REVIEW PAPER

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#### UROLOGICAL ONCOLOGY

# Effectiveness of periprostatic block to prevent pain in transrectal prostate biopsy: a systematic review and a network meta-analysis

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#### Article history

Submitted: Jan. 28, 2019 Accepted: April 8, 2019 Published online: April 8, 2019 **Introduction** The purpose of this study was to determine the effectiveness and harms of periprostatic block compared with other interventions in patients with clinically suspected prostate cancer who underwent transrectal biopsy to diminish pain.

**Material and methods** We included only clinical trials which involved male adults older than 18 yearsold suspected of having prostate cancer. The intervention performed was a periprostatic block and the comparators were topical anesthetics, sedatives, placebo/no intervention or combined therapies. The primary outcome was perianal or perineal pain and serious adverse effects (SAE). Literature search was conducted in MEDLINE, EMBASE, LILACS, CENTRAL and non-published literature from inception to March 2019. We performed a network meta-analysis in R.

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Department of Urology Calle 4B No. 36-00 76001 Cali, Colombia phone: +57 321 2195102 herney.garcia@ correounivalle.edu.co **Results** We included 43 studies in the meta-analysis. Thirteen studies compared periprostatic block vs. placebo/no intervention (the most frequent). Most of the studies had an unclear risk of bias for selection, performance and detection bias and low risk for attrition, reporting and other bias. Periprostatic block (lidocaine) + intrarectal gel (lidocaine + prilocaine) vs. periprostatic block (lidocaine) showed an RR-0.9 (95%CI – 1.9 to 0.074); intrarectal gel (lidocaine) vs. periprostatic block (lidocaine) had a RR 0.77 (95%CI 0.14 to 1.4); placebo/no intervention vs. periprostatic block (lidocaine) + intrarectal gel (lidocaine+prilocaine) RR 3 (95%CI 1.9 to 4); intrarectal gel (lidocaine) versus periprostatic block (lidocaine) + intrarectal gel (lidocaine) + intrarectal ge

**Conclusions** The blockage of the periprostatic plexus in the performance of a transrectal ultrasound-guided prostatic biopsy, alone or in combination with intrarectal analgesia or sedation, is an effective method to reduce pain.

Key Words: network meta-analysis () periprostatic block () prostatic neoplasm () systematic review () transrectal biopsy

# INTRODUCTION

More than 1.1 million cases of prostate cancer (PCa) cases were registered per year during the last few years, which represents around 8% of new cases and 15% in men all over the world [1]. PCa is the second leading cause of cancer-specific death in the United States and it is estimated that during the following years 26,120 new deaths will be caused by this condition [2].

Nowadays, more than 90% of PCa cases are diagnosed in the early stages, which get higher 5 year-overall survival (almost 100%) [2]. This is generally suspected by an abnormal digital rectal examination and/or an elevated prostate-specific antigen (PSA) [3]. Early detection might significantly reduce related morbidity and increase survival of these patients, this is why urologists need to diagnose and initiate treatment faster to increase the probability of a succesful outcome [4, 5]. Regarding the diagnosis, the prostate biopsy is the gold standard to make the diagnosis and we have two different approaches to perform this procedure: transperineal and transrectal. The latter is the most commonly used nowadays [6]. Although transrectal ultrasound-guided (TRUS) prostatic biopsy has been considered a minor procedure, people often experience pain, anxiety and disturbances before, during and after the procedure [7]. About 65–90% of men experience pain based on different factors: entering an ultrasound probe in the rectum, the movement of this device, size and geometry of the probe, the insertion of the needle for injecting anesthetics, the biopsy itself, among others [6, 7, 8].

Pain is the most important problem during this procedure and there are lots of approaches to reduce it and to improve adaptation of these patients; however, there is no consensus about what to choose [9]. The European Association of Urology recommend topical anesthesia plus periprostatic nerve bundle block (PPNB) [10]; however, there are multiple trials considering other approaches like a single PPNB, only topical gels, combined therapies, among others, additionally, there is some evidence supporting that the most painful moment is the application of the anesthetic [10, 11].

Based on literature, there is no standard of care to this approach and selection depends mainly on clinical condition, experience of the physician and clinical criteria, furthermore, we considered a systematic review to try to elucidate this problem. The purpose of this systematic review was to determine the effectiveness and harms of periprostatic block compared with other interventions in patients with clinically suspected prostate cancer who undergo transrectal biopsy to diminish pain during and after the procedure.

## MATERIAL AND METHODS

We performed this review according to the recommendations of the Cochrane Collaboration and following the PRISMA Statement. The PROSPERO registration number is CRD42018094806.

## **Inclusion criteria**

We included only clinical trials which involved male adults over 18 years-old suspected of having prostate cancer based on any of the clinical or biochemical indications and who underwent transrectal prostate biopsy according to standard procedure. The intervention was periprostatic block (injecting an anesthetic solution (bupivacaine 0.25%, lidocaine 1-2% or articaine 1%) on neurovascular bundles on each side of the prostate gland, this has to be guided by ultrasound and identifying the correct position by a hypoechoic bubble) and the comparators were topical anesthetics, sedatives, placebo/no intervention or combined therapies [12, 13].

The primary outcome was perianal or perineal pain (assessed by any validated tool i.e. visual analogue scale (VAS) and serious adverse effects (SAE) (fever, rectal bleeding >2 days, prostatitis and acute urinary retention) [14]. Secondary outcomes were other adverse effects (hematospermia, hematuria, rectal bleeding less than two days) [2]. There were no setting or language restrictions. The exclusion criteria were: transperineal biopsy and other conditions that might increase or produce pain during the biopsy.

#### **Information sources**

Literature search was conducted in accordance to the recommended procedure by Cochrane. We used medical subject headings (MeSH), Emtree language, DeCS and text words related in a complete search strategy (Appendix 1). We searched MEDLINE (OVID), EMBASE, LILACS and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to March 2019. To ensure literature saturation, we scanned references from relevant articles identified through the search, conferences, thesis databases, Open Grey, Google scholar and clinicaltrials.gov, among others. We contacted authors by e-mail in case of missing information.

#### **Data collection**

We reviewed each reference by title and abstract. Then we scanned full-texts of relevant studies, applied prespecified inclusion and exclusion criteria and then extracted the data. Disagreements were resolved by consensus and where disagreement could not be solved, a third reviewer was used to dissolve the conflict. Relevant data were collected in duplicate by using a standardized data extraction sheet that contained the following information: author names, year of publication, title, study design, geographic location, objectives, inclusion and exclusion criteria, number of patients included, losses to follow-up, timing, definition of outcomes (infection), outcomes and association measures and funding source.

### **Risk of bias**

The assessment of the risk of bias for each study was made using the Cochrane Collaboration tool for assessing the risk of bias, which covers: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other biases. We judged the possible risk of bias from extracted information, rated as 'high risk', 'low risk' or 'unclear risk'. We computed a graphic representation of potential bias using RevMan 5.3.

## Data analysis / synthesis of results

We performed the statistical analysis in R [15] with the command gemtc for a Bayesian network meta-analysis and Review Manager v5.3. For outcomes we reported information about risk differences (RD) with 95% confidence intervals according to the type of variables and we pooled the information with a fixed effect network meta-analysis according to the heterogeneity expected. The results were reported in forest plots of the estimated effects of the included studies with a 95% confidence interval (95% CI). Heterogeneity was evaluated using the I2 test. For the interpretation, it was determined that the values of 25%, 50%, and 75% in the I2 test corresponded to low, medium, and high levels of heterogeneity, respectively.

Assumption of transitivity was plausible and evaluated according to the kind of comparisons and considering the similarity of the distribution of the potential effect modifiers across the different pairwise comparisons. Additionally, for every treatment, we estimated the probability of being at each possible rank to infer the relative ranking of the treatments.

### **Publication bias**

An evaluation was conducted to identify reporting or publication bias using the funnel plot.

## Sensitivity analysis

We performed sensitivity analysis extracting weighted studies and running the estimated effect to find differences.

## **Geometry of the network**

We produced network diagrams to show the amount of evidence available for each outcome and the most frequent comparison. The size of the nodes was proportional to the total number of patients allocated to the treatments across all trials and the width of the lines was proportional to the total number of RCTs evaluating the comparisons.

## **Assessment of inconsistency**

We evaluated consistency using the node-splitting model through a Bayesian network meta-analysis.

## **Subgroup analysis**

We tried to perform subgroup analysis based on: age, geographical setting and kind of biopsy, but the information was similar on some variables and so dissimilar in other, therefore we decided against performing it.

# RESULTS

### **Study selection**

We found a total of 1299 studies with the search strategies and after eliminating 143 duplicates and those based on title and abstract screening, we finally included 43 studies [10, 16–57] in the qualitative



Figure 1. Flowchart.

and quantitative analysis (Figure 1). We updated the search to March 2019 and found 120 additional files, but none of them were relevant to this study (Excluded by title/abstract).

## **Characteristics of included Studies**

A total of 5,885 patients with a mean of 137 patients per study (range 40–430) were included. Seven studies used placebo as the only comparator [16, 19, 20, 29, 44, 45, 52], while five used no intervention as the comparator [17, 21, 33, 42, 55].

The indication of biopsy was not clearly described in one single article [51] and the most common indication was an abnormal PSA levels and/or suspicious digital rectal exam (DRE) [10, 16–57].

For the evaluation of the results, all the studies used an analogous scale of pain

(VAS) that ranges between 0–10 [10, 16–54, 56, 57]. The time for the most frequent outcome evaluation was immediately after the biopsy, which was performed in twenty-six studies [17–27, 29–31, 33, 36, 39, 40, 45, 47, 48, 50, 51, 53, 54, 56]. Thirteen studies have a result evaluation during the biopsy [10, 25, 32, 34, 37, 41–44, 49, 52, 55, 57], two studies at 15 minutes after the biopsy [16, 46], one study during the insertion of the needle [38], another study 20 minutes after [35] and one 30 minutes after of biopsy [28] (see Table 1).

### Summary of network geometry

Placebo/no intervention vs. periprostatic block only was the most frequent comparison, it was found in 13 studies [16–21, 29, 33, 42, 44, 45, 52, 55]. We found nine studies with the comparison between intrarectal gel (lidocaine) vs. periprostatic block (lidocaine) [18, 27, 28, 35, 40, 47, 53, 54, 57] and seven studies with intrarectal gel (lidocaine) vs. placebo/ no intervention [22, 23, 30, 34, 39, 41, 56].

Two studies followed the comparison with intrarectal gel (lidocaine) vs. periprostatic block (lidocaine) + intrarectal gel (lidocaine + prilocaine) [47, 54], while four studies used periprostatic block (lidocaine) + intrarectal gel (lidocaine + prilocaine) vs. periprostatic block (lidocaine) [10, 35, 50, 51].

Three studies had the following comparisons: 1. placebo gel vs. periprostatic block (lidocaine); 2. sedative vs. periprostatic block (lidocaine); 3. placebo/ no intervention vs. periprostatic block (lidocaine) + intrarectal gel (lidocaine + prilocaine); 4. intrarectal gel (lidocaine) vs. placebo gel; 5. sedative vs. placebo/no intervention (see Figure 2).

Yun 2016 was excluded from the network analysis since it had only one arm.



Figure 2. Network plot for outcome pain.

### **Risk of bias**

All of the studies were classified as low risk of bias in the following issues: incomplete outcome data, selective reporting and other bias. On the contrary, we found mostly unclear risk of bias in: random sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcome assessment.

Stirling 2002, Stirling 2002a and Szlauer 2008 [21, 23, 40] had high risk of bias in blinding of participants and personnel since they had incomplete masking, while some groups were aware of intervention. Wu 2001 [52], had a high risk of bias in the random sequence generation since it had randomization based on inappropriate tools.

Studies like Addla 2003, Kravchick 2005, Lynn 2002 and Ragavan 2005 were classified as high quality (low risk of bias) since they only had one issue on the unclear risk of bias [19, 22, 31, 32] (see Figure 3).

## **Exploration for inconsistency and ranking**

For the primary outcome and the node-splitting model we found that the following comparisons were consistent, but some of them were heterogeneous: periprostatic block A (lidocaine injection) versus combined [(periprostatic block (lidocaine) + intrarectal gel (lidocaine + prilocaine) (I2 = 99%; inconsistency p value = 0.12); periprostatic block A versus topical (intrarectal gel [lidocaine)] (I2=99%; inconsistency p value = 0.38); combined versus placebo / no intervention (I2 = 45%; inconsistency

# Table 1. Characteristics of included studies

Study	No. of patients	Participants	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Outcome assessment
Ozveri et al. (2003) [16]	100	Men, elevated total prostate-specific antigen (tPSA) and/or abnormal digital rectal examination (DRE)	Periprostatic block (Lidocaine)	Placebo			15 min after the procedure
Walsh et al. (2003) [17]	64	Abnormal DRE or an elevated PSA	Periprostatic block (Lidocaine)	No intervention			Immediately
Rodriguez et al. (2003) [18]	96	Abnormal prostate on digital rectal examination and/or elevated serum prostate specific antigen PSA, some patients have re-biopsy because of a prostatic intraepithelial neoplasia history (PIN), a continuous raised PSA level and a diagnosed cancer in previous prostate resection	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)			Immediately
Addla et al. (2003) [19]	98	Prescriptions were requested on a named patient basis at the beginning of each TRUS biopsy list	Periprostatic block (Lidocaine)	Placebo			Immediately
Berger et al. (2003) [20]	100	Men suspected of having prostate cancer Subjects were included a normal age-	Periprostatic block (Lidocaine)	Placebo			Immediately
Rodriguez et al. [53] (2002)	96	specific prostate-specific antigen (PSA) Abnormal DRE or an elevated PSA	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)			Immediately
Stirling et al. (2002) [21]	100	Referred for transrectal ultrasound from who informed consent was obtained were eligible	No intervention	Periprostatic block (Lidocaine)			Immediately
Lynn et al. (2002) [22]	86	Abnormal PSA level (>4 ng/mL) and/or an abnormal DRE, and prostatic biopsy for the first time	Periprostatic block (Lidocaine)	Intrarectal gel (Lidocaine)	Placebo gel	Placebo	Immediately
Stirling et al. (2002) [23]	150	Men requiring biopsy of the prostate	No intervention	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)		Immediately
Hiros et al. (2010) [24]	90	Abnormal PSA level (>4 ng/mL) and/or an abnormal DRE, and prostatic biopsy for the first time	Periprostatic block (Lidocaine)	Intrarectal gel (Voltaren)	Placebo gel		Immediately
Kim et al. (2011) [25]	430	Patients who visited the department of urology	Periprostatic nerve block with 1% lidocaine	Acetamino- phen 650 mg,	EMLA cream		During biopsy
Song et al. [56] (2004)	90	Abnormal DRE, level PSA>4 ng	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)	Placebo		Immediately
Yun et al. [57 ] (2006)	250	Increased PSA with or without abnormal digital rectal examination, 2) with lesion suspected malignancy on TRUS	Lidocaine gel intrarectal+PNB	Perianal block (Lidocaine)			During biopsy
Manikandan et al. (2003) [26]	235	Abnormal PSA levels and/or suspicious DRE	No intervention	Periprostatic block (Lidocaine)	Sedative (Entonox)		Immediately
Obek [27] et al. (2004)	300	Abnormal PSA levels and/or suspicious DRE	No intervention	Periprostatic block (Lidocaine)	Peripros- tatic block (Lidocaine) + Intrarectal gel (Lidocaine)	Tramadol infused intravenously in 30 minutes at a dose of 1.5 mg/kg in 100 cc	. Immediately

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#### Table 1. Continuation

Study	No. of patients	Participants	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Outcome assessment
Mallick et al. (2004) [28]	328	Abnormal digital rectal prostate examination or transrectal ultrasound scan and/or elevated prostate specific antigen (PSA) (greater than to 4 ng/ml).	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)			30 min
Vanni et al. (2004) [29]	40	Elevated PSA levels and/or suspicious DRE	Periprostatic block (Lidocaine)	Placebo			Immediately
Trucchi et al. (2005) [30]	60	Elevated prostate-specific antigen (PSA) level and its derivates (total and free PSA, free/total PSA ratio, PSA density, PSA velocity), abnormal digital rectal examination (DRE), abnormal transrectal sonography	No intervention	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)	-	Immediately
Kravchick et al. (2005) [31]	114	Abnormal digital rectal examination findings and/or an elevated prostate- specific antigen (PSA) level (4 ng/mL or greater)	Intrarectal gel (Lidocaine)	Intrarectal gel (DMSO + Lidocaine)	Perianal block (Lidocaine)	Periprostatic block (Lidocaine)	Immediately
Ragavan et al. (2005) [32]	165	Increased prostate specific antigen (PSA) with or without abnormal digital rectal examination	Periprostatic block (Lidocaine)	Diclofenac suppository	Periprostatic block (Lidocaine) + Diclofenac suppository		During biopsy
Feltes Ochoa et al. (2006) [33]	131	Abnormal PSA level (>4 ng/mL) and/or an abnormal DRE	Periprostatic block (Bupivacaine)	No intervention			Immediately
Song et al. (2006) [34]	90	Abnormal digital rectal examination and/or serum prostate-specific antigen (PSA) concentrations of 4 ng/mL or higher.	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)	Placebo		During biopsy
	250	Abnormal digital rectal examination, with lesion	Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)			
Yun et al. (2007) [35]		suspected malignancy on TRUS with or without abnormal digital rectal examination,					20 min. After biopsy
		Increased serum PSA (4 ng/ml or greater),	Periprostatic block (Lidocaine) + Intrarectal cream (Lidocaine + Prilocaine)	Intrarectal cream (Lidocaine +Prilocaine)		No intervention	
Giannarini et al. (2009) [10]	al. 280	and/or abnormal digital rectal examination or TRUS findings			block (Lidocaine)		During biopsy
Izol et al. (2012) [36]	100	Abnormal finding during the digital examination and/or elevated serum PSA levels higher than 2.5 ng/mL	No intervention	Periprostatic block (Lidocaine)	Intrarectal gel (Lidocaine)	Sedative (Midazolam + Fentanil)	Immediately
Lunacek et al. (2014) [54]	123	People with suspected PCa without active prostatitis underwent TRUS-guided biopsy	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)	Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine)		Immediately
Griwan et al. (2012) [37]	60	Patients with elevated prostate-specific antigen (PSA) levels (>4 ng/mL) and abnormal results on digital rectal examination (DRE),	Diclofenac patch 100mg	Periprostatic block (Lidocaine)	No intervention		During biopsy
Ozok et al. (2010) [38]	100	Patients with prostate-specific antigen (PSA) above the level of 2.5 ng/ml and/or with abnormal digital rectal examination (DRE) findings were included in the study	Periprostatic block (Lidocaine)	Periprostatic block (Lidocaine) + Tramadol hydrochloride 50 mg	Periprostatic block (Lidocaine) + Intramuscular Midazolam	Placebo	Pain during needle

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#### Table 1. Continuation

Study	No. of patients	Participants	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Outcome assessment
Sataa et al. (2010) [39]	100	Less than 70 years of age and in whom prostate biopsy was indicated for a prostate suspected malignancy to the rectal examination and / or an increase in the level of the specific antigen prostate (PSA) >3 ng/ml	Intrarectal gel (Lidocaine)	Periprostatic block (Lidocaine)	Placebo gel	_	Immediately
Szlauer et al. (2008) [40]	100	Indications for prostate biopsy included an abnormal digital rectal examination and/or an elevated serum PSA level	Intrarectal gel (60 mg lidocaine 2h)	Intrarectal gel (120 mg lidocaine 1h)	Intrarectal gel (120 mg lidocaine 2h)	Periprostatic block (Lidocaine)	Immediately
Raber et al. (2008) (41)	300	Abnormally elevated prostate-specific antigen (PSA) values or suspicious digital rectal exam (DRE) results	Periprostatic block (Lidocaine)	Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine)	Placebo		During biopsy
Jones et al. (2003) [42]	60	Men requiring biopsy of the prostate	Periprostatic block (Lidocaine)	No intervention			Immediately
Turgut et al. (2006) [3]	93	Suspicious digital rectal examination (DRE), abnormally elevated serum prostate-specific antigen (PSA) level or abnormal TRUS findings referred	Sedative (Midazolam)	Periprostatic block (Lidocaine)	No intervention		Immediately
Raber et al. (2008) (41)	73	Abnormal prostate on digital rectal examination and/or elevated prostate specific antigen (PSA> 4 ng/ml)	Periprostatic block (Lidocaine)	Placebo			Immediately
Jones et al. (2003) [42]	126	Abnormal digital rectal examination (EDR) and/or elevated prostate specific antigen (PSA)	Periprostatic block (Lidocaine)	No intervention			Pain following biopsy
Nambirajan et al. (2004) [45]	96	Abnormal digital rectal examination (DRE) or elevated PSA	Periprostatic block (Lidocaine)	Placebo			Immediately
Gurbuz et al. (2010) [46]	100	Elevated prostate-specific antigen (PSA) levels	No intervention	Perianal block (Lidocaine)	Periprostatic block (Lidocaine)	Intrarectal cream (Lidocaine + Prilocaine)	15 min
Park et al. (2005) [47]	61	Patients with a negative pathology after an initial sextant biopsy, with no sedatives or analgesia, were rebiopsied using the 12 extended biopsy technique.	Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine)	Perianal block (Lidocaine)	Intrarectal gel (Lidocaine)		Immediately
Basar et al. (2005) [48]	80	Patients with elevated prostate-specific antigen (PSA) levels or with normal PSA values but with prostate nodules on digital rectal examination (DRE) were included	Placebo cream	Intrarectal cream (Lidocaine + Prilocaine)	Periprostatic block (Prilocaine)	Periprostatic block (Lidocaine)	Immediately
Cantiello et al. (2009) [49]	200	Abnormal DRE findings, or an increased PSA level with or without abnormal DRE findings, or lesions suspicious for malignancy on TRUS with or without an abnormal DRE	Periprostatic block (Lidocaine + Naropine)	Periprostatic block (Antroline)			During biopsy
Kumar et al. (2012) [50]	240	All patients with indication for biopsy	Periprostatic block (Lidocaine)	Intrarectal cream (Lidocaine + Prilocaine)	Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine + Prilocaine)	-	Immediately

Study	No. of patients	Participants	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Outcome as- sessment
Dalva et al. (2013) [51]	90	NA	Perianal lidocaine- -prilocaine cream (EMLA, 5 gr) + periprostatic nerve block lidocaine	Periprostatic block (Lidocaine)			Immediately
Wu et al. (2001) [52]	40	All patients had laboratory indications for prostate biopsy (eg, elevated PSA level of 4.0 indications for prostate biopsy (eg, elevated PSA level of 4.0	Periprostatic block (Lidocaine)	Placebo			During biopsy

#### Table 1. Continuation

p value = 0.74); combined versus topical (I2 = 99%; inconsistency p value = 0.35); placebo gel versus placebo / no intervention (I2 = 0%; inconsistency p value = 0.33); placebo / no intervention versus topical (I2 = 90%; inconsistency p value = 0.18); sedative versus topical (I2 = 21%; inconsistency p value = 0.3) (Table 2). Ranks were higher for placebo and topical interventions (see Figure 4).

#### **Outcome: pain**

After running the Bayesian Network meta-analysis, we found that the periprostatic block (lidocaine), combined therapy [periprostatic block (lidocaine) + intrarectal gel [lidocaine + prilocaine)]; periprostatic block (lidocaine) + tramadol hydrochloride 50 mg; sedative and intrarectal gel (lidocaine) lowered the pain when compared with placebo. Additionally, any kind of placebo and intrarectal gel increased the pain when compared with the periprostatic block (lidocaine) (Figure 5).

#### **Mixed treatment comparisons**

As we stated before, the following comparisons were consistent on the network. For the comparisons: periprostatic block A versus topical [intrarectal gel (lidocaine)] and combined versus topical, we found that topical intervention increases pain. Similar to the placebo in the comparison: combined versus placebo / no intervention. On the otherside, there was decreased pain for the topical in the comparison: placebo/no intervention versus topical (see Table 2). There were no significant differences for the other comparisons.

#### Secondary outcomes

The secondary results obtained included adverse effects defined as fever, rectal bleeding >2 days, pros-

tatitis, urinary retention and death [27]. The following studies reported some of these events.

In the studies comparing periprostatic plexus block vs. placebo [16, 20], intrarectal gel vs. periprostatic plexus block vs. placebo and the study of intrarectal gel vs. periprostatic plexus block vs. placebo, fever was not reported as an adverse event during the follow-up period. In the study of placebo intrarectal cream vs. intrarectal cream vs. periprostatic plexus block [48] and in periprostatic block vs. intrarectal gel (Voltaren) vs. intrarectal gel placebo, no serious adverse events were reported [24].

In the study where the groups non-intervention vs. periprostatic plexus block vs. periprostatic plexus block in combination with intrarectal gel vs. tramadol infusion were compared, the following were reported in intervention group 1:1 fever event; group two: 1 event of urinary retention; and group three: one event of fever and six events of urinary retention [27].

In the study of intrarectal gel (lidocaine) vs. intrarectal gel (DMSO + lidocaine) vs. perianal block vs. periprostatic block without specification of belonging to a specific intervention, it was reported that 10 days after the biopsy, two patients presented with fever, and there was one urinary retention event [31].

In the comparison the study between periprostatic plexus block vs. intrarectal diclofenac suppository



Figure 3A. Risk of bias within studies.



Figure 3B. Risk of bias across studies.



Figure 4. Graphical representation of ranks.



Figure 5A. Interventions compared against Placebo.



Figure 5B. Interventions compared against Periprostatic block A.

vs. periprostatic plexus block in combination with diclofenac suppository, fever occurred in 1, 2 and 0 patients, respectively, in each intervention [32]. In the block of periprostatic plexus vs. intrarectal gel vs. placebo, intervention group 1 presented with

#### Table 2. Results for consistent comparisons

Comparison					
	Direct	-1.4	-2.5	-0.36	0.1285
Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine+Prilocaine) vs. Periprostatic block (Lidocaine)	Indirect	0.99	-2	4	
	Network	-0.9	-1.9	0.074	
	Direct	0.82	0.099	1.6	0.3869
Intrarectal gel (Lidocaine) vs. Periprostatic block (Lidocaine)	Indirect	-0.71	-4.2	2.7	
	Network	0.77	0.14	1.4	
	Direct	2.9	1.2	4.7	0.7479
Placebo/No intervention vs. Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine+Prilocaine)	Indirect	3.3	1.9	4.7	
	Network	3	1.9	4	
	Direct	0.9	-0.38	2.2	0.35525
Intrarectal gel (Lidocaine) vs. Periprostatic block (Lidocaine) + Intrarectal gel (Lidocaine+Prilocaine)	Indirect	1.8	0.4	3.2	
	Network	1.7	0.64	2.7	
	Direct	-0.51	-3.4	2.4	0.3387
Placebo/No intervention vs. Placebo gel	Indirect	1.2	-0.92	3.4	
	Network	0.19	-1.4	1.8	
	Direct	-1	-1.9	-0.08	0.18465
Intrarectal gel (Lidocaine) vs. Placebo/No intervention	Indirect	-2	-3.2	-0.85	
	Network	-1.3	-2.1	-0.6	
	Direct	2.7	-0.82	6.2	0.3
Intrarectal gel (Lidocaine) vs. Sedative	Indirect	0.6	-1.3	2.5	
	Network	0.96	-0.67	2.6	

three events of fever and urinary retention; intervention group 2: two events of fever; and intervention group 3: two events of fever and urinary retention [41].

In the comparison of periprostatic plexus block vs. placebo, the placebo group presented with one infection event without specification that required hospital admission [45].

In the intervention study of periprostatic plexus block in combination with intrarectal gel vs. placebo vs. intrarectal gel, there was one event of urinary retention in group 1; none of the groups presented fever [47].

Finally, in the comparison of periprostatic plexus block (lidocaine + naropin) vs. periprostatic plexus block (antrolin), there was one event of urinary retention and fever in both groups [49].

# DISCUSSION

To our knowledge, this is the first systematic review and online meta-analysis of clinical trials published to date in which we attempted to determine the efficacy of periprostatic block to prevent pain in transrectal prostate biopsy. We performed multiple comparisons between the analgesic therapies used to relieve pain during transrectal prostate biopsy.

Our findings showed that any type of intervention was significantly superior to the placebo to prevent pain. In addition, our results showed that patients undergoing transrectal prostatic biopsy with periprostatic block or combination therapy (periprostatic block + intrarectal gel) had significantly lower pain scores than patients treated only with topical intervention (intrarectal gel). Intrarectal gel and periprostatic block did not show significant differences.

In contrast with these results, certain published randomized controlled trials (RCTs), such as Ingberg in 2010, supported the idea that the pain experienced during transrectal prostate biopsy was mild and did not decrease significantly with periprostatic block, and they noted that the pain of the injection itself was similar to the pain of the biopsies. They concluded that pain from transrectal prostate biopsy was well tolerated without requiring anesthesia [58] and Wu et al. did not find significant differences between the intervention groups with or without periprostatic plexus block with respect to VAS pain scores at any time [52]. However, some of the limitations of these studies include the size of the sample and the evaluation of pain at the actual moment of the procedure.

Supporting the results obtained in this review, different studies indicate that there are significant differences in the perception of pain during the transrectal prostate biopsy, which can be seen in the study by Ozvery et al., who found that approximately 50% of patients who were subjected to transrectal prostate biopsy who did not receive the injection of lidocaine as an intrarectal block had VAS pain scores ranging from moderate severity to intolerable. In 2011, Ozverv and Izol et al. demonstrated that patient comfort was better and that it was possible to obtain lower pain scores with periprostatic plexus block or sedoanalgesia. In 2003, Izol and Addla suggested that local anesthesia for TRUS biopsy was simple and well tolerated and could significantly reduce the pain associated with the procedure, recommending its use as part of the standard TRUS prostate biopsy [19, 36].

Among the strengths of our review was the quality of the search strategies designed for each database, which were specific for the detection of records related to the review, along with the inclusion of a sizeable number of available studies. However, some of the limitations are based on the risk of unclear bias regarding the generation of random sequences. concealment of allocation, blinding of participants and staff and blinding of the evaluation of results, which was not possible to determine in the complete review of the studies. This limitation does not necessarily indicate poor or good methodological quality. However, it could lead to an underestimation of quality because the best tool available to assess quality is the Cochrane Collaboration tool, which requires an appropriate report to properly stratify the studies. However, the studies generally had a low risk of bias with respect to incomplete outcome data, selective reporting and other biases.

Only three studies, Stirling 2002, Stirling 2002a and Szlauer 2008 [21, 23, 40], blinded the participants and staff; the others had incomplete mask-

ing, or some groups were aware of the intervention to which they were going to be submitted, which generated a high risk of blinding bias for these clinical trials.

Finally, this review was performed to answer a question related to a urological procedure commonly performed in clinical practice, based on pre-established and standardized indications, due to the indispensable diagnostic need, as PCa is a presently prevalent disease. Being such a useful procedure, it is important to ask the question about the acceptability or not of the procedure as a consequence of the pain inherent to this study. The pain associated with prostate biopsy is a complex phenomenon with psychosocial and physical attributes, which include the threshold of an individual's innate pain, pre-procedure anxiety, fear of a possible diagnosis of cancer and social inhibition towards the rectal exam [18], factors that could cause the patient to delay having the biopsy even, when its requirement is of vital importance.

Therefore, according to the findings in this review, we recommend the use of periprostatic block alone or in combination with topical intrarectal analgesia or sedation as part of the standard TRUS prostate biopsy. It should be noted that sedation as analgesia during the study is a field that has been little evaluated because of the ease of performing a periprostatic block in the ambulatory practice of biopsy, a method worthy of future studies.

Despite recommending this intervention, it is suggested to conduct clinical trials with larger samples and better methodological quality to improve the recommendations derived from this systematic review and meta-analysis.

## CONCLUSIONS

Periprostatic plexus block in transrectal ultrasoundguided prostatic biopsy, alone or in combination with intrarectal analgesia or sedation, is an effective method to reduce the pain inherent to the performance of the procedure in comparison with placebo or intrarectal analgesia alone. However, more highquality trials are needed to support this conclusion and recommendation.

#### **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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