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Anaesthesia in Transrectal Prostate Biopsy: Which Is the Most Effective Technique?

Key Words

Anaesthesia · Prostate biopsy · Transrectal ultrasound

Abstract

Background: Prostate biopsy (PBx) techniques have changed significantly since the original Hodge's scheme, with an increase in the number and location of cores. These improvements have been realized in part because of the introduction of different local anaesthesia techniques. We critically analysed the literature discussing the role of anaesthesia techniques for use during PBx to find which technique provides the best pain relief for the patient and safety for the urologist. **Methods:** We performed a literature review by searching the Medline database for articles published between January 2000 and March 2010. Electronic searches were limited to the keywords 'transrectal prostate biopsy' and 'anaesthesia'. **Results:** Pain and discomfort perceived during PBx are the result of different anatomic factors: the introduction to and movement of the transrectal ultrasound probe in the rectum and the needle piercing the rectum and the prostate capsule. The anaesthesia techniques currently available can be divided into two groups: local (i.e. intrarectal lubricant agents, periprostatic nerve blocks, caudal blocks, pudendal nerve blocks, and their different combinations) and systemic (i.e. oral/intravenous drug administration and sedoanalgesia). **Conclusions:** The most effective

anaesthesia technique for transrectal PBx performed in out-patient settings is the periprostatic nerve blocks with 1 or 2% lidocaine 10 ml, which is associated with intrarectal lubricant agents, especially in younger people. Nevertheless, the current choice of the anaesthesia technique still depends both on patient characteristics (age, prostate size, number and location of cores, anxious personality, need for re-biopsy) and, above all, the urologist's experience and habits.

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Introduction

Prostate cancer (PCa) is one of the most common cancers in men, with about 700,000 patients diagnosed worldwide each year [1]. This figure is closely related to the development of early PCa detection programmes, which are based on an increased public awareness about this type of cancer, prostate-specific antigen screening efforts, and the improvement of systematic transrectal ultrasound (TRUS)-guided prostate biopsy (PBx) techniques. PBx is one of the most common procedures performed in the urologist's office today, with estimates as high as 800,000 biopsies annually in the United States. Thus, this procedure is now considered the standard for diagnosing PCa [2–6].

PBx has evolved from the digitally guided PBx technique, described by Astraldi [7] in 1937, to the standard sextant method, described by Hodge et al. [8] in 1989. In recent years, there has been rising interest in defining more accurate PBx schemes to improve the PCa detection rate. Intuitively, this aim could be achieved by adding more biopsies and by involving the prostatic areas not sampled by standard sextant schemes [9, 10].

Thus, if the sampling error were minimized through an increase in the number or location of cores, the discomfort related to the procedure would become more severe, requiring effective anaesthesia [11–16]. Conversely, improvements in anaesthesia techniques have allowed physicians to sample with a great number of cores and at different locations in the gland, achieving patient compliance and, finally, being able to perform the procedure in an office setting.

Men undergoing PBx experience considerable psychological stress, attributable to the fear of a potential cancer diagnosis, the anal route of penetration, that the subject organ is part of the sexual system, and the anticipated pain [17–19]. Therefore, many urologists have stressed the importance of anaesthesia as an integral part of PBx [20–23]. However, despite these considerations, using anaesthesia is still under debate because of doubt of its real benefits and the associated costs [24].

Materials and Methods

We performed a literature review by searching the Medline database for articles published between January 2000 and March 2010. Electronic searches were limited to the English language and the keywords ‘transrectal prostate biopsy’ and ‘anaesthesia’. 156 abstracts were screened, whereof 88 articles were finally selected for review, based on the citation index and the impact factor.

Results

Anatomic Factors

Pain and discomfort perceived during PBx result from different factors: the neuroanatomy of the anal canal and prostate and the pelvic fasciae. Therefore, knowledge of these anatomic structures is essential to choosing the best anaesthesia technique [25–43] (table 1).

Discomfort and Pain Sources during Transrectal PBx

It is well known that several different factors contribute to discomfort and pain during PBx, such as introduc-

tion and movement of the TRUS probe into the rectum, the geometry of the ultrasound probe itself, the needle piercing through the rectal wall, needle passage through the prostate capsule, and the number of biopsy cores taken. The discomfort of probe insertion results from the somatic sensation caused by stretching the anal canal distal to the dentate line, which is full of sensory fibres [25–27]. Thus, the variability of perceived discomfort might be related to differences in anorectal compliance, as outlined by Giannarini et al. [44], who have even suggested the possibility of omitting anaesthesia in those patients with high anorectal compliance. Finally, some authors have stated that pressing the probe against the rectum might also minimize the discomfort of the biopsy needle traversing the rectal mucosa, similar to pulling the skin tight to minimize the discomfort of phlebotomy [4].

Whereas the rectal mucosa has a relatively low sensitivity to pain, the prostate capsule and prostate parenchyma are very sensitive, and pain can be transmitted through the neurovascular bundles, especially with the biopsy needle perforating the prostate capsule [25, 26, 45, 46]. The device is represented by a spring-driven 18-gauge needle core biopsy device or biopsy gun, which can be passed through the needle guide attached to the ultrasound probe. A fundamental step during PBx is the magnification of the imaging modality, which has to be maximal for visualization of the needle passage. The biopsy gun advances the needle 0.5 cm and samples the subsequent 1.5 cm of tissue, with the tip extending 0.5 cm beyond the area sampled. The pain derived from needle passage through the prostate capsule can be relieved by anaesthesia.

Anaesthesia Techniques during Transrectal PBx

Anaesthesia during PBx is currently considered mandatory, and performing the procedure without anaesthesia is considered malpractice [9] (table 2). Various types of anaesthesia – such as intrarectal lubricant agents (IRLA), periprostatic nerve blocks (PPNB), intraprostatic anaesthesia (IPA), pelvic plexus blocks (PPB), caudal blocks (CB), pudendal nerve blocks (PNB), PPNB with IRLA, oral and intravenous drugs, rectal and inhaled drugs, sedoanalgesia, and no anaesthesia use at all – have been investigated, but the best method has not yet been defined, because success depends on the patient's characteristics and the urologist's experience and habits. The characteristics of the ideal anaesthesia method during PBx are described in table 3.

Table 1. Anatomical structures involved in determining discomfort and pain during PBx

Anatomical structure	Features	Role in determining discomfort and pain during PBx
<i>Anal canal</i>		
Rectal mucosa	Relatively low sensitivity to pain	The pain caused by PBx is not closely related to the rectal mucosa itself
Part of the anal canal distal to the dentate line	Full of sensory fibres	The mechanical stretching of these fibres during the introduction of the probe might cause discomfort to the patient
<i>Prostate nervous anatomy</i>		
Prostatic plexus: the nerves pass the tip of the seminal vesicles at the dorso-lateral border of the prostate on the surface of the rectum and are lateral to the prostate capsular arteries and veins, finally representing the neuro-vascular bundles of the prostate	Sensory fibres located in the prostate capsule or stroma	They transmit the sensation of pain during PBx
Pudendal nerves	Innervation of pelvic floor muscles and organs, including the periurethral sphincter	Pelvic floor activity directly affects the functional integrity of the pelvic viscera, including the bladder and prostate
<i>Prostate fasciae</i>		
Denonvilliers fascia	The fascia adheres to the posterior face of the prostate and the seminal vesicles between the gland and the rectum	The nervous structures of the prostate are distributed between the layers of endopelvic fascia and the prostatic fascia; this is one of the most important features for understanding the diffusion of local anaesthesia in different prostatic zones
Prostatic fascia	This fascia surrounds the entire prostate, being laterally in direct continuity with the fibromuscular stroma of the gland; laterally, it fuses with the endopelvic fascia, and subsequently, it becomes indistinguishable from Denonvilliers fascia	
Endopelvic fascia	This term refers to the parietal pelvic fascia in the region of the prostate, overlying the levator ani muscle	

Local Anaesthesia

Local anaesthesia procedures involve only the nervous structure closely related to the prostate. In particular, urologists typically perform IRLA administration, PPNB, use of PPNB and IRLA together, IPA, and PPB in the outpatient setting. CB and PNB require the presence of an anaesthetist because of the knowledge and individuation of the macroscopic nervous structures required and the need for patient monitoring after drug administration. Most times, this technique requires hospitalization according to 'day surgery' procedure guidelines.

Intrarectal Local Anaesthesia

The use of topical anaesthesia in urology was first reported in 1884, when Pease described the use of cocaine during cystoscopy. Thus, several synthetic topical anaesthetic-lubricant agents have been introduced in the urologist's daily procedures, including prostate biopsy. Many authors have underlined that discomfort and pain associated with PBx mainly stem from the discomfort associated with anal canal sensation [47]. The rectal mucosa has a rich absorptive capacity, and IRLA might result in some local effects.

Many authors have advised the use of IRLA. The ideal substance might grant satisfactory lubrication in order to

Table 2. International guidelines for anaesthesia use during PBx

Association	Guideline
AUA	Mandatory
EAU	Ultrasound-guided PPB is state of the art, regardless of whether the site is apical or basal. Intrarectal instillation of a local anaesthetic agent is clearly inferior to periprostatic infiltration.
NCCN	Both topical LG and injectable nerve blocks have been shown to be safe and efficacious in reducing discomfort. Topical lidocaine was more efficacious in reducing pain during probe insertion, whereas periprostatic injection reduced pain during PBx itself. For exceptional cases, intravenous sedation or general anaesthesia may be advantageous.

AUA = American Urological Association; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network.

Table 3. Characteristics of the ideal anaesthesia method during PBx

Granting enough muscle relaxation of the anal sphincter to make digital examination of the prostate and manoeuvring of the TRUS probe easier
Preventing the discomfort and/or pain caused by introduction of the TRUS probe and the insertion of the needle through the prostate gland and finally assuring immobilization of the patient during the procedure
Low incidence of side effects
Suitable in an office setting
Low cost

reduce friction and protect the mucosa during instrumentation. Moreover, it might be safe, easily handled and cost-effective. The most commonly used agent is lidocaine, alone or in combination with other molecules (table 4). Lidocaine was synthesized by Lofgren and Lundqvist in Sweden in 1943 and introduced into clinical practice in 1947 [48, 49]. Today, lidocaine gel (LG) is the most widely used lubricant agent during PBx, but it has only a small effect on anal sphincter tone – that is, it has low efficacy for the insertion and movements of the probe during the procedure [50–52]. In fact, IRLA with LG alone had no impact on the general tolerance of PBx compared with placebo. Thus, the analgesic efficacy of this method has not been universally confirmed [23].

Based on such results, some authors have tried to use lidocaine in combination with other molecules in gel versus placebo (table 4). Two Italian groups have described their experience using a cream mixture of lidocaine and prilocaine (EMLA; AstraZeneca, London, UK), alone or in combination with PPNB with lidocaine. These groups have demonstrated that the combination of the two an-

Table 4. Main lidocaine combinations for IRLA

Drug combination	Trade name
Lidocaine with prilocaine	EMLA
1.5% lidocaine with 0.3% nifedipine	Antrolin
DMSO with lidocaine	–
0.2% GTN paste	–

aesthesia techniques is better than using the drugs separately to control discomfort caused by probe insertion [19, 44]. Nevertheless, Giannarini et al. [44] have demonstrated the importance of IRLA administration with EMLA for ensuring good control of anorectal discomfort and the pain of prostate capsule piercing, especially in young men.

Cantiello et al. [18] recently reported their experience with Antrolin cream (trademark filed in Italy with the Ministry of Health) in addition to PPNB with lidocaine and naropine. The cream is a mixture of a topical anaes-

thetic agent (1.5% lidocaine) and a myorelaxant (0.2% nifedipine) that acts by blocking the slow calcium channels located along the anal sphincter fibro-muscular cell membranes, achieving muscle relaxation. The aim of the cream is to provide pain control during probe insertion, which LG alone cannot grant. The authors have found that pain during probe insertion might be significantly reduced using Antrolin, also improving the PPNB administration phase and the biopsy procedure throughout its duration.

Another molecule used as part of IRLA is dimethyl sulphoxide (DMSO). The most important property of DMSO is its capacity to carry other drugs with it across cell membranes. It is readily absorbed through the skin and relieves musculoskeletal pain when applied topically to painful areas. Moreover, it has been employed in urology with intravesical instillation in the symptomatic treatment of interstitial cystitis and primary amyloidosis of the bladder. Demir et al. [53] recently published the first trial to evaluate the efficacy of LG in combination with DMSO directly instilled into the rectum and LG in patients with anorectal pathologies, such as haemorrhoids, fissures, abscesses, fistulae, and infections, as well as with functional disorders – pathologies that make PBx a particularly painful procedure. The authors based the trial on the excellent drug-absorptive qualities of the rectum and the proximity of the neurovascular pedicles, hypothesizing that the nerve component is anaesthetized by instilling 40% DMSO with LG directly into the rectum. They have reported the best pain control with this combination during the probe insertion phase. There were no observed side effects.

Two English groups have documented the use of topical glyceryl trinitrate (GTN) 0.2% paste, which is frequently used for the conservative management of chronic (>5 years) anal fissures. Its mechanism of action is thought to be smooth muscle relaxation and transient decreases in anal sphincter tone. Both groups have demonstrated that topical GTN paste is safe and easy to use. Above all, it is an effective and well-tolerated method of decreasing pain associated with PBx, especially during the initial insertion of the probe. Much of the anxiety a patient has when undergoing a biopsy is related to anal penetration of the ultrasound probe. The maximum benefit from GTN appears to have been in younger patients and those patients undergoing repeat biopsy who had previously failed to tolerate the procedure [54, 55].

In conclusion, part of a patient's discomfort during PBx is caused by introduction of the probe, which induces mechanical stretching of the sensory fibres located in

Table 5. Injection sites for PPNB

Apex only
Bilateral neurovascular bundle regions only, defined as:
• basolateral nerve plexus
• posterolateral nerve plexus
• periprostatic nerve plexus
• prostate-vesicular junction injections
Apex and neurovascular bundle
Base, mid and apex dorsolaterally
Lateral to the tip of the seminal vesicles

the part of the anal canal distal to the dentate line. This discomfort might be improved with IRLA using drugs that cause smooth muscle relaxation and transient decreases in anal sphincter tone. Further trials are necessary to establish the drug with the best cost-benefit ratio.

Periprostatic Nerve Block

Since Nash et al. [22] first described the use of PPNB before PBx in 1996, many trials and meta-analyses have suggested that infiltration of local anaesthetic drugs around the nerve bundles might provide the best pain control during the procedure [56]. Today, this technique is fundamental when performing extended biopsy schemes (i.e. >12 cores). After introducing the TRUS probe into the rectum, a spinal needle (7 in, 22 gauge) is then inserted along the biopsy channel of the transducer and the different anaesthetic drugs injected in different locations of the prostate under TRUS guidance [20, 45, 57–59] (table 5). In PPNB, the most frequently used anaesthetic drug remains lidocaine, even if bupivacaine and mepivacaine are used as well (table 6). The choice of drug is closely related to the duration of action, the side effect profile and costs, and lidocaine has a long duration of action with a low incidence of side effects and low cost. In daily practice, the choice essentially depends on the urologist's experience and habits.

Despite the diffuse preference for lidocaine, the optimal dosage, concentration and location on the prostate capsule remains unclear when performing PPNB (table 7). The best injection site seems to be localized in the angle between the prostate and the seminal vesicles, which can be easily identified as a hypoechoic area on TRUS. A concentration of 1% lidocaine is sufficient to provide pain relief. The most common dosage is 10 ml divided into 5 ml per side.

It has been shown that apical biopsies are more painful than those at other sites. PPNB provides particularly

Table 6. Local anaesthetic agents used during PPNB and their characteristics

Agent	Duration of action	Main side effects	Cost
Lidocaine	120 min	nausea; drowsiness; mental/mood changes; tinnitus; dizziness; vision changes; tremors; numbness; headache; backache; fever; unusually fast or slow pulse; trouble breathing; seizures; chest pain	5 EUR
Bupivacaine	240 min	excitation and/or depression; restlessness; anxiety; dizziness; tinnitus; blurred vision; tremors, possibly leading to convulsions; depression of the myocardium; decreased cardiac output; heart block; hypotension; bradycardia; ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation; cardiac arrest	138 EUR
Mepivacaine	90 min	abnormal skin sensations; anxiety; backache; changes in speech patterns; chills; constricted pupils; depression; headache; inability to urinate or defecate; light-headedness; metallic taste; numbness and tingling of the mouth and lips; numbness in the legs and feet; tinnitus; sexual dysfunction; twitching; weakness, blurred vision; changes in hearing; chest pain; convulsions; dizziness; drowsiness; excessive sweating; excitement; fainting; increased body temperature; increased heartbeat; interrupted breathing; irregular heartbeat; itching; light-headedness; loss of consciousness; nausea; persistent numbness; redness; restlessness; slow heartbeat; sneezing; tremors; vomiting	36 EUR

good apical anaesthesia, because it ensures the spread of the local anaesthetic agent along the tissue planes of Denonvilliers fascia to the seminal vesicles, bathing the entire posterior surface of the gland. This plane might also be observed on TRUS. Both the single apical injection and the bilateral basal injection techniques are effective in terms of pain prevention during PBx. The main advantage of the single apical injection technique is its ease of use and the requirement for one half the amount of the local anaesthetic agent [60–64].

Despite the abundance of reports in the literature regarding the evaluation of PPNB efficacy and the determination of the optimum value for the number, amount and site of injection, little emphasis has been placed on complications and limitations associated with this method (table 8). Moreover, the studies aiming to determine the incidence of complications associated with PPNB before PBx have been limited to haemorrhagic or infectious complications, which are also common when PPNB is not used. Nevertheless, some authors have reported a higher incidence of bacteriuria, fever, and hospitalization after introduction of anaesthetic drugs. As recently reported by Turgut et al. [65], the frequency of complications and the limitations related to local anaesthetic infiltration is about 2%.

Seymour et al. [60] have stated that patients occasionally complained of a mild ‘stinging’ sensation during the injection of the PPNB agent. In another study, Song et al. [66] reported an incidence of vasovagal syncope of only

1%. However, vasovagal reactions during PBx without the use of local anaesthesia have been reported in 1 out of 300 men.

The symptoms of systemic lidocaine toxicity associated with accidental intravascular injection, such as dizziness, visual disturbance, tinnitus, metallic taste, light headless, and respiratory distress – as well as the necessity to aspirate before injecting the agent to avoid inadvertent intravascular injection – have been reported by several authors. There is an abundance of vessels in the area targeted for local anaesthetic infiltration: by mapping the vasculature in this region, colour Doppler sonography may help to prevent inadvertent intravascular injection of anaesthetic agents, as suggested by Seymour et al. [60].

The same group also emphasized that patients should have an empty bladder because of the risk of bladder control loss resulting from the temporary relaxing effect of the anaesthetic agent on the external sphincter [60]. In keeping with this phenomenon, Turgut et al. [65] have reported that 1.5% of patients had urinary incontinence within the first 10 min after anaesthesia infiltration. In contrast, Addla et al. [67] have noted that periprostatic local anaesthesia caused no significant change in post-biopsy continence.

Another problem related to periprostatic anaesthetic infiltration might be the risk of image artefacts derived especially from the injection of minute amounts of air

Table 7. Literature review of recent news on anaesthesia techniques in transrectal PBx (2007–2009)

Authors, year	Pa-tients	Anaesthesia technique	Anaesthetic agent used	PPNB injection site	Conclusion
Yurdakul et al. [77], 2009	100	Group 1: n = 25, no local anaesthesia Group 2: n = 25, IRLA with 2% LG Group 3: n = 25, IRLA with 2% LG and PPNB with 5 ml of bupivacaine (0.25%) Group 4: n = 25, IRLA with 2% LG and PPNB with 5 ml of ropivacaine (0.25%)	Lidocaine Bupivacaine Ropivacaine	Periprostatic	IRLA and PPNB have provided the best pain control, independent of the drug used
Bingqian et al. [78], 2009	200	Group 1: n = 100, PPNB and intraprostatic local anaesthesia with 5 ml of 2% lidocaine Group 2: n = 100, PPNB and intraprostatic local anaesthesia with 5 ml of 0.9% NaCl Group 3: n = 100, no anaesthesia	Lidocaine	Region of the prostatic vascular pedicle at the prostate base just lateral to the junction between the seminal vesicle and the prostate on each side	Combining PPNB and intraprostatic local anaesthesia has provided significantly better pain control than PPNB; the combination may be of maximum benefit in patients who have a prostate volume ≤ 48 ml or younger patients (≤ 66 years of age)
Skriapas et al. [79], 2009	147	Group 1: n = 74, IRLA with lidocaine cream 2% and PPNB Group 2: n = 73, lubricant gel and PPNB	Lidocaine	Periprostatic	IRLA with lidocaine cream 2% has significantly reduced anal discomfort and pain before probe insertion for TRUS-guided PBx in young patients
Giannarini et al. [44], 2009	280	Group 1: n = 70, combined perianal-intrarectal lidocaine-prilocaine cream and 1% lidocaine PPNB Group 2: n = 70, perianal-intrarectal lidocaine-prilocaine cream alone Group 3: n = 70, 1% lidocaine PPNB alone Group 4: n = 70, no anaesthesia	Lidocaine Prilocaine	Area just lateral to the junction between seminal vesicles and the prostate base, 5 ml per side	The combination of perianal-intrarectal lidocaine-prilocaine cream and PPNB has provided better pain control than the two modalities alone; the magnitude of this effect is higher in younger men (≤ 65 years of age), men with a prostate volume ≥ 49 ml, and men with lower anorectal compliance
Cantiello et al. [18], 2009	200	Group 1: n = 100, PPNB with a solution of 5 ml lidocaine 1% and naropine 0.75% alone Group 2: n = 100, previous administration of the topical anaesthetic agent Antrolin and PPNB with a solution of 5 ml lidocaine 1% and naropine 0.75% alone	Lidocaine Naropine	Into the neurovascular bundles at the seminal vesicle-bladder-rectum angle on either side (5 ml per side)	Antrolin used with PPNB has been better than PNB alone in reducing pain and discomfort
Akan et al. [58], 2009	117	Group 1: n = 60, PPNB with 5 ml of lidocaine Group 2: n = 57, PPNB with 5 ml of lidocaine in the single apical injection	Lidocaine	Group 1: region just lateral to the junction between the base of the prostate and the seminal vesicles on both sides (2.5 ml per side) Group 2: apex of the prostate to provide the distribution of lidocaine toward the base of the prostate under Denonvilliers fascia	The single apical injection and the bilateral basal injection techniques are both effective in terms of pain prevention; the main advantage of the single apical injection technique is its ease of use and the requirement for one half the amount of the local anaesthetic agent
Cam et al. [46], 2008	200	Group 1: n = 100, PPNB with 1% lidocaine and intraprostatic lidocaine injection Group 2: n = 100, PPNB with 1% lidocaine and injection of 0.9% NaCl	Lidocaine	Region of the prostatic vascular pedicle at the prostate base just lateral to the junction between the seminal vesicle and the prostate	Adding intraprostatic local anaesthesia has provided a significantly efficient strategy
Raber et al. [19], 2008	300	Group 1: PPNB with 2% lidocaine Group 2: topical anaesthesia of the anal ring, anal canal and anterior rectal wall combined with PPNB Group 3: placebo	Lidocaine	The neurovascular bundle at the seminal vesicle base on either side	Combined prilocaine-lidocaine cream topically placed with PPNB is superior to PPNB alone and may be of maximum benefit for younger patients (mean: 60 years of age)
Ashley et al. [59], 2007	243	PPNB with 1% lidocaine in all groups	Lidocaine	Group 1: seminal vesical-prostatic base blockade Group 2: intraprostatic blockade Group 3: apical-rectal blockade	The seminal vesicle-prostatic base blockade is less effective than intraprostatic and apical-rectal blockade at controlling pain

Table 8. Main complications when performing PPNB and solutions for avoiding them

Complication	Cause	Author	Incidence	Solution
Mild 'stinging' sensation during injection of the agent for PPNB	Needle passage through the rectal wall and prostate capsule	Seymour et al. [60]	Occasionally	Inject slowly
Dizziness Visual disturbance Tinnitus Metallic taste Light-headedness Respiratory distress	Systemic lidocaine toxicity associated with accidental intravascular injection	Seymour et al. [60] Aus et al. [3] Obek et al. [81]	4%	Map the vasculature in this region with the help of colour Doppler sonography Inject slowly
Urinary incontinence within the first minutes after anaesthesia infiltration	Temporary relaxing effect of the anaesthesia on the external sphincter	Seymour et al. [60] Turgut et al. [65]	1.5%	Micturition before the procedure
Vasovagal syncope Bacteriuria Fever Hospitalization	Partly because of the biopsy itself	Song et al. [66] Obek et al. [81]	1%	Use narcosis Antibiotic prophylaxis Antibiotic prophylaxis –

along with the anaesthetic agent. This technical error is easily avoided by carefully bleeding the syringe containing the anaesthetic drug prior to the injection [65]. In contrast, Berger et al. [68] have reported that the administration of 5 ml of anaesthesia on each side of the gland did not cause technical difficulties with imaging so long as the substance was injected outside the gland.

In conclusion, PPNB is an easy, safe, acceptable and reproducible technique that should be considered in all patients undergoing PBx, regardless of the age of the patient and the number of cores. Today, PPNB is recommended by conclusive expert opinion and contemporary clinical guidelines, because it grants comfort and pain relief for patients in an outpatient setting with a good cost-benefit ratio (table 3). The most frequently used drug is 1–2% lidocaine, but the injection location, dosage and concentration rely substantially on the urologist's preferences.

Intraprostatic Anaesthesia

IPA was first introduced by Mutaguchi et al. [26], who observed in their nonrandomized trial significantly better pain control with intraprostatic infiltration than with the traditional periprostatic approach. The investigators hypothesized that better analgesia could be provided by anaesthetizing the prostate itself, which is the source of pain.

Recently, Ashley et al. [59] confirmed that mid and apical biopsies of the prostate are more painful than base biopsies, while apical and intraprostatic blockades appear

to provide superior analgesia to the seminal vesical-prostatic base blockade. In 2008, Cam et al. [46] published a randomized, prospective study to evaluate the efficiency of adding IPA to the usual PPNB approach during PBx with 12-core sampling. They hypothesized that the combination of the two techniques provided more extensive coverage of sensory fibres. In fact, the authors reported significant advantages in the combination group with respect to overall intensity throughout the procedure without any differences in terms of complications in the two groups.

Today, IPA prolongs the duration of PBx itself but seems to provide improved pain control compared to PPNB. Nevertheless, the use of IPA requires more randomized trials before it can be adopted in daily practice.

Pelvic Plexus Block

Some authors have reported their experience with blocking the entire pelvic plexus, which can be easily identify under colour Doppler ultrasonography not influenced by the left lateral decubitus position. Wu et al. [69] first described this technique, using 5 ml of 1% lidocaine directly lateral to the tip of the seminal vesicles under grey-scale ultrasound guidance in a placebo-controlled study. They found that this approach did not diminish biopsy-associated pain. Conversely, Akpinar et al. [27] recently published a study about PPB using 2 ml of 2% lidocaine, comparing its efficacy against widely used PPNB with the same dosage and concentration of lidocaine injected between the prostate base and the seminal

vesicle on either side. The authors concluded that PPB under Doppler ultrasonographic guidance provides superior analgesia to PPNB, because its action is proximal to the prostate. In this way, the anaesthesia is delivered to nerves that give rise to the prostatic plexus and other sensory fibres, which may in turn affect prostatic nociceptive response.

Similar to IPA, use of PPB requires more randomized trials in order to be adopted in daily practice. Moreover, this procedure should be performed only by urologists skilled in colour Doppler ultrasonography, which might represent a limit for this anaesthesia technique.

Caudal Block

The efficacy and safety of CB for surgeries on the part of the body primarily innervated by lumbosacral nerve roots is well known, and perianal procedures involving the prostate gland have been reported, especially in the Japanese literature [69–74]. Thus, theoretically, an appropriate caudal anaesthetic agent might be the optimal method for use during PBx, even if the procedure should be performed by an anaesthetist. In recent years, two contradictory studies have assessed the efficacy of CB for relief of pain during PBx. Horinaga et al. [73] found that CB provided less effective anaesthesia than PPNB, but it is interesting to note that there was no anaesthetist among the authors of the study. Conversely, Ikuerowo et al. [74] reported that the rate of effective analgesia was 82.3% of the patients when CB was applied. In both studies, a more concentrated local anaesthetic solution was used, possibly causing motor and sensory dysfunction and delaying the patient's return to daily activity.

Cesur and colleagues [75] recently published a prospective, double-blind, randomized trial studying the effect of 'walking' CB compared with IRLA with LG for PBx. They randomly allocated 100 patients to two groups: the LG group (10 ml of gel containing 2% lidocaine given intrarectally) and the caudal group (20 ml of 0.1% bupivacaine with 75 µg of fentanyl caudally injected). The authors reported a significantly lower level of pain in the caudal group. Moreover, all patients were able to walk without assistance immediately after the procedure.

As an additional advantage, in contrast to PPNB, CB provides perianal analgesia and anal sphincter relaxation, making it much easier to manoeuvre the TRUS probe even in painful anal conditions (such as anal fissure or haemorrhoids). However, despite its efficacy, CB requires the presence of an anaesthetist, giving the entire procedure a greater cost and reducing the possibility of performing PBx in an outpatient setting.

Pudendal Nerve Block

Adsan et al. [76] reported their experience with unilateral PNB using 10 mg of 1% prilocaine, maintaining that urologic procedures can be successfully performed only with the blockade of the anorectal region. The patient is in lithotomy position, and PNB is performed transperineally with TRUS guidance using a 22-gauge spinal needle by one anaesthetist. The injection was carried out percutaneously posterior to the ischial spine at the attachment of the sacrospinous ligament without any radiologic guidance or electrostimulation. The authors demonstrated statistically significantly lower pain scores for probe insertion and manipulation during the diagnostic procedure compared to the placebo group. Nevertheless, the success rate of PNB is undoubtedly related to the experience of the clinicians administering it – that is, the anaesthetists. Again, the cost of the entire procedure becomes higher, with a reduced possibility of performing the procedure in an outpatient setting.

Combining PPNB with IRLA

Different studies have reported that the combination of PPNB and IRLA has been superior to PPNB alone when used to relieve PBx-related pain by reducing discomfort during the introduction of the TRUS probe and periprostatic infiltration. The rationale was to avoid or decrease the pain induced by TRUS probe insertion and needle punctures necessary for delivering the local anaesthetic infiltration.

Different drugs can be used in IRLA with PPNB (table 4). Most of the authors have described a reduction in pain perception during probe insertion and during PBx without general or local side effects or major complications [18]. Generally, the patients more likely to benefit from this combination are younger men (≤ 65 years of age), because they are more inclined to stress symptoms, such as fear of potential cancer diagnosis, the anal route of penetration and the anticipated pain. Another group of patients that can benefit from the combination of PPNB and IRLA are those with lower anorectal compliance because of haemorrhoids or anal strictures [19, 44, 77–79].

Systemic Analgesia Combined with PPNB

Oral and Intravenous Drugs

Tramadol is a synthetic analogue of codeine. Its analgesic action is in the central nervous system, with inhibition of the re-uptake of norepinephrine and serotonin

and a low affinity for opioid receptors. Thus, the increased concentrations of those two neurotransmitters in the central nervous system result in analgesia with minimal respiratory and/or cardiovascular side effects. Moreover, tramadol has a low cost and requires no special monitoring.

This drug is generally administered either orally or intravenously for the treatment of acute moderate or severe pain. Hirsch et al. [80] evaluated the analgesic advantage of tramadol in patients undergoing PBx in ambulatory settings compared with topical analgesia. The authors concluded that the combination of lidocaine administered rectally with oral tramadol is a simple and safe technique that provides good analgesic effect, and therefore, can be recommended for PBx. These findings verify and further support the data from Obek et al. [81], who have demonstrated that the analgesic efficacy of intravenous tramadol is similar to that of PPNB.

Pendleton et al. [82] published a double-blind, prospective, randomized, controlled trial involving 60 men randomized to receive placebo plus periprostatic 1% lidocaine (the control group, $n = 30$) or 30 or 75 mg of tramadol/650 mg of acetaminophen orally plus periprostatic 1% lidocaine (the experimental group, $n = 30$) before undergoing biopsy. The authors found that oral administration of 75 mg of tramadol/650 mg of acetaminophen 3 h before periprostatic injection of 1% lidocaine as a nerve block is safe and easy to administer and can significantly decrease pain without causing additional complications.

Intravenous nonsteroidal anti-inflammatory drugs have also been studied and administered to relieve pain during PBx. Their analgesic efficacy is considered high, and some authors have tried to verify their efficacy in PBx. For example, Mireku-Boateng [83] has reported the use of ketorolac alone during anaesthesia for PBx, demonstrating that the drug significantly reduces procedural pain and allows the patient to tolerate PBx better without the need to perform PPNB. Similar to IPA and PPB, oral or intravenous drug administration still requires more randomized trials before being adopted in daily practice.

Using PPNB with Other Systemic Drugs

PPNB can be used with drugs administered via other routes, such as the intrarectal (suppository) and inhalator routes. The aim is to provide a reduction in anxiety and pain during PBx, leading to a more comfortable procedure in the outpatient setting. The most common drugs used with PPNB are diclofenac and nitrous oxide. Diclofenac suppository has systemic anti-inflammatory and

analgesic properties and its addition to PPNB might provide both procedural and post-procedural pain relief. A 100-mg dose of diclofenac suppository is easily administered and safe in the majority of patients. The absorption is rapid, and the drug attains a peak concentration in <40 min. Thus, it is generally useful for acute pain relief.

Ragavan et al. [84] have described the combination of PPNB and 100-mg diclofenac suppository at least 40 min before 12-core PBx. They found that the administration of diclofenac allows better pain control both during and after PBx.

Nitrous oxide is used in a mixture with 50% of oxygen (Entonox; BOC, Guildford, UK). This mixture may interact with opioid receptors both at the spinal and supraspinal levels, although its action is still controversial. The drug takes about 1 or 2 min to take effect, and it resolves 4–5 min after discontinuation. It is widely used in the United Kingdom to provide analgesia during labour and also for minor procedures in emergency departments. It is colourless, odourless, easily available and inexpensive. Moreover, it does not require training to administer. Entonox does not alter haemodynamic or oxygen saturation except in those patients with significant cardiovascular or respiratory compromise. Minor side effects include light-headedness, dry mouth, nausea and tingling in the fingers associated with hyperventilation. Entonox may be useful in individuals who have increased anal tone (haemorrhoids or anal fissure) or who are anxious.

Two groups have evaluated the efficacy of Entonox inhalation to provide pain relief during PBx. Both groups concluded that Entonox inhalation provides significant pain relief similar to PPNB. The use of Entonox essentially depends on the urologist's habit [85, 86]. Today, use of these drugs remains uncommon among urologists who perform PBx in an outpatient setting.

Sedoanalgesia

Sedoanalgesia may be preferred when extensive or repeated biopsies are needed: the degree of discomfort and the acceptability of repeat procedures becomes a particularly important issue in this group of patients. Awsare et al. [87] published a retrospective study about the use of sedation for PBx with propofol as an intravenous injection over 1 ± 5 min, administered by an anaesthetist with noninvasive monitoring. The use of propofol is associated with rapid recovery and a minimal 'hangover' period, but after its use, the patient must have an escort to return home and be advised not to drive for at least

24 h. All procedures were undertaken in the routine day theatre, and the use of anaesthesia staff obviously has cost implications. Nevertheless, the authors who have concluded that sedation can significantly reduce patient discomfort and make PBx a more satisfactory experience for the patient. This is particularly important in the proportion of men who need to be considered for repeat biopsies. In the authors' and our opinion, any cost calculation must be balanced against the improved level of the overall patient experience.

No Anaesthesia

Some authors have investigated the acceptability of TRUS and PBx without anaesthesia, despite the fact that performing PBx without anaesthesia is actually considered malpractice according to international guidelines (table 3). Westenberg et al. [88] have studied the tolerance of PBx in a New Zealand population, reporting that 69% of patients had found the procedure only slightly or not at all uncomfortable. Moreover, 21% of patients would prefer the same technique (no anaesthesia) if they were to require an additional biopsy. Only younger patients or those with significantly higher discomfort during the procedure have evidenced the necessity of anaesthesia if a second PBx were necessary. The authors concluded that PBx without anaesthesia is well tolerated by New Zealand men. Moreover, von Knobloch et al. [89] have compared experienced patients with a history of a previous PBx without PPNB to the current biopsy with PPNB. In this study, the Visual Analogue Scale pain score difference for the two procedures was substantial with approximately 1.7 vs. 4.5 ($p < 0.0001$).

Despite good pain control reported by a small number of trials, it is necessary to emphasize the importance of administering anaesthesia during PBx for both ethical and medical reasons.

Conclusions

In the past few years, a radical improvement in anaesthesia techniques has become evident, leading to the diffusion of the extended PBx and saturation PBx schemes in the outpatient setting. Different anaesthesia techniques have been described in the literature with the aim of finding the best procedure in terms of high cost-benefit ratios for the patient according to the urologist's preferences.

IRLA could control discomfort caused by probe insertion and PBx-associated pain. IPA seems to provide some improvement compared to PPNB, but the anaesthesia technique itself significantly prolongs the procedure, and more randomized trials are needed. PPB administration requires that urologists be skilled in colour Doppler ultrasonography, which might represent a limit for diffusion of this technique. CB and PNB require the presence of an anaesthetist and add considerable cost to the procedure as well as reducing the possibility of performing PBx in an outpatient setting.

Today, PPNB is recommended by both conclusive expert opinion and contemporary clinical guidelines (European Association of Urology, American Urological Association, National Comprehensive Cancer Network). It is generally considered the 'gold standard' for providing comfort and pain relief for patients undergoing PBx, despite the variability in route of administration and dosage and regardless of patient age and the number of cores. The most widely used drug is 1 or 2% lidocaine because of its low incidence of side effects, low cost and efficacy. The most common injection site is the angle between the prostate base and the seminal vesicles bilaterally.

The combination of PPNB and IRLA or systemic drugs is still controversial, even if an increasing number of trials have demonstrated better control of discomfort caused by TRUS probe insertion achieved with IRLA. Pain control during the PBx procedure seems to be superior with systemic analgesics, especially nonsteroidal anti-inflammatory drugs. Sedoanalgesia should be preferred when extensive or repeated biopsies are needed.

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