

Pain Free TP: Reducing Pain in Prostate Biopsies with Methoxyflurane

Transperineal prostate biopsies: The diagnosis of prostate cancer has historically been based on prostate-specific antigen (PSA), digital rectal examination (DRE), and transrectal ultrasound-guided (TRUS) prostate biopsies. However, prostate cancer diagnostics have improved considerably in recent years through the introduction of multiparametric magnetic resonance imaging (MRI) and the transition from transrectal to transperineal (TP) prostate biopsies. Australia and New Zealand have led this change in practice, with the proportion of prostate cancer diagnoses achieved via the transperineal route in this region increasing from 26% to 57% between 2015 and 2019. This change was driven by increasing and high rates of biopsy-related sepsis with the transrectal approach, thought to be related to the repeated passing of the biopsy trocar through rectal flora, with an associated mortality rate of approximately 0.14% and significant healthcare system costs globally. While both transrectal and TP biopsies are performed under transrectal ultrasound guidance, with TP biopsies the needle passes through the perineal skin instead of the rectal wall. Risk of sepsis seems virtually eliminated with TP biopsies, allowing rationalisation of antibiotic peri-procedural prophylaxis, and the approach may also be superior for detecting anterior tumours. A systematic review and meta-analysis comparing the two modalities found the transperineal approach resulted in equivalent diagnostic accuracy (relative risk [RR]=1.01), significantly lower risks of rectal bleeding (RR=0.02) and fever (RR=0.26), but higher levels of pain (RR=1.83). One of the biggest barriers to widespread adoption of TP biopsies has been the need for it to be performed under general anaesthesia, due to the use of a grid-stepper unit requiring multiple perineal biopsy punctures. However, the introduction of freehand biopsy techniques and perineal access systems has enabled transperineal prostate biopsies to be performed under local anaesthesia. This is still often a painful and unpleasant experience for the patient.

Local anaesthetic transperineal prostate biopsies: Local anaesthetic transperineal (LATP) prostate biopsies have several advantages over TP biopsies performed under general anaesthesia, including the avoidance of complications of general anaesthesia, improved diagnostic efficiency, and freeing up theatre time and resources that can be otherwise utilised. In a series of over 1200 patients undergoing LATP biopsies the procedure was found to have a very low complication rate, comparable diagnostic rate, short learning curve, and to be well tolerated; mean pain scores during the procedure were 2.4 (probe insertion), 3.0 (local anaesthetic injection), and 2.5 (biopsies). In another series of over 170 patients undergoing LATP biopsies in the outpatient setting the overall complication rate was 2.8%, and median pain scores were 1.1 (probe insertion), 3.8 (local anaesthetic injection), and 2.8 (biopsies). The local anaesthetic (LA) injection seems to be the most painful aspect of the procedure and is independent of the number of biopsies taken. Similar pain scores, complication rates and cancer detection rates have been reported in other LATP biopsy series. Although median pain scores for LATP biopsies are low, some patients do experience significant pain with the procedure, and it is generally considered more painful than TRUS biopsies; factors that have contributed to the slow uptake of LATP biopsies in some regions.



Methoxyflurane and Pain-free TRUS B: Methoxyflurane (Penthrox*) is an inhaled anaesthetic and analgesic usually self-administered by a handheld device. It works quickly, has minimal toxicity, and results in a rapid return of psychomotor performance when administration is ceased, resulting in its use becoming popularised in community health emergency settings and during hospital procedures. A recent systematic review confirmed its utility in reducing procedural pain during cancer-related procedures and recommended expanding its application to these. Pain-free TRUS B was a randomised controlled trial co-ordinated by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP), which will co-ordinate Pain-free TP. The publication reporting results of Pain-free TRUS B in the British Journal of Urology International was awarded the BJUI Global Prize in 2023. This trial examined the utility of adding inhaled methoxyflurane to local anaesthetic for transrectal prostate biopsies in 420 patients and demonstrated that methoxyflurane resulted in significant improvements in discomfort, overall experience, and willingness to undergo repeat biopsies, as compared to placebo. The global movement from transrectal to TP biopsies gained momentum after the development of this trial. Thus Pain-free TP seeks to determine if the benefits of methoxyflurane apply to LATP biopsies. Due in part to penetration of the highly sensate perineal skin, pain during LATP biopsies does seem to be higher than for transrectal biopsies; it is therefore possible that methoxyflurane may have even greater utility in the LATP biopsy context than for transrectal biopsies.

Pilot data: In addition to the robust data from >390 participants undergoing prostate biopsies under local anaesthesia (195 with additional methoxyflurane) in Pain-free TRUS B, pilot data on 45 patients undergoing LATP biopsies at Auckland Hospital was collected. Mean pain score during injection of the LA was 4.4 (95% CI 3.7-5.1, SD 2.32) and mean pain score during the biopsies was 3.2 (95% CI 2.6-3.8, SD 2.02). Additionally, there were no admissions, urinary tract infections or episodes of urinary retention within 30 days of the procedure. In combination, the data from Pain-free TRUS B and this pilot study demonstrate the feasibility of the Pain-free TP trial. In combination with the literature, this data clearly demonstrates increased pain scores with LATP biopsies as compared to TRUS biopsies under LA, signalling a possible positive effect of an adjunct inhaled agent on pain scores for LATP biopsies.

Aims and Hypothesis:

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1. Assess the utility of the addition of methoxyflurane to LA for patients having TP biopsies.

2. Assess the cost-effectiveness of the addition of methoxyflurane to LA for TP biopsies.

- 3. Assess if any differences in LATP biopsy technique result in lower pain scores.
- 4. Validate LATP biopsies as an acceptable and reasonable approach.

<u>Hypothesis</u>: Methoxyflurane will reduce pain and improve patients' experience of LATP biopsies.

Significance and impact: Pain-free TP has the potential to transform the standard of care for analgesia for patients undergoing LATP biopsies internationally. This is a highly important outcome given the immense number of patients undergoing prostate biopsies, which is only



likely to increase given the mounting evidence to support both PSA screening and active surveillance. Up to 20% of patients may experience significant distress during prostate biopsies, and as a result may develop aversive attitudes toward further biopsies. Reduced pain during the procedure may have additional benefits including improved compliance with recommendations for repeat biopsies, improved biopsy accuracy, and a reduced need for rebooking of the procedure under GA if the procedure cannot be adequately completed. This trial will also validate LATP biopsies as an acceptable approach and accelerate the global trend away from transrectal biopsies and toward both the TP and LA approaches. LATP biopsies have several inherent personal, system, societal and health economic advantages including avoidance of complications of general anaesthesia, reduced infective complications, improved diagnostic efficiency, and freeing up theatre resources.