –	3.04 $\pm$ 1.49 2.76 $\pm$ 1.01 1.20 $\pm$ 0.65 1.04 $\pm$ 0.68	–	2
Raber, 2005 [13]	RCT	12	5 mL EMLA perianally and transrectally (100) 5 mL placebo (100)	0.952 $\pm$ 1.09 1.39 $\pm$ 2.38	1.852 $\pm$ 2.59 3.18 $\pm$ 2.89	Vasovagal symptoms	3
Raber, 2008 [14]	RCT	14	5 mL of 2% lidocaine PNB (100) 5 mL EMLA intrarectally and perianally + 5 mL of 2% lidocaine PNB (100) 5 mL gentamicin cream (100)	1.48 $\pm$ 2.33 0.29 $\pm$ 0.99 1.46 $\pm$ 2.22	0.43 $\pm$ 1.47 0.37 $\pm$ 1.39 3.02 $\pm$ 3.03	Fever, urinary retention, hematuria, hematospermia, dysuria, rectal bleeding	2
Adamakis, 2004 [15]	RCT, B	–	10 mL sonographic gel intrarectally (40) 10 mL 5% EMLA (78) 10 mL 2% lidocaine in prostatic base (80)	– – –	5.1 $\pm$ 1.5 4.8 $\pm$ 1.5 2.5 $\pm$ 1.5	Hematuria, fever, septicemia,	4

Table 1. (continued)

First author, year	Study design	Number of prostatic core	Treatment arms (number of patients)	Pain during probe insertion (mean $\pm$ SD)	Overall pain	Complication	Jadad score
De Maria, 2006 [16]	RCT, B	10	5 g lidocaine-prilocaine gel intrarectally and perianally (50) Ultrasound gel intrarectally and perianally (48)	–	4.06 6.54	Macroscopic hematuria, hemospermia, rectal bleeding	2
Leung, 2006 [17]	RCT, B	6	10 mL of 2% lidocaine gel intrarectally (169) 10 mL plain lubricant gel intrarectally (169)	–	1.75 $\pm$ 1.55 1.79 $\pm$ 1.51	–	4
Argüelles, 2008 [18]	RCT	8–10	Lubricant gel (39) Lidocaine gel intrarectally (38) 5 mL of 1% lidocaine PNB (40)	–	4.37 $\pm$ 2.41 4.22 $\pm$ 2.46 1.88 $\pm$ 2.03	Rectal bleeding, reaction Vagal	2
Chang, 2001 [19]	RCT, B	>8	10 mL 2% lidocaine gel intrarectally (56) 10 mL lubricant gel intrarectally (52)	–	2.83 $\pm$ 1.89 2.89 $\pm$ 2.09	Brief vasovagal episode	3
Desgrandchamps, 1999 [20]	RCT	–	15 mL of 2% lidocaine gel intrarectally (56) 15 mL of trans-sonic gel (53)	–	–	Rectal bleeding, hematuria, dysuria, fever	4
Fink, 2005 [21]	RCT, B	>10	Placebo suppository (25) 10 mL 2% lidocaine gel intrarectally (25) Lidocaine suppository 1 h before biopsy (25) Lidocaine suppository 2 h before biopsy (25)	–	36.2 40.9 29.2 21.2	–	5
Sataa, 2010 [22]	RCT, B	–	10 mL of 2% lidocaine gel intrarectal (33) 10 mL of 2% lidocaine PNB (33) 10 mL of placebo gel intrarectal (34)	–	4.6 3.5 4.4	–	4
Tobias-Machado, 2006 [23]	RCT	12	20 mL 2% lidocaine gel (20) 10 mL 1% lidocaine PNB (60) 15 mL lubricating gel (20)	–	–	Hematuria, rectal bleeding, urinary retention, UTI, vasovagal reaction.	3
Goluza, 2011 [24]	RCT	–	60-mg lidocaine suppository intrarectally (80) glycerin suppository as placebo (80)	–	3 $\pm$ 1 4.1 $\pm$ 1.3	–	–
Lynn, 2002 [25]	RCT, B	6	10 mL 1% lidocaine PNB (30) 11 mL 2% lidocaine gel intrarectally (27) Plain gel intrarectally (14) 10 mL 0.9% saline (15)	–	0.5 2.7 4.8 4.3	–	3
Song, 2006 [26]	RCT	6	20 mL of 2% lidocaine gel intrarectally (30) 5 mL of 2% lidocaine PNB (30) 5 mL of 0.9% saline (30)	–	5.5 $\pm$ 2.7 3.6 $\pm$ 2.1 5.8 $\pm$ 1.9	Gross hematuria, rectal bleeding, hemospermia	2
Başar, 2005 [27]	RCT	8–12	Placebo cream (20) 1 g 2.5% lidocaine – 2.5% prilocaine gel (20) 6 mL 1% prilocaine PNB (20) 60 mg 1% lidocaine PNB (20)	–	5.5 2.91 2.47 2.21	Hematuria, rectal bleeding	2
Alavi, 2001 [28]	RCT	6–14	10 mL 1% lidocaine PNB (75) 10 mL 2% lidocaine gel intrarectally (75)	–	2.4 $\pm$ 3.02 3.7 $\pm$ 1.99	–	3
Kravchick, 2005 [29]	RCT	6	10 mL 2% lidocaine gel rectal (28) 10 mL 40% DMSO with 2% lidocaine gel intrarectally (30) 10 mL 1% lidocaine perianal injection (29) 10 mL 1% lidocaine PNB (27)	2.763 $\pm$ 1.3415 1.38 $\pm$ 0.5327 1.893 $\pm$ 0.3073 4.42 $\pm$ 1.1592	4.147 $\pm$ 1.2955 2.65 $\pm$ 1.0654 2.103 $\pm$ 0.7049 2.15 $\pm$ 0.8016	Rectal bleeding, urethrorrhagia, hematuria, vasovagal episodes	3
Mallick, 2004 [30]	RCT	–	15 mL 2% lidocaine gel intrarectally (166) 10 mL 1% lidocaine PNB (162)	–	1.5 $\pm$ 2.4 2.5 $\pm$ 4	hematuria	2

Table 1. (continued)

First author, year	Study design	Number of prostatic core	Treatment arms (number of patients)	Pain during probe insertion (mean $\pm$ SD)	Overall pain	Complication	Jadad score
Mallick, 2005 [31]	RCT	~10	15 mL of 2% lidocaine gel intrarectally (180) 10 mL of 1% lidocaine PNB (176)	–	2.0 $\pm$ 3.8 2.1 $\pm$ 3.7	Postural dizziness, haematuria, haemospermia	2
Matlaga, 2003 [32]	RCT, B	12 (8–15)	22 mL of 1% lidocaine PNB (27) 10 mL of 2% lidocaine gel intrarectally (23)	1.2 1.8 ($p = 0.13$)	0.5 4.2 ($p < 0.0001$)	None reported	4
Rodriguez, 2003 [33]	RCT, B	–	10 mL 2% lidocaine gel intrarectally (43) 10 mL 1% lidocaine at the apex of the prostate (53)	–	2.76 $\pm$ 1.69 1.73 $\pm$ 1.26	–	2
Szlauer, 2008 [34]	RCT, B	10	60 mg lidocaine suppository 2 h before biopsy (25) 120 mg lidocaine suppository 1 h before biopsy (25) 120 mg lidocaine suppository 2 h before biopsy (25) 5 mL 2% lidocaine PNB (25)	–	3.63 $\pm$ 1.9 3.56 $\pm$ 2.0 3.58 $\pm$ 1.6 1.8 $\pm$ 1.8	–	4
Von Knobloch, 2002 [35]	RCT	10	No anesthesia + 6 mL 2% lidocaine mucosal anaesthetic (34) 5–10 mL 1% articaine PNB + 6 mL 2% lidocaine mucosal anaesthetic (34)	–	3.29 (1–8) 1.85 (1–8) $p < 0.0001$	–	2

RCT, randomized controlled trial; B, blind; PNB, periprostatic nerve block; EMLA, lidocaine-prilocaine cream; none reported.

cebo [10, 13, 15–24]. Data could not be extracted from 5 studies. Thus, 4 studies for lidocaine-prilocaine cream, 3 studies for lidocaine gel, and 1 study for lidocaine suppository was assessed. The MD of mean pain after biopsy in lidocaine-prilocaine cream, lidocaine gel, and lidocaine suppository was -0.69 (95% CI -1.36 to -0.02), -0.09 (95% CI -0.56 to 0.37) and -1.10 (95% CI: -1.46 to -0.74) respectively. Meta-analysis of 12 studies demonstrated that ITA could significantly relieve pain after biopsy compared with placebo (random effect model; MD -0.56 ; 95% CI -0.99 to -0.13 ; $p = 0.01$; Fig. 5).

ITA versus PNB

Nineteen studies including 2,303 patients investigated the mean overall pain after biopsy in ITA versus PNB [4–8, 15, 18, 22, 23, 25–34]. However, the data were available in 17 of 19 studies. Heterogeneity was observed in pooled analysis ($p < 0.00001$; $I^2 = 91\%$). The MD of the mean pain after biopsy for lidocaine-prilocaine cream, lidocaine gel and lidocaine suppository was 1.02 (95% CI -0.38 to 2.42), 1.48 (95% CI 0.74 – 2.22), and 1.79 (95% CI 0.97 – 2.61) respectively. Meta-analysis of 19 studies demonstrated a statistically sig-

nificant difference in favor of PNB (random effect model; MD 1.39 ; 95% CI 0.81 – 1.98 ; $p < 0.00001$; Fig. 6).

ITA versus (PNB + ITA)

Three studies including 278 patients compared the efficiency of PNB plus ITA with ITA [4, 12, 35]. The heterogeneity was observed in the meta-analysis ($p = 0.0005$, $I^2 = 87\%$). The combination of PNB and ITA was superior to ITA in reducing pain during the prostate biopsy (random effect model, MD: -1.15 , 95% CI -2.05 to -0.26 , $p = 0.01$; Fig. 7).

Adverse Events

The adverse event data of 7 studies were comparative. The result is listed in Table 2. There is no significant difference in ITA versus control and ITA versus placebo. Most of the adverse events were minor complications, such as mild hematuria and mild rectal bleeding, which did not require any treatment. The most serious adverse events were vasovagal symptoms and septic infection. No patient died because of prostate biopsy in the included RCTs.

Fig. 3. Forest plot of the meta-analysis on topical anesthesia versus control after probe insertion.

Fig. 4. Forest plot of the meta-analysis on topical anesthesia versus placebo after probe insertion.

Discussion

TRUS-guided prostate biopsy is the standard procedure for the diagnosis of prostate cancer in urological practice; more pain and discomfort will accompany with the increasing number of biopsies. ITA is regarded as a feasible and effective method for performing TRUS-guided prostate biopsy. This systematic review and meta-analysis provided a comprehensive assessment of ITA with control and 2 other widely used methods – PNB and ITA combined with PNB. Eventually, we found that ITA could significantly reduce the pain during probe insertion. However, it was inferior to PNB in reducing pain during prostate biopsy. On the other hand, ITA combined with

PNB was more effective in reducing prostate biopsy-related pain than ITA alone.

Due to the location of prostate cancer, the biopsy sample site was recommended to be as far posterior and lateral in the peripheral gland as possible [4, 12, 35]. Therefore, pain was more prone to be triggered when prostate biopsy was performed, and application of anesthesia into this area may potentially reduce the pain. Anesthesia not only gave patients comfort, but also gave urologist the opportunity to increase the number of biopsies.

Whether ITA could alleviate pain during prostate biopsy remained controversial. Tiong et al. [2] observed that ITA was not significantly better than placebo or control in reducing the pain during prostate biopsy. Despite

Fig. 5. Forest plot of the meta-analysis on topical anesthesia versus placebo after prostate biopsy.

the fact that ITA technique had the advantage of being noninvasive and is easier to performance in comparison with PNB, ITA was not the ideal type of anesthesia because it apparently could not eliminate pain during prostate biopsy. In contrast, PNB was more powerful in eliminating prostate biopsy-related pain, which was more painful than the pain that occurred during probe insertion.

Although PNB is effective in reducing pain during TRUS-guided biopsy, it cannot completely eliminate the pain originating from introduction and movement of the transrectal probe and transrectal anesthetic injection to the prostate gland. However, the inferolateral nerve of the prostate is in close proximity to the rectal wall, and rectal mucosa has excellent drug absorptive capacity. ITA could theoretically minimize probe-related anorectal discomfort and pain originating from initial rectal wall piercing [8, 36]. Furthermore, the present

meta-analysis and systematic review confirmed that ITA could significantly reduce the pain that occurs while manipulating the probe and inserting the transrectal anesthetic injection during TRUS-guided prostate biopsy.

While both ITA and PNB had its own shortcoming of eliminating the pain during prostate biopsy, several studies found that the combination of ITA and PNB could overcome their own shortcomings and exert their own merits [8, 36]. This opinion was also confirmed by our systematic review that combining of PNB and ITA is superior to ITA alone. Combining ITA and PNB results in effective pain control during the manipulation of the probe and while the PNB needle pierces the rectal wall in the process of performing prostate biopsy.

Due to the combined anesthesia is a complex procedure compared with PNB or ITA alone respectively. Cantiello recommended that potentially re-biopsy candidates

Fig. 6. Forest plot of the meta-analysis on topical anesthesia versus PNB after prostate biopsy. PNB, periprostatic nerve block.

Fig. 7. Forest plot of the meta-analysis on PNB combined with topical anesthesia versus topical anesthesia after prostate biopsy. PNB, periprostatic nerve block.

Table 2. Meta-analysis of adverse events and serious adverse events

	Comparison	No. of included study	No. of included patients	I^2 , %	Risk ratio (95% CI)	p value
Adverse events	ITA vs. control	1 [4]	159	–	–	No statistically difference 0.79
	ITA vs. placebo	5 [15, 19, 20, 23, 27]	415	2	0.98 (0.85–1.13)	
Serious adverse events	ITA vs. control	1 [4]	134	–	0.33 (0.01–8.04)	0.50
	ITA vs. placebo	2 [13, 15]	318	0	0.48 (0.15–1.58)	0.23

ITA, intrarectal topical anesthesia.

should use the combined anesthesia of ITA and PNB. In addition, Bingqian et al. [36] demonstrated that combined anesthesia may be of the greatest benefit in patients with prostate volume 48 mL or less or patients 66 years or younger, whereas Giannarini et al. [4] found that men younger than 65 years old and with prostate volume greater than 49 mL were more prone to pain during prostate biopsy, and that they should undergo combining anesthesia.

Combining of ITA and PNB was a safe procedure. The most frequent complications related to biopsy were hematuria, hematochezia, and dysuria, which were mild and self-limiting. There were no reports of increased complications from published studies. Thus, we may suggest that ITA combined with PNB should be considered the best option to be performed in selected patients, such as young patients experiencing re-biopsy.

The principal limitation of our meta-analysis was that it could not rule out the heterogenetic nature of the study. And we did not stratify the outcomes by the different number of biopsy cores. However, no study so far has provided the evidence about the optimum anesthesia for a different number of biopsy cores. Thus, well-designed clinical trials are required to overcome these drawbacks.

In brief, according to the results of our meta-analysis, ITA could reduce pain after probe insertion and pain af-

ter biopsy, although it was inferior to PNB in reducing pain during prostate biopsy. In addition, ITA combined with PNB was more effective than ITA alone.

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Statement of Ethics

All analyses were based on previous published studies and thus no ethical approval or patient consent was required.

Disclosure Statement

All authors declare no financial interests.

Author Contributions

Y.Y. and Z.L.: literature search, full-texts screening, data analysis. Q.W.: help with the data extraction. X.W., Y.Z., D.C., L.Y., and Z.T.: drafting the manuscript. L.L. and P.H.: study design.

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