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 Silbert1,2

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 therapies 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, Carrières-sur-Sine, France) microtip spinal needle (22/27 gauge×103 mm) with introducer (20 gauge×38 mm). 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%), 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 than 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 31412 individuals, Nath et al reported the incidence of PLPH 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%. 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 antiplatelet agents. The widespread use of antiplatelet agents and anticoagulants 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 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.

Acknowledgements The authors wish to acknowledge the following research staff who contribute to the AIBL and DIAN studies: Ms Beverley Clinch, Professor Steve Collins and Dr Qaio- Xin Li, alongside St Vincent’s Hospital Research Assistants. Most importantly, we wish to thank the research participants who volunteer their time and contribute to our growing understanding of neurodegenerative disease.

Contributors KA: data collection, analysis and writing first draft. LE: data collection, analysis and review of manuscript. DAS: analysis and review of manuscript. CLM: review of manuscript. BS: participant liaison and writing first draft.

Funding The performance of the LP was funded by the Australian Imaging, Biomarker and Lifestyle Study of Ageing (AIBL) and Dominantly Inherited Alzheimer Network (DIAN) studies.

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-A028/86.2. 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID ID
Brendan Silbert http://orcid.org/0000-0002-5126-0852

REFERENCES
1 Rinaldi C, Wood MJ A. Antisense oligonucleotides: the next frontier for treatment of neurological disorders. Nat Rev Neurol 2018;14:9–21.10.1038/nrneurol.2017.148
2 Zahir-Jouzdani F, Mottaghitabar F, Dinarvand M, et al. siRNA delivery for treatment of degenerative diseases, new hopes and challenges. J Drug Deliv Sci Technol 2018;45:428–41.
3 Silbert BS, Scott DA. Informed consent in patients with frailty syndrome. Anesth Analg 2020;130:1473–81.
4 West E, Stuckelberger A, Pautex S, et al. Operationalising ethical challenges in dementia research—a systematic review of current evidence. Age Ageing 2017;46:678–87.
5 Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: results of the multicenter lumbar puncture feasibility study. Alzheimers Dement 2016;12:154–63.
6 Hampel H, Shaw LM, Aisen P, et al. State-Of-The-Art of lumbar puncture and its place in the journey of patients with Alzheimer’s disease. Alzheimers Dement 2022;18:159–77.
7 Rubin L, Sprecher H, Kabaha A, et al. Meningitis following spinal anesthesia: 6 cases in 5 years. Infect Control Hosp Epidemiol 2007;28:1187–90.
8 Ginosar Y, Smith Y, Ben-Hur T, et al. Novel pulsatile cerebrospinal fluid model to assess pressure manometry and fluid sampling through spinal needles of different gauge: support for the use of a 22 G spinal needle with a tapered 27 G pencil-point tip. Br J Anaesth 2012;108:308–15.
9 Nath S, Koziarz A, Badihivela JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. The Lancet 2018;391:1197–204.
10 Carson D, Serpell M. Choosing the best needle for diagnostic lumbar puncture. Neurology 1996;47:33–7.
11 Wright BLC, Lai JTF, Sinclair AJ. Cerebrospinal fluid and lumbar puncture: a practical review. J Neurol 2012;259:4530–45.
12 Chin KJ, Perlas A, Chan V, et al. Ultrasound imaging facilitates spinal anesthesia in adults with difficult surface anatomic landmarks. Anesthesiology 2011;115:94–101.
13 Millington SJ, Silva Restrepo M, Koenig S. Better with ultrasound: lumbar puncture. Chest 2018;154:1223–9.
14 Pavlin DJ, Links S, Rapp SE, et al. Vaso-vagal reactions in an ambulatory surgery center. Anesth Analg 1993;76:31–5.
15 Moen V, Dahlgren N, Inestad L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology 2004;101:950–9.