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Original Article

'Pain-free TRUS B': a phase 3 double-blind placebo-controlled randomized trial of methoxyflurane with periprostatic local anaesthesia to reduce the discomfort of transrectal ultrasonography-guided prostate biopsy (ANZUP 1501)

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Objective

To determine whether the addition of inhaled methoxyflurane to periprostatic infiltration of local anaesthetic (PILA) during transrectal ultrasonography-guided prostate biopsies (TRUSBs) improved pain and other aspects of the experience.

Patients and Methods

We conducted a multicentre, placebo-controlled, double-blind, randomized phase 3 trial, involving 420 men undergoing their first TRUSB. The intervention was PILA plus a patient-controlled device containing either 3 mL methoxyflurane, or 3 mL 0.9% saline plus one drop of methoxyflurane to preserve blinding. The primary outcome was the pain score (0–10) reported by the participant after 15 min. Secondary outcomes included ratings of other aspects of the biopsy experience, willingness to undergo future biopsies, urologists' ratings, biopsy completion, and adverse events.

Results

The mean (SE) pain scores 15 min after TRUSB were 2.51 (0.22) in those assigned methoxyflurane vs 2.82 (0.22) for placebo (difference 0.31, 95% confidence interval [CI] −0.75 to 0.14; $P = 0.18$). Methoxyflurane was associated with better scores for discomfort (difference −0.48, 95% CI −0.92 to −0.03; $P = 0.035$, adjusted [adj.] $P = 0.076$), whole experience (difference −0.50, 95% CI −0.92 to −0.08; $P = 0.021$, adj. $P = 0.053$), and willingness to undergo repeat biopsies (odds ratio 1.67, 95% CI 1.12–2.49; $P = 0.01$) than placebo. Methoxyflurane resulted in higher scores for drowsiness (difference +1.64, 95% CI 1.21–2.07; $P < 0.001$, adj. $P < 0.001$) and dizziness (difference +1.78, 95% CI 1.31–2.24; $P < 0.001$, adj. $P < 0.001$) than placebo. There was no significant difference in the number of ≥ grade 3 adverse events.

Conclusions

We found no evidence that methoxyflurane improved pain scores at 15 min, however, improvements were seen in patient-reported discomfort, overall experience, and willingness to undergo repeat biopsies.

Keywords

biopsy, methoxyflurane, pain, prostate, prostatic neoplasms, #PCSM, #ProstateCancer

Introduction

Pain and other adverse experiences during TRUS-guided prostate biopsy (TRUSB) have been reported to cause significant distress and negative attitudes to future biopsies in up to 20% of men [1]. Periprostatic infiltration of local anaesthetic (PILA) reduces the pain associated with the procedure and has become a standard of care [2]. However, PILA itself can cause discomfort as a result of both the insertion of the ultrasound probe, and the passage of the needle [3]. Performing the procedure under sedation or general anaesthesia is an alternative, but this can result in other side effects and complications, and is a significant strain on hospital resources in institutions that perform large numbers of prostate biopsies [4,5]. While many other strategies, including hypnotherapy [6], have been studied as adjuncts or alternatives to PILA in performing TRUSB, these approaches have either not proven effective or not been widely utilised for various reasons [5,7].

Methoxyflurane is an inhalational anaesthetic with analgesic effects that can be self-administered with a handheld device. Methoxyflurane has a rapid onset of action, prompt return of psychomotor performance following administration, and a favourable toxicity profile [8]. While inhaled methoxyflurane has been used in the pre-hospital emergency setting for decades, its use for hospital procedures is more recent [8]. For example, compared with conventional, i.v. sedation during colonoscopy, methoxyflurane had similar effects on pain control and procedural success [9]. A previous study regarding the utility of methoxyflurane during prostate biopsy suggested that methoxyflurane and PILA together might be more effective than methoxyflurane alone [10], a concept consistent with the principle of multi-modal analgesia. We conducted a randomized phase 3 trial to determine if methoxyflurane improved pain and other outcomes when added to PILA for TRUSB.

Participants and Methods

Trial Design and Participants

The 'Pain-Free TRUSB' trial was a multicentre, placebo-controlled, double-blind, randomized phase 3 trial for men undergoing their first TRUSB for an elevated PSA or abnormal DRE. The trial was conducted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) in collaboration with the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, the University of Sydney.

Consumers were involved in the conception of the study and were members of the Trial Management Committee. Central ethical approval was obtained in August 2015 (X15-0217 & HREC/15/RPAH/286) and local ethical approval was obtained for all sites. All participants provided written informed consent. This trial was registered with ClinTrials.gov (NCT02604225).

Men scheduled to undergo TRUSB were suitable for inclusion if they were biopsy-naïve and able to comply with study requirements. Exclusion criteria included significant renal or hepatic disease, personal or family history of malignant hyperthermia, hypersensitivity to fluorinated anaesthetics, concurrent barbiturates or tetracycline antibiotic usage, and concurrent significant illness.

The trial was performed in accordance with the International Conference on Harmonization Good Clinical Practice and applicable regulations in Australia and New Zealand.

Randomization

Participants were centrally randomized on a web-based system using minimization with a random component stratified by age (18–60 years vs >60 years) and study site, in a 1:1 ratio to PILA plus a patient-controlled device containing 3 mL methoxyflurane (active group: MOF-PILA), or 3 mL 0.9% saline (placebo group: PLA-PILA).

Intervention

An unblinded pharmacist placed either a methoxyflurane-containing or placebo-containing identical looking inhaler in a plastic bag according to treatment allocation. One drop of methoxyflurane was placed in the plastic bag for both groups to give all inhalers the characteristic fruity odour of methoxyflurane and thereby maintain double-blinding of participants and urologists. Participants received instructions on how to use the device and were asked to begin using it approximately 1 min before insertion of the rectal probe. All participants received PILA in the form of approximately 2.5 mL 2% lidocaine injected into each of the two sides of the base of the prostate gland at the junction of the seminal vesicle, using a 23-gauge needle, administered approximately 5 min before commencement of the biopsies. Prophylactic antibiotics were used according to standard of care at that institution. Regular medications were continued as usual, except for anticoagulants and antiplatelet agents that were managed as per institutional standards. The number of biopsies to be taken was not dictated in the protocol. While the effects of methoxyflurane are known to wear off quickly, usually within a few minutes, participants were advised that they should take extra care as a pedestrian and they should not drive or operate heavy machinery until they had completely recovered.

Data Collection

All participant data were recorded in an electronic database at NHMRC Clinical Trials Centre. Assessments included Patient's Experience of TRUS Biopsy (PETB) questionnaires

completed 15 min and 7–35 days after biopsy, modified PETB questionnaires completed by the urologist soon after biopsy, and adverse events assessed soon after biopsy and 7–35 days later. The PETB questionnaire (Appendix S1) was based on a questionnaire developed to assess patient's experiences of prostate biopsy [11], and the 7–35 day interval was decided based on previous data, including results from the ProBE study that assessed short-term outcomes of TRUS biopsy in patients recruited to the ProtecT trial and collected data at these time points [1].

Primary and Secondary Endpoints

The primary endpoint was the patient-reported score for pain 15 min after biopsy, using a numeric rating scale from 0 (no trouble at all) to 10 (worst I can imagine). Predefined secondary endpoints included scores for other aspects of the experience, rated on identical numeric rating scales, also rated 15 min after biopsy and 7–35 days later: (i) discomfort; (ii) feeling embarrassed; (iii) the sounds; (iv) fear of the biopsy; (v) fear of the results; (vi) drowsiness; (vii) feeling dizzy or lightheaded; (viii) nausea; (ix) vomiting; and (x) the whole experience. Other secondary endpoints included ratings from 0 (much better) to 10 (much worse) for how the experience compared with what had been expected, in relation to: (i) pain; (ii) discomfort; and (iii) the whole experience. Additional secondary endpoints included willingness to undergo repeat biopsies, biopsy completion (80% or more of planned biopsies), urologists' ratings of PETB questionnaire items, patients' and urologists' predictions of treatment group, adverse events, and hospitalizations.

Statistical Analyses

A sample size of 420 was calculated to provide >85% power at the two-sided 5% level of significance to detect a 0.8-point difference in mean pain score. This magnitude of effect was chosen *a priori* as the minimum clinically important difference. This would correspond to a reduction of more than 33% of men reporting troublesome levels of pain based on pilot data [10] and data from a previous randomized controlled trial [12].

A detailed statistical analysis plan was finalized prior to unblinding. The primary analysis was a comparison of the randomly allocated treatment groups on pain score 15 min after biopsy using an analysis of variance, with centre fitted as a covariate. Additional covariates were added as part of a secondary analysis to explore possible prognostic or modifying effects of baseline characteristics. Comparisons between treatment groups on other continuous secondary endpoints were undertaken using a similar approach to that used on the primary endpoint. Ordinal secondary endpoints were analysed using logistic regression, with centre fitted as a covariate. All analyses were performed on an intention-to-treat basis. A two-sided alpha of 5% was applied to all hypothesis tests and to construct confidence intervals. To help guide the interpretation of *P* values from secondary analyses, given the numerous comparisons performed, we grouped the secondary endpoints involving multiple scales into three families (i.e. PETB at 15 min, PETB at 7–35 days, urologist PETB assessment) and calculated Benjamini–Hochberg adjusted *P* values.

Results

Characteristics

Between January 2016 and November 2019, 420 men were enrolled from nine Australian and New Zealand centres; 209 men were randomized to MOF-PILA and 211 men were randomized to PLA- PILA (Fig. 1). Baseline characteristics and biopsy outcomes were similar in the two groups (Table 1).

Follow-Up

All participants were followed for at least 30 days after their biopsy to assess for any adverse events or hospitalizations. Responses to the PETB questionnaire by participants and urologists were recorded for ≥97% of men in both groups at all time points. Over 92% of PETB questionnaires due 7–35 days after biopsy were received within the required time period. All responses were included in the analysis.

Endpoints

Pain Score After 15 min

The mean (SE) pain score 15 min after the biopsy was 2.51 (0.22) for MOF-PILA and 2.82 (0.22) for PLA-PILA (difference 0.31, 95% CI −0.75 to 0.14; $P = 0.18$).

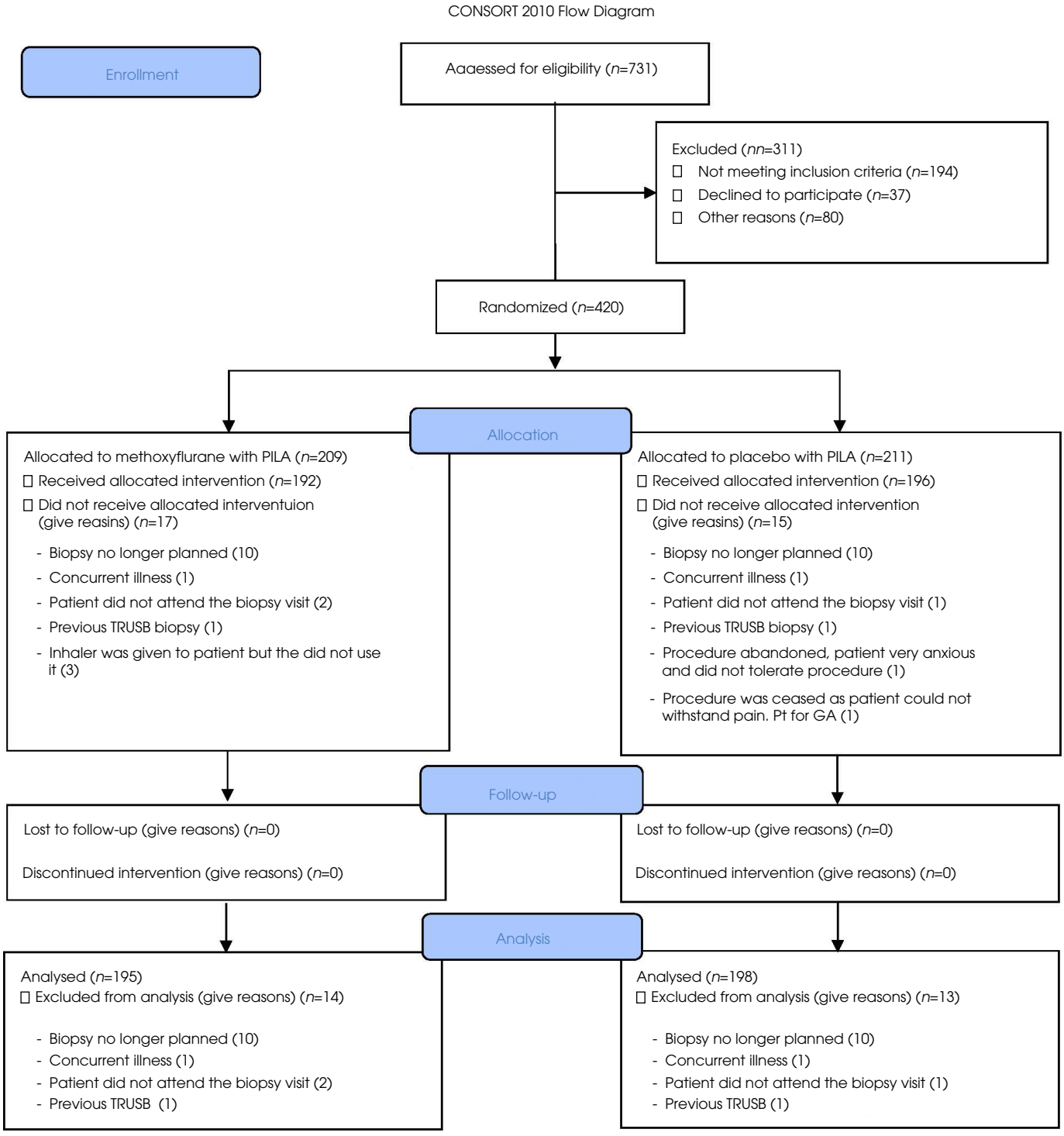
Recollected Pain Score After 7–35 days

The mean (SE) pain score recollected 7–35 days after biopsy was 2.56 (0.25) for MOF- PILA and 2.79 (0.24) for PLA-PILA (difference −0.23, 95% CI −0.72 to 0.27; $P = 0.4$, adjusted [adj.] $P = 0.6$).

Other PETB Questionnaire Scores

Mean scores and differences for pain and other domains of the PETB questionnaire, after 15 min and as recollected 7–35 days after the biopsy, are shown in Fig. 2. After 15 min, men in the MOF-PILA group reported lower scores for discomfort (difference −0.48, 95% CI −0.92 to −0.03; $P = 0.035$, adj. $P = 0.076$), but higher scores for drowsiness

Fig. 1 CONSORT diagram of the trial.



(difference 1.64, 95% CI 1.21–2.07; $P < 0.001$, adj. $P < 0.001$), and dizziness (difference 1.78, 95% CI 1.31–2.24; $P < 0.001$, adj. $P < 0.001$) than men in the PLA-PILA group. After 7–35 days, men in the MOF-PILA group recollected lower scores for bother by the sounds during the biopsy (difference −0.53, 95% CI −0.96 to −0.10; $P = 0.016$, adj. $P = 0.073$), but higher scores for drowsiness (difference 1.23, 95% CI 0.76–1.70; $P < 0.001$, adj. $P < 0.001$) and dizziness (difference 1.21, 95% CI 0.70–1.71; $P < 0.001$, adj. $P < 0.001$) than men in the PLA-PILA group. No difference between treatment

Table 1 Baseline characteristics and biopsy outcomes according to intention to treat.

Variable	Methoxyflurane with PILA (MOF-PILA) *N* = 195	Placebo with PILA (PLA-PILA) *N* = 198
Country, *n* (%)		
Australia	48 (25)	51 (26)
New Zealand	147 (75)	147 (74)
Age, years		
Median (IQR)	66 (61–70)	66 (61–69)
Weight, kg		
Mean (SD)	88.3 (14.5)	86.8 (16.5)
PSA, ng/mL		
Median (IQR)	6.4 (5.0–9.4)	6.3 (5.2–9.2)
MRI, *n* (%)		
Performed prior	21 (11)	21 (11)
Not performed prior	174 (89)	177 (89)
Prostate volume, ng/mL		
Median (IQR)	40 (30–57)	39 (28–53)
Other analgesia, *n* (%)		
Any analgesia in prior 24 h	26 (13)	32 (16)
Paracetamol in prior 24 h	19 (10)	24 (12)
NSAID in prior 24 h	7 (4)	9 (5)
Other analgesia in prior 24 h	1 (1)	2 (1)
Biopsy firings		
Median (IQR)	12 (12–12)	12 (12–12)
Biopsy results, *n* (%)		
Cancer detected	107 (55)	125 (63)
No cancer detected	87 (45)	71 (36)

IQR, interquartile range; NSAID, non-steroidal anti- inflammatory drug.

groups at both time points was observed for embarrassment, nausea, vomiting, the whole experience, fear of the biopsy, and fear of the results.

In relation to how the procedure compared to their expectations 15 min after the biopsy, men in the MOF-PILA group reported better scores for pain (difference −0.56, 95% CI −1.02 to −0.10; $P = 0.02$, adj. $P = 0.53$), discomfort (difference −0.70, 95% CI −1.16 to −0.25; $P = 0.003$, adj. $P = 0.011$), and the whole experience (difference −0.50, 95% CI −0.92 to −0.08; $P = 0.021$, adj. $P = 0.053$) than men in the PLA-PILA group. After 7–35 days, there was no significant difference between the groups in recollected scores for the same domains.

Willingness to Undergo Repeat Biopsies

Fifteen minutes after their biopsy, 115 men (60%) in the MOF-PILA group and 92 men (47%) in the PLA-PILA group responded that they would be 'very willing' to undergo repeat prostate biopsies in the future if required (odds ratio [OR] 1.67, 95% CI 1.11–2.52; $P = 0.01$). When asked after 7–35 days, 102 men (54%) in the MOF-PILA group and 94 men (49%) in the PLA-PILA group responded similarly (OR 1.19, 95% CI 0.79–1.78; $P = 0.4$).

Biopsy Completion (80% or More of Planned Biopsies)

Biopsies were completed in 193 men (99%) in the MOF-PILA group and 195 men (99%) in the PLA- PILA group (OR 1.00, 95% CI 0.01–87.75; $P = 1$).

Urologist Modified PETB Questionnaire Scores

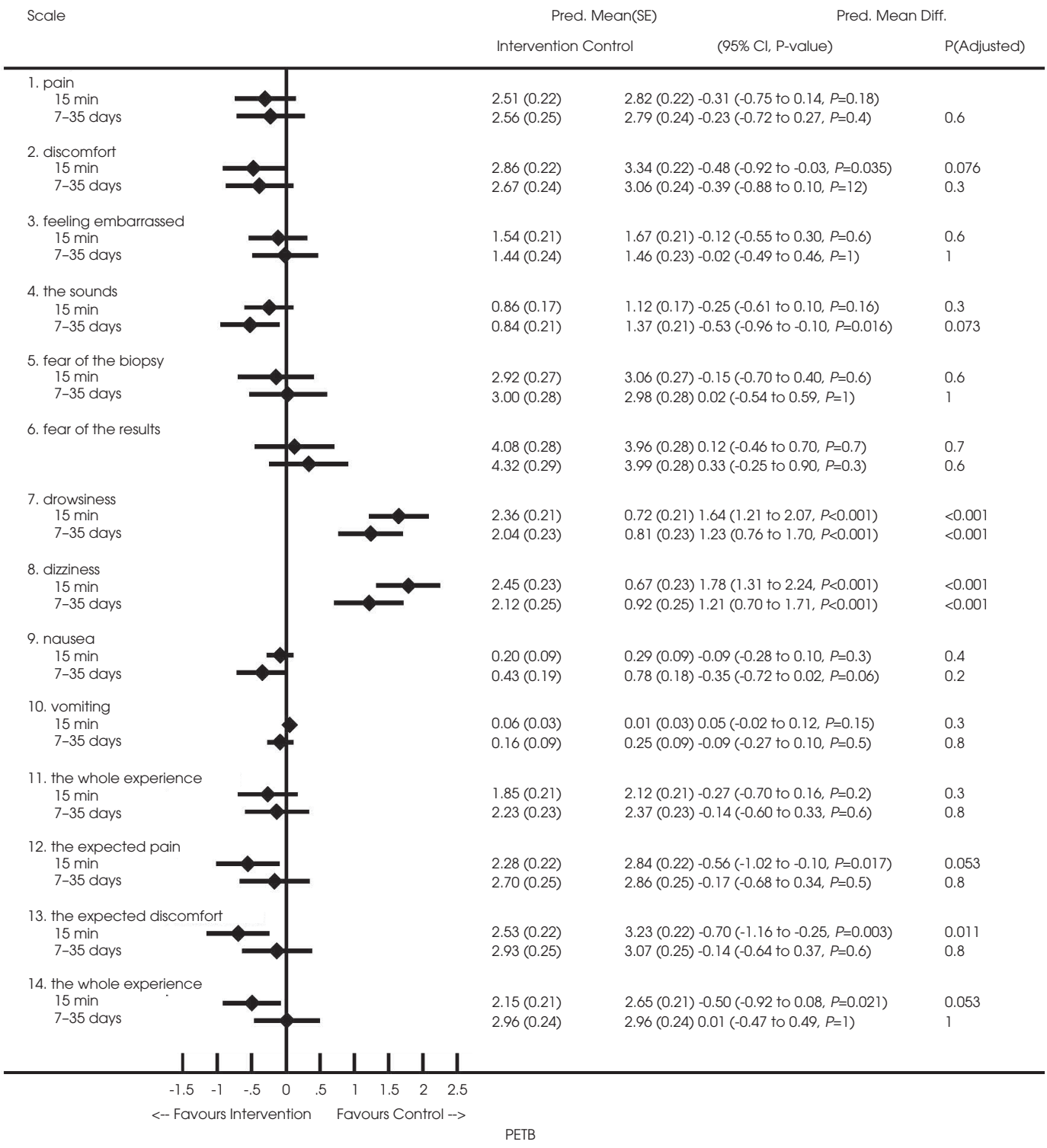
The mean scores for pain and other domains of the PETB questionnaire, recorded by the urologist soon after the procedure, are shown in Fig. 3. Urologists reported lower scores for men in the MOF-PILA group than for men in the PLA-PILA group for pain (difference −0.69, 95% CI −1.07 to −0.30; $P < 0.001$, adj. $P = 0.001$), discomfort (difference −0.84, 95% CI −1.25 to −0.43; $P < 0.001$, adj. $P < 0.001$), embarrassment (difference −0.65, 95% CI −1.00 to −0.30; $P < 0.001$, adj. $P < 0.001$), bother from the sounds (difference −0.56, 95% CI −0.89 to −0.23, $P = 0.001$, adj. $P = 0.002$), fear of the biopsy (difference −0.66, 95% CI −1.04 to −0.28; $P = 0.001$, adj. $P = 0.001$), fear of the results (difference −0.47; 95% CI −0.83 to −0.12; $P = 0.009$, adj. $P = 0.011$), and bother from the overall experience (difference −0.47, 95% CI −0.85 to −0.10; $P = 0.014$, adj. $P = 0.016$). Urologists' scores for men in the MOF-PILA group were higher than for men in the PLA-PILA group for drowsiness (difference 1.58, 95% CI 1.21–1.95; $P < 0.001$, adj. $P < 0.001$), dizziness (difference 1.29, 95% CI 0.94–1.64; $P < 0.001$, adj. $P < 0.001$), and nausea (difference 0.24, 95% CI 0.01–0.47; $P = 0.039$, adj. $P = 0.042$). In relation to how the procedure compared to the urologists' expectations for the procedure, men in the MOF-PILA group were assessed as having better pain (difference −0.97, 955 CI −1.37 to −0.58; $P < 0.001$, adj. $P = 0.001$), discomfort (difference −0.98; 95% CI −1.38 to −0.58; $P < 0.001$, adj. $P = 0.001$), and whole experience (difference −0.97, 95% CI −1.36 to −0.57; $P < 0.001$, adj. $P = 0.001$) than men in the PLA-PILA group.

Participant and Urologist Prediction of Treatment Group

Fifteen minutes after their biopsy, 117 men (61%) in the MOF-PILA group predicted their treatment group correctly vs 98 men (50%) in the PLA-PILA group (OR 1.63, 95% CI 1.08–2.46; $P = 0.02$).

When asked 7–35 days after their biopsy, 112 men (59%) in the MOF-PILA group predicted their treatment group correctly vs 97 men (51%) in the PLA-PILA group (OR 1.42, 0.94–2.15; $P = 0.09$). The urologist predicted the correct treatment group in 131 men (68%) in the MOF-PILA group vs 98 men (50%) in the PLA-PILA group (OR 2.15, 95% CI 1.42–3.27, $P < 0.001$).

Fig. 2 Graphical representation of patient Patient's Experience of TRUS Biopsy questionnaire scores for Q1–14 at 15 min and 7–35 days with *P* values.



Adverse Events and Hospitalizations

Adverse events that occurred during the procedure or follow-up period are summarized in Table 2. The frequencies of dizziness (51% vs 30%; difference 22%, 95% CI 12–35%; $P < 0.001$) and somnolence (44% vs 26%; difference 18%, 95% CI 8.9–28%; $P < 0.001$) were higher in the MOF-PILA group than in the PLA-PILA group. Five men (2.6%)

experienced adverse events ≥ grade 3 in the MOF-PILA group and eight (4.1%) in the PLA-PILA group (difference 1.5%, 95% CI −2.1 to 5.1; $P = 0.4$). Hospitalizations within 30 days of the biopsy occurred in four men (2.1%) in the MOF-PILA group (duration 1–3 days) vs eight men (4.1%) in the PLA-PILA group (duration 1–25 days). There were no intensive care unit admissions or deaths.

Discussion

Our primary endpoint, difference in patient-rated pain scores 15 min after biopsy, was not met. Beneficial effects were nevertheless observed in several secondary endpoints, including lower scores for discomfort, and for how the procedure compared with the patient's expectations for pain and discomfort. The strength of evidence for some of these secondary endpoints was however weaker on adjustment for multiplicity. Urologists' assessments suggested less pain for men assigned MOF-PILA than PLA-PILA. Potential reduced discomfort with the addition of methoxyflurane may be partly attributable to reduced awareness of the TRUSB probe, the insertion and manipulation of which may be experienced as discomfort as opposed to pain by some men [3,12]. These sensations may not be effectively reduced by PILA, which in itself requires insertion of the TRUSB probe before administration.

Pain is not the only relevant outcome; results also suggested an improved overall experience of the biopsy with the addition of methoxyflurane to PILA. Men in the MOF-PILA group reported better scores for the whole experience relative to expectations, as did the urologist who performed the procedure, and more men in the MOF-PILA group reported willingness to undergo repeat biopsies in the future if required. These results reinforce the notion that pain is not the only, or perhaps even the worst, aspect of undergoing prostate biopsies [11].

Whilst there is increasing use of the transperineal route for prostate biopsy, transrectal biopsy is still the most widely used prostate biopsy technique [4], remaining highly relevant internationally, with over 2 million estimated to be performed annually in Europe and North America combined [13].

Fig. 3 Graphical representation of urologist Patient's Experience of TRUS Biopsy questionnaire scores for Q1–14 with *P* values.

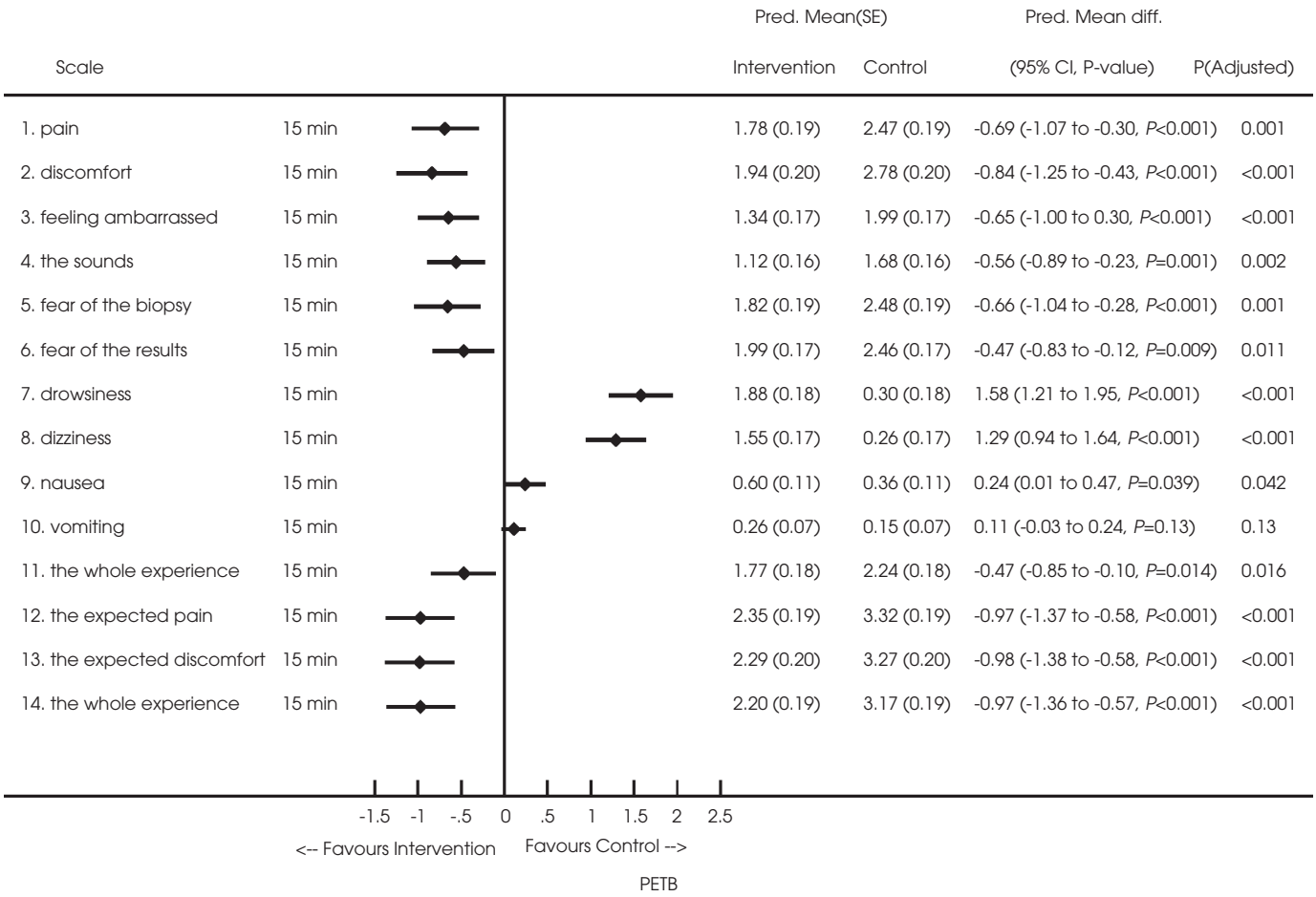


Table 2 Adverse events during procedure or follow-up.

CTCAE version 4.03	Methoxyflurane plus PILA (MOF-PILA) *N* = 192			Placebo plus PILA (PLA-PILA) *N* = 196		
Event	**Gr. 1–2**	**Gr. 3**	**Gr. 4**	**Gr. 1–2**	**Gr. 3**	**Gr. 4**
Dizziness	100 (52)	0	0	59 (30)	0	0
Somnolence	86 (44)	0	0	52 (27)	0	0
Haematuria	47 (24)	0	0	52 (27)	0	0
Haematospermia	26 (14)	0	0	33 (17)	0	0
Rectal bleeding	18 (9.4)	0	0	24 (12)	0	0
Infection	6 (3.1)	0	2 (1.0)	2 (1.0)	0	6 (3.1)
Nausea	5 (2.6)	0	0	5 (2.5)	0	0
Fever	3 (1.6)	0	0	7 (3.6)	0	0
Headache	6 (3.1)	0	0	3 (1.5)	0	0
Altered taste	4 (2.1)	0	0	1 (0.5)	0	0
Lethargy	3 (1.6)	0	0	2 (1.0)	0	0
Urine retention	3 (1.6)	0	0	1 (0.5)	0	0
Diarrhoea	1 (0.5)	0	0	3 (1.5)	0	0
Pre-syncope	2 (1.0)	0	0	1 (0.5)	0	0
Constipation	1 (0.5)	0	0	2 (1.0)	0	0
Other*	11 (5.7)	3(1.6)	0	10 (5.1)	2 (1.0)	0

*CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Gr., grade; PILA, periprostatic infiltration of local anaesthetic. Data are numbers of patients with at least one episode of that event (% of patients). There were no grade 5 events (deaths). Analyses of safety endpoints undertaken on all randomized patients with a safety assessment that received study treatment. *No other individual adverse event occurred in more than two men. Grade 3 adverse events included fracture, serum amylase increase, and vasovagal episode in the MOF-PILA group; and, pain, and vasovagal episode in the PLA-PILA group.*

Transrectal biopsy has several advantages over the transperineal approach [4], including the established tolerability and acceptability of the procedure when performed under PILA [2,5,14] that is supported by data from this study. Scores for pain and other adverse aspects measured with the PETB questionnaire were generally very low for men in the PLA-PILA group, which may be a reason that the trial did not demonstrate a significant reduction in patient-rated scores for pain with the addition of methoxyflurane. These low pain scores with transrectal biopsy are consistent with previous data, including the ProBE study [1,12]. More widespread adoption of this approach might improve resource utilization and save costs [4], particularly if incorporated into streamlined prostate cancer assessment pathways such as the 'one-stop' prostate clinic [15,16]. The implications of this should not be underestimated given increasing evidence to support PSA screening [17], active surveillance [18], and the impact these will have on the number of men undergoing prostate biopsy. The addition of methoxyflurane to PILA increased the frequency of some adverse events including transient dizziness, drowsiness, and somnolence. However, these events were rated to be mild (grade 1 or 2), with no events of grade ≥3. There were no increases in nausea, headache, lethargy, or pre-syncope with the addition of methoxyflurane to PILA. There were very few hospitalizations or adverse events of grade 3 or 4, and no deaths. All grade 4 complications were infection-related, however, there were no intensive care unit admissions, implying that these complications consisted of inpatient treatment with i.v. antibiotics; this grading of infective complications was consistent between the two groups and not specific to or any higher in the MOF-PILA group.

Four other aspects of these data warrant discussion. Firstly, recall bias: patients' responses to the PETB questionnaire changed considerably over time; scores for most domains were lower (less severe) after 15 min than when recollected 7–35 days later. Furthermore, recollections as to how the biopsy compared with expectations were no different between the groups at 7–35 days, whereas better scores were seen with methoxyflurane after 15 min. These findings suggest that factors apart from the biopsy may affect a patient's recollection of the biopsy experience; for example, procedural complications, anxiety and the impact of a subsequent prostate cancer diagnosis [1,11]. Secondly, differences in PETB scores between the randomly allocated treatment groups were more apparent when assessed by urologists than by patients. Thirdly, both patients' and urologists' correct prediction of treatment allocation in the placebo group was exactly 50%, suggesting effective double-blinding in that group. Higher rates of correct prediction of treatment in the methoxyflurane group, by both urologists and patients, may be explained by awareness of treatment effects, for example, analgesia, drowsiness, or dizziness. Finally, although the number of biopsies was not dictated in the protocol for practical reasons in view of the multicentre nature of this trial, the number of biopsies taken was consistently 12 cores across all sites. This may reflect both that centres that used a consistent approach to biopsies were approached regarding participation in the trial, as well as the fact that relatively few patients had a pre-biopsy MRI, and therefore patients were unlikely to undergo additional targeted biopsies.

There are several limitations to this study. Firstly, 65% of participants were recruited from a single institution. Secondly, 15% of patients used another analgesic in the prior 24 hours, which might have reduced their reported pain scores. Thirdly, the use of questionnaires completed by urologists and patients as outcome measures was susceptible to bias if the assigned treatment was apparent to those completing the form. Finally, a transrectal approach, limited use of MRI (11%), and limited use of systematic templates might reduce the generalizability of our findings.

In conclusion, we found no evidence that methoxyflurane improved pain scores at 15 min, but it was safe and did improve patient discomfort, overall experience, and willingness to undergo repeat biopsies. Inhaled methoxyflurane is an option worthy of consideration for men undergoing TRUSB with PILA.

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Conflict of Interest

Dr Ian Davis reports grants from Cancer Australia, during the conduct of the study, other from Bayer, other from Astellas, other from Janssen, other from Movember Foundation, and other from Merck Sharp & Dohme, outside the submitted work, and is unremunerated chair of the ANZUP Cancer Trials Group. Dr Jeremy Grummet reports grants from Cancer Australia, during the conduct of the study. Dr Stockler reports grants from Astellas, grants from Amgen, grants from Astra Zeneca, grants from Bayer, grants from Bionomics, grants from Bristol-Myers Squibb, grants from Celgene, grants from Medivation, grants from Merck Sharp & Dohme, grants from Pfizer, grants from Roche, grants from Sanofi, and grants from Tilray, outside the submitted work. The remaining authors have nothing to disclose.

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Abbreviations: adj., adjusted; ANZUP, Australian and New Zealand Urogenital and Prostate Cancer Trials Group; NHMRC, National Health and Medical Research Council; OR, odds ratio; PETB, Patient's Experience of TRUS Biopsy; PILA, periprostatic infiltration of local anaesthetic; TRUSB, TRUS-guided prostate biopsy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Patient's experience of TRUS biopsy.