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A novel method for long-term monitoring of intracranial pressure in rats

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HIGHLIGHTS

- We developed a long-term method for monitoring intracranial pressure in rats.
- The novel method was evaluated and found to be valid and reliable.
- The novel method with epidural recordings is safer for the animals than ventricular recordings.
- This new method enables long-term studies to explore intracranial pressure fluctuations.
- The new method may be useful over a wide range of experimental disease models.

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ABSTRACT

Background: In preclinical neurological studies, monitoring intracranial pressure (ICP) in animal models especially in rodents is challenging. Further, the lack of methods for long-term ICP monitoring has limited the possibilities to conduct prolonged studies on ICP fluctuations in parallel to disease progression or therapeutic interventions. For these reasons we aimed to set up a simple and valid method for long-term ICP recordings in rats.
New method: A novel ICP method employing epidural probes was developed and validated by simultaneously ICP recordings in the lateral ventricle and in the epidural space. The two pressures were recorded twice a week for 59 days and the correlation was studied.
Results: The two pressure recordings correlated exceptionally well and the R^2 values on each recording day ranged between 0.99 and 1.00. However, the ventricular probes caused a number of complications including loss of patency and tissue damage probably due to cerebral infection, whereas the epidural probes were safe and reliable throughout the entire study.
Comparison with existing methods: Epidural probes are much easier to implant than ventricular probes. In addition, these new probes are far less invasive and induce no apparent mechanical tissue damage and highly decrease the infection risk associated with ICP recordings.
Conclusion: Epidural ICP recorded with this new method is identical to the ventricular ICP for at least 59 days but is far less complicated and safer for the animals. The long-term method described is reliable, valid, inexpensive, and may be used in multiple disease models to study ICP.

1. Introduction

In neurosurgery and neurological care units intracranial pressure (ICP) measurements are widely used for decision making and diagnostics. Therefore precise and valid ICP recordings are of crucial importance. But also in experimental research consistent ICP recordings are of essential value for evaluation of animal models and therapeutic effects.

The need for continuous and accurate recordings has challenged researchers for decades and in basic animal science these

Abbreviations: CSF, cerebrospinal fluid; ICP, intracranial pressure.

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Table 1
Mean resting ICP in rats in preclinical studies employing different measuring sites and transducers.

Author	Method/model	Resting ICP (mmHg) (mean ± SD)	Number of animals	Type of transducer
Povlsen et al. (2013)	Cisterna magna catheter	8 ± 2	20	Fluid-filled system
Barth et al. (1992)	Permanent cisterna magna catheter	4.1	12	Fluid-filled system
Morimoto et al. (1996)	Cisterna magna catheter	7 ± 1	16	Fluid-filled system
Zwienenberg et al. (1999)	Cisterna magna catheter	6 ± 0.9	10	Fluid-filled system
Shahrokhi et al. (2010)	Lumbar cannulation	5.4 ± 0.34	10	Fluid-filled system
Kusaka et al. (2004)	Lumbar cannulation	7.1	18	Fluid-filled system
Jallo et al. (1997)	Subdural space	6.3 ± 1.15	4	Fluid-filled system
Silasi et al. (2009)	Epidural space	4.75	7	Telemetric transducer
Andrews et al. (1988)	Epidural space	0–8	30	Fluid filled system
Uldall et al. (2013) (current study)	Epidural space/ventricular	5.7 ± 0.92	27	Fluid filled system
Malkinson et al. (1985)	Subarachnoid space	15.56 ± 0.94	26	Fluid filled system
Jennische et al. (2008)	Intraparenchymal	4.1	14	Fiber optic transducer
Zwienenberg et al. (1999)	Intraparenchymal	11 ± 1.3	10	Fiber optic transducer
Verlooy et al. (1990)	Intraparenchymal	11 ± 1.4	10	Fiber optic transducer
Goren et al. (2001)	Intraparenchymal	16 ± 2	24	Fiber optic transducer
Mandell and Zimmermann (1980)	Ventricular catheter	47 ± 1.47	27	Fluid filled system
Jiang and Tyssebotn (1997)	Ventricular catheter	4.2 ± 0.9 and 9.3 ± 1.3 (*with/without anesthesia*)	6	Micro chip transducer
Zwienenberg et al. (1999)	Ventricular catheter	8 ± 1.6	10	Fluid filled system

methodological problems have never been fully clarified. In the clinical setting a critical approach toward the reliability of different methods and equipment exist and studies on correlations between ICP recordings from various anatomical regions (brain sites) applying various instruments are contradictory (Coroneos et al., 1972; Nornes and Sundbarg, 1972; Powell and Crockard, 1985; Gambardella et al., 1992; Schickner and Young, 1992; Weinstabl et al., 1992; Bruder et al., 1995; Raabe et al., 1998; Zhong et al., 2003; Poca et al., 2007; Eide, 2008). Direct ventricular cannulation developed by Lundberg in 1960 is still considered the "gold standard" for ICP measurements (Lundberg, 1960). However, in the preclinical setting ICP recordings are far from standardized and reported mean ICP in rats varies significantly (4–47 mmHg) even when applying the same methods and transducer systems (relevant studies are summarized in Table 1). Such variation underlines the importance of validation of ICP recording methods and techniques in basic research. A number of methods for measuring ICP in rats have been described including; use of epidural monitors (Andrews et al., 1988; Silasi et al., 2009; Murtha et al., 2012), subdural (Jallo et al., 1997), ventricular (Mandell and Zimmermann, 1980; Jiang and Tyssebotn, 1997), cisterna magna catheters (Barth et al., 1992; Morimoto et al., 1996; Povlsen et al., 2013), intraparenchymal transducers (Goren et al., 2001; Jennische et al., 2008), and recently lumbar cannulation (Kusaka et al., 2004; Shahrokhi et al., 2010). ICP measurements in the epidural space are considered to be less invasive compared to other ICP recording sites, which is important both for the well-being of the animals and for further molecular analyses of brain tissues; thus this method is very appealing.

The validity, reliability, and stability of preclinical ICP methods have only been addressed in two publications (Verlooy et al., 1990; Zwienenberg et al., 1999). However, none of the methods have been applied for long-term studies for validation of durability. The longest recording periods described for rats are 5 days for continuous recordings (Silasi et al., 2009) and 7 days for repeated measures (Jallo et al., 1997; Jiang and Tyssebotn, 1997). In the study by Jallo et al., rats were routinely followed for 7 days and in addition 3 rats were kept for 3 weeks and the researchers report that the ICP catheters remained patent in this period. Thus, the evidence for the overall value of continuous ICP-recordings in basic research is very limited and further methodological studies are warranted. Long-term ICP recordings are necessary to conduct high quality preclinical research involving disease mechanisms, disease progression and/or pharmacological intervention. In order for such methods to be successful, they must be safe for the animals, reliable, simple and remain stable over time.

We hypothesized that it was possible to setup a valid long-term ICP recording method in the epidural space of rats, which would be less invasive and safer than the ventricular cannulation method.

In the present study, we aim to perform reliable long-term ICP recordings in rats. We further aim to evaluate the safety of ICP measurements in the epidural and ventricular space.

Lastly we also aim to investigate any potential ICP-difference between genders with this novel method in respect to future gender-specific disease models.

2. Materials and methods

2.1. Animals

Twenty-seven Sprague-Dawley rats were included, 19 females and 8 males (Taconic, DK) 8–11 weeks old at the time of surgery. The animals were kept in single cages or in small groups (2–3 rats). All animals were housed in the animal facility at Research Institute, Glostrup Hospital in a 12 h light/dark circle with free access to water and standard rodent diet. All experimental procedures were approved by the Danish Animal Experiments Inspectorate (license number 2009/561–1664).

2.2. Study design

The rats were divided into two groups: Group 1; 13 female and 8 male rats with both ventricular and epidural ICP probes. Group 2; 6 female rats with only epidural ICP probes.

In both groups, ICP was recorded on the day of surgery (day 0) followed by ICP recordings and body weight measurements with three to four days interval (day 3, 7, 10, 14, 17, 21, 25, 28, 31, 35, 38, 42, 46, 49, 52, 56, 59). The collection of ICP data was initiated between 9 and 10 a.m. on all recording days. Confirmation of proper ICP recording was confirmed by response to jugular vein compression or compressing the abdomen, both of which will transiently obstruct the venous blood flow from the cerebral tissue augmenting ICP.

To establish the correlation between epidural and ventricular ICP in group 1, both pressures were recorded simultaneously and ICP was manipulated by gentle compression of the neck over the jugular veins to elevate ICP transiently (between 20 and 300% dependent on the force applied) (see Fig. 1A). Following ICP