


Cerebrospinal fluid sampling for research of Alzheimer's disease and other neurodegenerative diseases when lumbar punctures are performed by anaesthetists

Kelly J Atkins,^{1,2} Lisbeth Evered,^{1,2,3} David A Scott,^{1,2} Christopher Fowler,⁴ Colin L Masters,⁴ Brendan Silbert ^{1,2}

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¹Department of Anaesthesia and Acute Pain Medicine, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia

²Department of Critical Care, Melbourne Medical School, The University of Melbourne, Melbourne, Victoria, Australia

³Department of Anesthesiology, Weill Cornell Medicine, New York, New York, USA

⁴The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Victoria, Australia

Correspondence to

Dr Brendan Silbert;
brendan.silbert@svha.org.au

ABSTRACT

Objectives An increasing number of people are undergoing lumbar puncture (LP) for the purposes of research. Performing LP for research purposes introduces considerations that differ from LP performed for clinical, diagnostic or therapeutic reasons. The demand for research LP will greatly increase as biomarkers are used to both diagnose and monitor disease progression in clinical trials. Minimising adverse events is paramount because research participants receive no clinical benefit and often need repeat procedures. We describe the experience of performing LP for research by anaesthetists. **Methods** We reviewed the clinical protocol and incidence of adverse events in 326 research LP in an anaesthesia department.

Results There was a lower incidence of adverse events compared with previous reports when LP was undertaken for clinical reasons. The incidence of severe post-LP headache was 1.3% when an atraumatic spinal needle with a 27 gauge tip and a 22 gauge shaft was used.

Conclusions We describe the practice to sample cerebrospinal fluid (CSF) by LP for research purposes. Specific practices include the sitting position of the participant, aspiration rather than passive CSF withdrawal, attention to the sterility of the procedure, monitoring of vital signs and importantly the use of 22/27 gauge microtip spinal needle.

Trial registration numbers ACTRN12612000493842, NCT04623242.

INTRODUCTION

Cerebrospinal fluid (CSF), obtained via lumbar puncture (LP), is a key component of research for Alzheimer's disease and neurodegenerative disorders when it offers no diagnostic or therapeutic advantage. Indications for research LP will increase as both disease progression and response to putative therapeutics in research settings are monitored by analysis of CSF samples.^{1,2}

Research LP is distinguished from clinical LP by a standard of care equal or greater

than for clinical management,³ a different informed consent⁴ and a requirement for a positive participant experience to facilitate retention. Complications of LP include post-LP headache (PLPH), paraesthesia, back pain, vasovagal events, nerve injury, nausea, vomiting and dizziness.^{5,6}

Anaesthetists commonly perform spinal anaesthesia, for which the clinical skills are essentially identical to those required for research LP. We describe the LP for research as distinct from diagnostic or therapeutic indications in an anaesthesia department.

MATERIALS AND METHODS

Between 2011 and 2021, after written informed consent, participants underwent LP by anaesthetists for one of two institutionally approved research studies on Alzheimer's disease:

1. Australian Imaging, Biomarker and Lifestyle Study of Ageing (AIBL) (ACTRN12612000493842).
2. Dominantly Inherited Alzheimer Network (DIAN) (NCT04623242).

All relevant information pertaining to the LP was recorded on a specific case report form at the time of the LP.

Lumbar puncture

A medical history, coagulation studies and full blood count were performed prior to the procedure. All anticoagulants were stopped. Drugs that may interfere with coagulation, including aspirin and anti-inflammatory drugs were ceased.

Participants fasted and LP was undertaken in the clean environment of an anaesthetic room with blood pressure and pulse oximetry

monitoring. The LP was performed with a strictly aseptic technique. All personnel wore surgical scrubs as is routine for spinal anaesthesia to prevent the rare complication of CSF infection.⁷

Participants were seated upright, the back prepared with antiseptic and draped. A sterile regional pack was used. Lidocaine 1% was injected subcutaneously prior to the LP. For the first five DIAN LP, a 24 gauge Sprotte needle was used. Subsequently, the LP was undertaken with a Temena (Polymedic, Carrieres-sur-Sine, France) microtip spinal needle (22/27 gauge×103mm) with introducer (20 gauge×38mm). The microtip 22/27 gauge needle has an atraumatic 27 gauge point and a 22 gauge shaft. The small calibre atraumatic point minimises CSF leak, while the larger gauge shaft maximises CSF flow for extraction.⁸

Specifically, this spinal needle is 103 mm in length with the proximal 88 mm having a 22 gauge external diameter (external diameter 0.68 mm, internal diameter 0.54 mm) and the distal 14 mm having a 27 gauge external diameter (external diameter 0.40 mm, internal diameter 0.19 mm) with a pencil point tip. Using a pulsatile CSF model, flow characteristics of this spinal needle are similar to a 22 gauge spinal needle. From Poiseuille's law, flow rates are proportional to the fourth power of needle radius and inversely proportional to only the first power of needle length. Thus, the 14 mm length at 27 gauge would be expected to reduce flow rates, but this effect would be dwarfed by the increased shaft radius of the remaining 88 mm at 22 gauge.⁸

If there was difficulty using this fine needle, we used a pencil point 25 gauge spinal needle and 19 gauge introducer.

Puncture was in the second or third lumbar interspace, using surface markings. CSF (1–2 mL) was aspirated for microbiological and biochemical assessment, then 8–25 mL of CSF was collected by gravity flow (DIAN) or aspiration (AIBL) using a polypropylene syringe. Participants were then elevated at 45°, and admitted to the day case recovery lounge for observation of vital signs, oral intake and discharge (accompanied) at a minimum of 30 min postprocedure. Participants were followed up with a structured interview.

RESULTS

Of the 326 scheduled LP (figure 1), 24 procedures (AIBL n=23; DIAN n=1) were cancelled prior to admission. Of the remaining scheduled 302, 260 were AIBL and 42 were DIAN participants. For the AIBL study, 201 participants were enrolled and underwent a median of 1 LP (range: 1–6). For the DIAN study, the 14 participants enrolled received a median of 4 LP (range: 1–6).

AIBL study

The median age was 73.9 years (range 34–87). Of 260 scheduled LP (figure 1), 10/260 (3.8%) were unsuccessful. Reasons included technical failure, n=7 (2.6%),

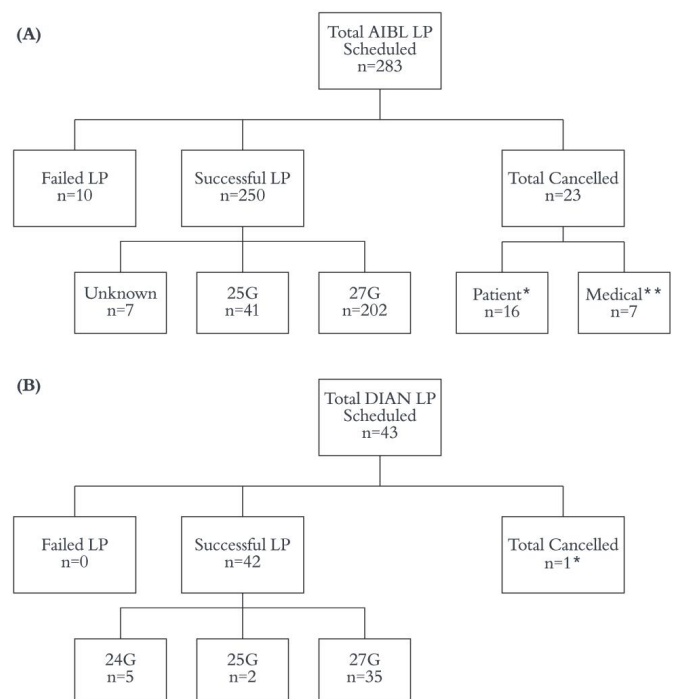


Figure 1 (A) Flow chart of lumbar punctures scheduled and completed by needle utilised. size for the Australian Imaging, Biomarker and Lifestyle Study of Ageing (AIBL). (B) Flow chart of lumbar punctures scheduled and completed by needle size for the Dominantly Inherited Alzheimer's Disease Network Study. Note: LP = lumbar puncture. *Procedure cancelled due to patient withdrawal or inaccessibility. **Procedure cancelled due to medical reasons.

vasovagal event, n=2 (0.8%) and participant anxiety, n=1 (0.4%). CSF was successfully taken in the remaining 250 (96.2%) procedures. For two procedures, in which there was difficulty locating the vertebral interspace, ultrasound was used to verify midline and vertebral interspace with success.

Most LP (n=202/250, 80.8%) were successful with the 22/27 gauge microtip needle. However, 34 LP required changing to a 25 gauge pencil point spinal needle. A further five were successful with an initial attempt using a 25 gauge pencil point spinal needle. Needle specification was not recorded for seven cases.

DIAN study

The median age was 43.7 (range 22–59). LP was successful in all 42 LP (figure 1).

The first five LP were performed with a 24 gauge Sprotte needle but after a severe PLPH, the 22/27 gauge microtip needle was used for all subsequent cases. The majority of LP (n=35/42, 83.3%) were successful with this needle. A further two procedures were successful after switching to a 25 gauge Sprotte spinal needle (figure 1).

Adverse events

Severe PLPH (lasting more the 48 hours) was reported in 5/292 successful LP (noting that 2 of these 5 LP were performed using a 24 gauge Sprotte spinal needle—one required a blood patch) (table 1).

Table 1 Incidence of adverse events (%) in successful lumbar punctures by needle gauge

| Adverse Event | 24 gauge (n=5) | 25 gauge (n=43) | 27 gauge (n=237) |
|-------------------|----------------|-----------------|------------------|
| Severe headache | 2 (40) | 0 | 3 (1.3) |
| Mild headache | 0 | 2 (4.6) | 28 (11.8) |
| Paraesthesia | 0 | 4 (9.3) | 12 (5.1) |
| Mild discomfort | 0 | 9 (20.9) | 12 (5.1) |
| Skin Irritation | 0 | 1 (2.3) | 2 (0.8) |
| Back ache | 0 | 4 (9.3) | 7 (3.0) |
| Bleeding | 0 | 1 (2.3) | 1 (0.4) |
| Vasovagal episode | 1 (20) | 1 (2.3) | 4 (1.7) |
| Total | 3 | 22 (51.1) | 69 (29.1) |

Note: No adverse events were recorded in the n=7 procedures with unknown needle gauge.

Out of the 237 procedures with a 22/27 gauge microtip spinal needle, there were 3 (1.3%) cases of severe headaches; all settled spontaneously or with minor analgesics. Mild self-limiting headaches were reported in 2/43 (4.6%) using a 25 gauge Sprotte needle and 28/237 (11.8%) with a 22/27 gauge microtip spinal needle. When drawing more than 20 mL of CSF either by gravity or aspiration, it was common to observe a mild transient headache.

DISCUSSION

We describe the experience of performing LP for the purpose of research in contrast to previous reports which are predominated by clinical indications.

Post-LP headache

That the use of atraumatic needles greatly decrease PLPH is beyond dispute. In a meta-analysis of 31 412 individuals, Nath *et al* reported the incidence of PLHP was 4.2% for atraumatic needles and 11.5% for cutting needles.⁹ LP for research needs to move beyond the use of atraumatic needles, to emphasise the use of small calibre 27 gauge atraumatic needles. Using this needle, we report an incidence of severe headache of 1.3% (none of whom required hospital admission or blood patch) and mild headache of 11.8%. One participant required a blood patch for severe headache after the use of a 24 gauge atraumatic spinal needle. Duits *et al.* reported mild headache of 11.5%, with severe headache leading to functional impairment of 6.2%.⁵ Of relevance to research, the unique characteristics of the 22/27 gauge microtip spinal needle achieved an adequate flow rate to obtain CSF samples of 15–25 mL, dispelling suggestions that larger gauge needles are required to obtain sufficient CSF for investigational biomarker assays.¹⁰ For cases in which there was difficulty locating the CSF with the 22/27 gauge microtip needle (the fine 27 gauge tip may bend when

hitting a firm interspinous ligament or bone), an atraumatic 25 gauge spinal needle was used successfully.

Minimising the risk of spinal bleeding

Ensuring tests of clotting and platelet counts are normal prior to LP, is essential to minimise the risk of spinal haematoma.¹¹ We worked in conjunction with the prescribing physician and the participant to cease anticoagulation. The LP did not proceed if this was not medically advisable. The widespread use of anticoagulants and antiplatelet agents must be considered when determining eligibility for research. Although we routinely perform LP for spinal anaesthesia with patients on aspirin and non-selective cyclooxygenase inhibitors (i.e., non-steroidal anti-inflammatory drugs; NSAIDs), we did not schedule such patients for a research LP because the threshold of risk is higher than for clinical management.

Ultrasound guided LP

In two participants, location of the CSF was difficult, and ultrasound was successfully used to locate both the midline and the vertebral interspace. The role of ultrasound in LP is now well established.^{12 13} Whether the initial LP should be attempted using surface markings, and ultrasound scanning reserved for difficult cases or used to scan all cases prior to attempting LP in order to improve the success rate is still to be resolved.

Participant positioning

The sitting position allows more accurate location of the dorsal spines and improves CSF flow confirming needle position and a more rapid collection for gravity feed. However, sitting may predispose to a vasovagal episode. We monitor pulse oximetry, so slowing of the heart rate is discernible, and the participant may be laid flat before the manifestation of clinical symptoms. The incidence of vasovagal events was 6/302 (2%) compared with reports of up to 10.6%¹⁴ and there were no cases of syncope. The advantages and easy resolution of side effects make this position preferable to the lateral position.

Back pain

The incidence of backache was 3% with a 27 gauge tip. In all cases pain was mild and resolved with oral analgesics. Back pain after LP performed in memory clinics is reported at 16%–17%.⁵ The low rate may have been related to the routine use of lidocaine, or the fine gauge of the spinal needle.

Minimising the risk of infection

The incidence of meningitis after spinal anaesthesia is reported at 1 in 53 000.¹⁵ It is assumed that meningitis can be minimised by employing a strict aseptic technique (as for all surgical procedures). Although rare, this is a devastating complication, and we consider it unacceptable to perform LP without full aseptic precautions. Importantly, since meningitis has been reported to derive from people with pathogenic bacteria in the nasopharynx,⁷ we ask all staff to wear protective surgical masks.

CONCLUSION

The use of CSF continues to be a key component of research into neurodegenerative disease. Ongoing involvement from research participants is essential and at least in part, contingent on providing a positive experience. LP within this context involves some distinct changes to the long-standing approach of LP for clinical purposes.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by 1. Australian Imaging, Biomarker and Lifestyle Study of Ageing (AIBL) (ACTRN12612000493842); institutional ethics approval St Vincent's Health HREC-A 028/86.2. Dominantly Inherited Alzheimer Network (DIAN) (NCT04623242); institutional ethics approval Melbourne Health HREC/13/MH/250. Participants gave informed consent to participate in the study before taking part.

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ORCID iD

Brendan Silbert <http://orcid.org/0000-0002-5126-0852>

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