Fluid Percussion Injury Model

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Abstract Research models of traumatic brain injury (TBI) hold significant validity towards the human condition, with each model replicating a subset of clinical features and symptoms. Hallmarks of traumatic brain injury in man can be faithfully reproduced in the laboratory using fluid percussion injury. Variations in the surgical procedure provide the ability to induce focal diffuse or mixed focal and diffuse brain injury in various laboratory species. Being fully scalable, fluid percussion can induce mild, moderate, or severe brain injury in subjects of either sex, at any age. This chapter outlines the procedures for midline (diffuse) fluid percussion brain injury in adult and post-natal 17 and 35 male Sprague-Dawley rats and lateral (mixed) fluid percussion brain injury in adult male mice. With these procedures, it is possible to generate brain-injured laboratory animals for studies of injury-induced pathophysiology and behavioral deficits, for which rational therapeutic interventions can be implemented.

Keywords Fluid percussion · Rat · Mouse · Juvenile · Adolescent · Brain injury · Concussion · Trauma

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Model Selection

Midline fluid percussion permits the study of experimental traumatic brain injury (TBI) in a model that is reproducible, clinically relevant, and scalable between species and injury severities. Brain injury is induced by a rapid (~20 ms) fluid pulse through a craniectomy onto the intact dura that follows the inner curvature of the skull and creates an elastic decompression of the brain [2, 10]. While fluid percussion injury (FPI) necessitates breaching the cranial vault, the skull is sealed to the injury device, recreating a closed system, which approximates a closed head injury with decompressive craniectomy. The mechanical forces disrupt cell membranes, blood vessels, and neuronal processes. By increasing the angle from which the pendulum hammer falls, greater pressures can be generated to travel through the fluid-filled cylinder and impact the brain. At a moderate level of injury 20–25% of animals die as a result of the injury within the acute post-traumatic period (15 min), generally from respiratory failure and pulmonary edema. This is a normal and desired feature of TBI models, as it reflects human TBI.

In laboratories worldwide, subtle variations in surgical and injury procedures reproduce the spectrum of brain injuries found in the human population. Primarily, the location of injury site determines the major features of the injury, where a midline location induces a *diffuse injury* and a lateral location induces a *focal injury with a diffuse component* [4, 5, 12]. Fluid percussion injury reproduces the acute reflex suppression, functional deficits, and histopathology evident after TBI in man [3, 6, 11]. The model continues to be implemented to evaluate pathophysiological mechanisms underlying histological and behavioral deficits, and therapeutic interventions to mitigate degeneration and promote the recovery of function [11].

Materials

Animals

Fluid percussion brain injury has been successfully performed on various species, including cats, rabbits, pigs, rats, and mice. The adaptation of fluid percussion to rats [3, 7, 8] was followed by its implementation in mice [1]. The procedures outlined in this chapter focus on adult male Sprague-Dawley rats (approximately 300–400 g), post-natal day (PND) 17 and PND35 male Sprague-Dawley rats, and 8-week-old adult male C57BL/6 mice (approximately 20–30 g). To maximize the success of brain injury, examine all animals for any signs of ill health (e.g., rough coat, bleeding or dirty eyes, runny or bleeding nose, and scratched around eyes or nose area). Weigh all animals prior to surgery in order to track injury-induced weight loss.

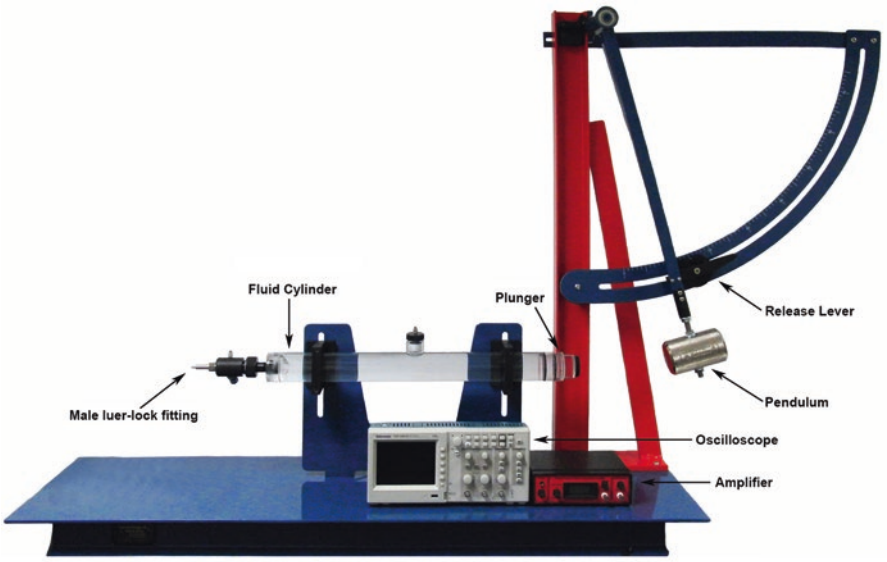

Fig. 1 Fluid percussion injury device. Injury is induced by a 20 ms fluid pulse delivered onto the intact dura via a craniectomy and surgically implanted injury hub. The fluid pulse is generated by the pressure wave produced when the weighted end of the pendulum arm strikes the plunger of a fluid-filled cylinder. The force of the pulse is detected by a transducer and the signal is amplified before being sent to the oscilloscope which outputs the millivolts. The millivolts can then be converted to atmospheres of pressure

Equipment

Injury Device

1. Fluid percussion injury device (Fig. 1)
2. Custom Design and Fabrication
3. Virginia Commonwealth University
4. http://www.radiology.vcu.edu/research/customdesign/fpi.html

Product information including assembly manual, operation manual, and product brochure are provided on the manufacturer's website.

- **Note:** the plunger impact pad on the fluid cylinder should be replaced every 8–12 months. Information and instructions for the setup, cleaning, and maintenance of the FPI device can be found in the FPI Operation Manual: http://www.radiology.vcu.edu/docs/FPIOperationManual.pdf.

- Recording oscilloscope (recommended: Tektronix, Model 1001B)
- Industrial Velcro to secure the device to the bench to prevent movement
- High-vacuum grease (e.g., Fisher Scientific, #14-635-5D)
- Dishwashing solution to clean fluid cylinder
- Jet Dry finishing rinse to minimize air bubbles in the cylinder upon filling

Anesthesia

- Vaporizer for delivery of inhaled anesthesia
- Tubing/petcocks
- Induction chamber
- Isoflurane
- Oxygen and regulator
- Rodent nose cone for inhaled anesthetic that is compatible with the stereotaxic frame.
- **Note:** When using an inhaled anesthetic, it is recommended that all procedures are performed in a well-ventilated area, on a downdraft or similar table, or in a type II biosafety cabinet to minimize anesthesia exposure to the surgeon.

Surgical Supplies

- Gauze sponges
- Cotton tip applicators
- Heating pad (recommended: Deltaphase isothermal heating pad, BrainTree Scientific, #39DP)
- 20 gauge needles (recommended: 1″ length)
- 1-mL syringes
- ≥10-mL syringes, Luer-lock tip
- Small animal trimmer for fur removal (e.g., Wahl, Mini Arco Animal Trimmer)
- Ophthalmic ointment to prevent drying of eyes during surgery
- 4% chlorhexidine solution (or Betadine scrub) for preparation of the incision
- 70% ethanol (or alcohol pads)
- Cyanoacrylate (e.g. Super Glue)
- Perm Reline and Repair resin, liquid and powder (All for Dentist, #H00327)
- Antibiotic Ointment
- Saline-filled syringe, blunted needle bent 90°

Surgical Instruments

- Small animal stereotaxic frame
- Scalpel handle and blade
- Delicate bone scraper (Fine Science Tools, #10075-16)
- Wedelstaedt Chisels ¾ DE (Henry Schein, #600-4972)
- Bull Dog clips (Fine Science Tools, #18050-28, #18051-28)
- Needle holder and scissors

Rat Surgical Instruments

- Dremel tool with engraving cutter #106
- Trephine: 4.7 mm-adult (Miltex, #26-140)

  4.0 mm-PND35; 3.0 mm-PND17 (Fig. 2, custom made; Machine Shop, Arizona State University, Tempe, AZ) contact Rachel Rowe, rkro222@email.arizona.edu
- Fingernail drill with 5/64″ drill bit (Miltex, #33-232)
- Stainless steel skull screws (2-56 × 3/16″) (Small parts Inc., #MX-0256-03B-25)

Mouse Surgical Instruments

- Trephine (3.0 mm) (Fig. 2, Machine Shop, Arizona State University, Tempe, AZ) contact Rachel Rowe, rkro222@email.arizona.edu
- Weed whacker line for cranial disc (1.7 mm diameter)
- Side-grasping forceps (7 × 7) (Henry Schein, #6-124XL)
- 3 M Vetbond tissue adhesive (Henry Schein, #700-3449)

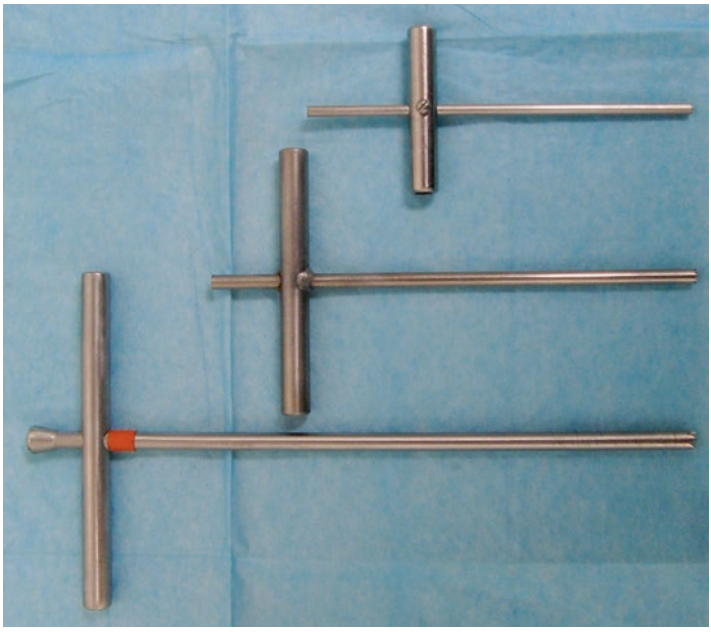

Fig. 2 Custom designed and machined trephines. Trephine of diameter 4.7 mm (bottom) used for the adult rat. 4.0 mm trephine (center) used for PND 35 rats. 3.0 mm trephine (top) used for the mouse PND 17 rat. The trephines displayed are scaled for different aged rodents to accommodate the size difference of their skulls during developmental ages

Injury Hub (Fig. 2)

- 1 ½″ needle (20 gauge) (Becton Dickinson, #305176)
- Syringe (1 cc)
- Razor blades
- Tissue forceps (Henry Schein, #6-114)

Rat Injury Hub

- Cosmetic pencil sharpener

Mouse and PND17 Injury Hub

- Luer-loc extension tubing (Baxter, #2C5643)

Procedure

Administer Anesthesia and Secure in Head Holder

- Follow a standard surgery sheet, recording the progress of the surgery (see Appendix).
- Anesthetize the animal with 5% isoflurane for 5 min in an induction chamber.
- Shave or remove hair from scalp, as appropriate.
- Secure and level the animal in a stereotaxic frame equipped with a nose cone for continuous inhalation of isoflurane (2.0–2.5%). The back of the front incisors should be flush with the bite bar, without tension applied to the teeth. If you observe mouth breathing, check the positioning of the teeth over the bite bar and/or reposition the nose cone to allow for normal respiration.
- Apply ophthalmic ointment to the eyes to keep them moist during the surgery.
- Prepare the surgical area with 70% alcohol and betadine solution (antiseptic).
- Monitor anesthesia by observing muscle relaxation, in addition to assessing the toe pinch reflex. Animals under appropriate anesthesia will have a steady respiration rate.

Cranial Surgery for Hub Placement

- Make a midline sagittal incision extending from between the eyes to the base of the skull, just past the ears. To minimize bleeding, avoid cutting the muscle at the base of the skull (Figs. 3a, 4a, and 5a).

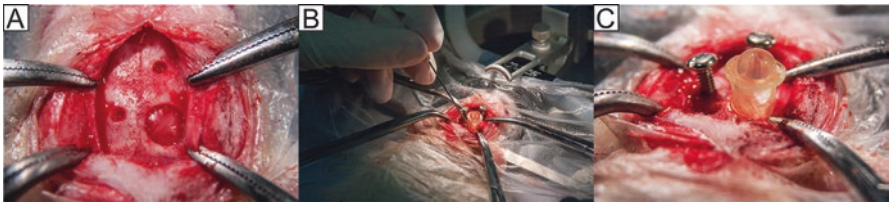

Fig. 3 Cranial surgery for hub placement for lateral FPI in the rat. The rat's head is shaved and the animal is secured in a stereotaxic frame with a continuous flow of isoflourane via a nose cone**.** A midline incision is made to expose the skull and the overlying fascia is removed. A Dremel tool is used to make three pilot holes. The screw holes are expanded with a finger nail drill and 5/64″ drill bit (**a**). A 4.7 mm diameter trephine is used to create a cranial disc that is removed to expose the underlying dura (**a**). A stainless steel screws are secured into the screw holes (**b**). Small drops of cyanoacrylate gel are placed on the outside of the constructed injury hub, and the hub placed inside the craniectomy (**b**). After the cyanoacrylate gel dries, the injury hub and screw are covered in methyl methacrylate cement and the injury hub is filled with saline (**c**)

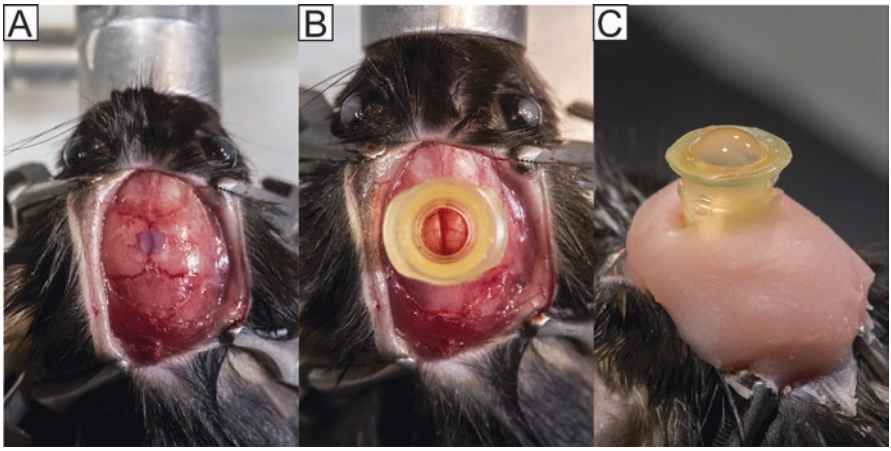

Fig. 4 Cranial surgery for hub placement in the mouse. A midline incision is made to expose the skull and the overlying fascia is removed (**a**). Vetbond tissue adhesive is used to secure a disc shaved from weed whacker line at the location of the craniectomy (**a**). A 3 mm diameter trephine is used to create a cranial disc that is removed to expose the underlying dura (**b**). Small drops of cyanoacrylate gel are placed on the outside of the constructed injury hub, and the hub placed outside the craniectomy (**b**). After the cyanoacrylate gel dries, the injury is covered in methyl methacrylate cement and the injury hub is filled with saline (**c**)

- Expose the skull and scrape the fascia from the skull using a delicate bone scraper, cotton swabs, and gauze. Clear away temporal muscle as necessary. If greater exposure is needed, stretch the skin by applying pressure with the fingers.
- Attach Bull Dog clips to the edges of the incision (two anterior, two posterior) to expose the surgical site. When the Bull Dog clips fall down, the weight will hold the incision open (Figs. 3a, 4a, and 5a).

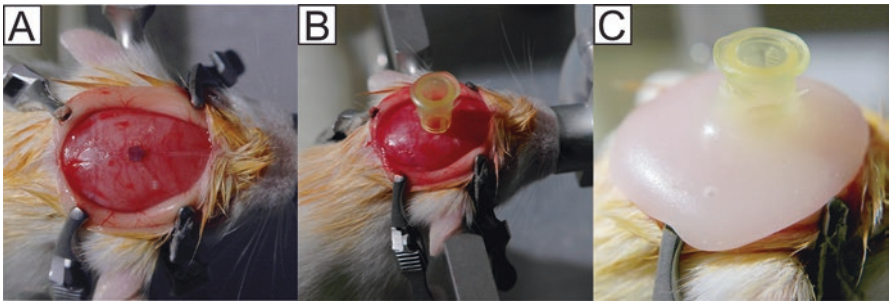

Fig. 5 Cranial surgery for hub placement in PND 17 rat. A midline incision is made to expose the skull and the overlying fascia is removed (**a**). Vetbond tissue adhesive is used to secure a disc shaved from weed whacker line at the location of the craniectomy (**a**). A 3 mm diameter trephine is used to create a cranial disc that is removed to expose the underlying dura. Small drops of cyanoacrylate gel are placed on the outside of the constructed injury hub, and the hub placed outside the craniectomy (**b**). After the cyanoacrylate gel dries, the injury is covered in methyl methacrylate cement and the injury hub is filled with saline (**c**)

Cranial Surgery for Hub Placement-Adult Rat

- Mark the locations on the skull for the screw hole(s) and craniectomy center. The skull screw is used to secure the injury hub in place.
  - For midline FPI, position one screw hole 1 mm lateral to bregma and 1 mm rostral to the coronal suture on the right side. For PND 35 rats, no screw hole is needed.
  - For lateral FPI, position the one screw hole 1 mm lateral to bregma and 1 mm rostral to the coronal suture on the ipsilateral side to the craniectomy; position the second hole midway between bregma and lambda and 1 mm lateral to the central suture contralateral to the craniectomy.
- Drill pilot holes at both markings using the Dremel tool and burr bit.
- Expand the screw hole with a finger nail drill and 5/64″ drill bit (Fig. 3a).
- Place the centering pin inside the 4.7 mm diameter trephine. Anchor the centering pin in the pilot hole at the craniectomy center. For PND 35 rats, place the pin inside the 4.0 mm diameter trephine and anchor in pilot hole.
- Continually turn and spin the trephine to make a craniectomy without disrupting the underlying dura. Keep trephine clean by using a toothbrush to remove bone debris from the trephine teeth. Apply saline to moisten the bone and aid in trephination. As needed, angle the trephine to evenly cut around the craniectomy.
- Frequently check the progress of the craniectomy by applying mild pressure to the center of the craniectomy using forceps or an applicator stick. As the skull thins, the craniectomy will move independently of the skull. The craniectomy is complete when the bone can move freely in all directions.

- Remove the bone piece, working around the circumference using the wedelstaedt and scalpel, or two wedelstaedt instruments without disrupting the dura. When the bone has been removed, gently clear any blood from the craniectomy site using a cotton-tipped applicator (Fig. 3a).
- **Note:** If the surgery site continues to bleed when the skull is removed, lightly remove blood with gauze. Adding saline can create hydrostatic pressure that will reduce bleeding. If the site continues to bleed, control the bleeding with Gelfoam. Excessive wiping or dabbing at the craniectomy site will prevent blood clotting and worsen the bleed.
- Secure a stainless steel screw in the skull screw hole. Hold the screw with tissue forceps and advance the screw with a screwdriver (Fig. 3c).

Cranial Surgery for Hub Placement-Mouse and PND 17 Rat

- Shave weed whacker line with a razor blade as thin as possible to make a circular disc that is an equal thickness on all sides. Disc should be level when placed on the skull (Figs. 4a and 5a).
- Pick up the disc with side-grasping forceps. Dip the cranial disc into a drop of Vetbond tissue adhesive placed on a nonabsorbent surface.
- Place the disc at the location of the craniectomy (midway between bregma and lamda on the sagittal suture). To drop the disc, release the forceps and use a wooden applicator stick to position the disc. Once in position, use a twisted Kimwipe tissue to wick away any excess Vetbond (Figs. 4a and 5a). Allow the Vetbond to fully dry before beginning to trephine.
- Place the 3.0 mm trephine over the disc and perform the craniectomy by continually turning and spinning the trephine without disrupting the underlying dura. Keep trephine clean by using a toothbrush to remove bone debris from trephine teeth. Apply saline to moisten the bone and aid in trephination. As needed, angle the trephine to evenly cut around the craniectomy.
- **Note:** If the disc comes off while trephining, clean excess dried glue from the skull and apply a new disc using Vetbond. However, if the bone can move independently of the skull in an area, use a small dot of superglue to attach a new disc (Vetbond will run and may touch the surface of the dura compromising the surgery).
- Frequently check the progress of the craniectomy by applying mild pressure to the center of the craniectomy with forceps or an applicator stick. As the skull thins, the craniectomy will be able to move independently of the skull. The craniectomy is complete when the bone can move freely in all directions.

- Under magnification, remove the bone piece working around the circumference using the wedelstaedt and scalpel, or two wedelstaedt instruments without disrupting the dura (Fig. 4b). When the bone has been removed, gently clear any blood from the craniectomy site.

- **Note:** If the surgery site continues to bleed when the skull is removed lightly remove blood with gauze. Adding saline can create hydrostatic pressure that will reduce bleeding. If the site continues to bleed, control the bleeding with Gelfoam. Excessive wiping or dabbing at the craniectomy site will prevent blood clotting and worsen the bleed.

Injury Hub

Injury Hub Construction

- Attach a 22 gauge, 1½″ needle to a 1 cc syringe. Place the needle into a laboratory bench pad (Fig. 6a).
- Cut the female Luer-Loc hub from the needle using a razor blade (Fig. 6a). The cut is made parallel to the Luer-loc with an outer diameter of ~4.7 mm for the rat, ~4.0 mm for the PND35 rats, and ~3.0 mm for the mouse and PND17 rat.
- **Note:** To confirm the proper diameter you can place the trephine through the hub and confirm a tight fit.
- Inspect the cut edge of the injury hub and trim to size and level as necessary (Fig. 6b).
- For the rat, bevel the cut edge of the injury hub with a cosmetic pencil sharpener.
- Shave thin burrs around the injury hub starting at the Luer-Loc edge in the direction of the cut edge using a razor blade (Fig. 6c).

Injury Hub Placement

- Hold the hub in tissue forceps (behind the teeth). Apply small drops of cyanoacrylate gel on the outside of the hub, just above the cut end.

Fig. 6 Injury hub construction. Firmly attach a 20 gauge needle to a 1 cc syringe and insert the needle into a laboratory bench pad to prevent the needle from becoming projected after it is cut (**a**). Use a razor blade to cut off the tip of the needle (**a**). The injury hub is checked and refined for level (**b**). For the rat, the injury hub is beveled using a cosmetic pencil sharpener. Using a razor blade, score the exterior of the hub making burrs at even intervals around the hub (**c**). When finished, the cut end should be flat and even, and parallel to the Luer-Loc plane

- Position the hub over the craniectomy (using magnification for the mouse). For the rat, the injury hub fits inside the craniectomy (Fig. 3b, c). For the mouse and PND 17 rat, the injury hub fits outside the craniectomy (Figs. 4b and 5b).
- Using a wooden applicator stick (cut a sharp angle) gently scrape the cyanoacrylate gel down the injury hub onto the skull. Apply more cyanoacrylate gel if needed to the junction between the injury hub and the skull to firmly adhere the injury hub to the skull in addition to creating a seal.
- After the cyanoacrylate gel dries, cover the injury hub (and screw) in methyl methacrylate cement (Figs. 4c and 5c). Apply the methyl methacrylate cement from a 1 cc syringe when it is thick enough to hold shape.
- When the methacrylate cement has dried, fill the injury hub with saline (Fig. 4c).
- Place a suture at both the anterior and posterior edges of the incision.
- Remove the animal from the stereotaxic frame and anesthesia. Place the animal in a recovery cage on a heating pad until the animal is awake and alert. Monitor animals for outward signs of pain or distress.

Injury

Before using the injury device, check that when the weighted pendulum arm is hanging in a neutral position (at 0°) that it is flush and centered on the foam pad at the end of the plunger. Adjust as needed by injecting or removing fluid from the device. Drop the pendulum hammer several times to prime the device.

- Reanesthetize the animal after an approximately 60 min recovery period from surgery.
- Visually inspect inside the injury hub for debris, blood, or dried dental acrylic. Clean out the injury hub using a small cotton tip applicator or irrigate with saline if necessary.
- Fill the injury hub with sterile saline until a bead of fluid is formed by surface tension. Remove any air bubbles from inside the hub.
- To avoid air between the hub and device, press the plunger so that a drop of fluid is produced at the end of the injury device. Connect the female Luer-Loc injury hub on the animal to the male Luer-Loc fitting on the injury device. Create continuity between the fluid of the cylinder and the fluid in the injury hub.
- **Note:** Rats should be held in your left hand lying on their right side. Attach the rat directly to the device. For mice, attach them to the device using a Luer-Loc extension tube.
- Check the animal for a toe pinch response. Once a normal breathing pattern returns (1–2 breaths per second) and the animal has a positive toe pinch response, release the pendulum to injure the animal. Secure the pendulum after it strikes the plunger once and return it to the catch.
- Immediately after the injury, start a timer to measure the duration of physiological responses.

- Remove the injury hub by pressing on the bridge of the nose for leverage. Visually inspect the hub for obstructions.
- Observe and record the duration and extent of apnea or seizure. Note the condition/appearance of the surgical site and brain tissue beneath the injury site and record brain herniation and hemorrhage. If the dura is breached, the animal should be euthanized and not included in the study.
- Control bleeding if necessary. Leave the craniectomy open. Close the wound (i.e., suture or staple) and apply topical lidocaine and antibiotic ointment.
- Place the animal in a supine position on a heating pad. The time elapsed from the injury until the animal spontaneously rights is recorded as the righting reflex time.
- Once the animal has righted, place it in a designated recovery area equipped with a heating pad.
- When the animal regains normal ambulatory behavior, it can be returned to its home cage.

Postoperative Care

Postoperative Evaluations

- Following injury, animals should be visually monitored for continued recovery every 10 min post-injury (for the first hour). Within 15–20 min after injury, surviving animals should be alert. Within 1 h after injury, animals should be ambulatory. Brain-injured and uninjured control animals typically show no outward effects once they have recovered from anesthesia, and resume normal eating, drinking, and grooming patterns. Typically animals return to sleep, as the injury occurs during their sleep cycle.
- Postoperative evaluations should be done daily (for a minimum of 3 days). Follow the Postoperative Evaluation Sheet to record the external examination, physical examination, suture site, and a pain evaluation. Typically, animals require no special supportive care after surgery. This injury does not produce overt signs of post-operative pain, and does not call for pain monitoring or drugs to manage pain. Caution should be taken in administering such compounds, as they can influence outcome (for review see [9].

Postoperative Weight

- Weigh animals daily. Record weights on the evaluation sheet.
- Animals can lose up to 20% of their body weight after surgery and injury. It is beneficial to prophylactically provide mash (chow + water) and/or place normal chow on the floor of the cage to facilitate weight gain.
- If by the second day post-injury, there is continued weight loss, the animals will likely require fluid injections (0.9% sterile saline) to prevent dehydration. Consult a local veterinarian for advice.

- Weight loss exceeding 20% of pre-injury body weight indicates significant injuries that require intensive post-operative care or euthanasia.

Advantages, Limitations, Complications

Advantages

The clinical relevance of the model allows the study of brain injury phenomena, from behavior to molecular biology. The model achieves face validity by the nature of the mechanical forces applied to the brain, and the ensuing pathophysiological responses. The recovery period after surgery, before injury, enhances the face validity of the brain injury model by returning the animals to a condition that more closely resembles the human condition (in which brain injury occurs in the absence of anesthesia). Also, the open craniectomy reduces the effects of injury-induced elevation of intracranial pressure.

The midline injury results in bilateral diffuse pathology that globally suppresses function, such that therapeutic interventions can be tested against injured control. The lateral injury results in ipsilateral focal injury and contralateral diffuse injury, such that the injury is distinct for every brain region. Only specific lateralized functions may be suppressed after lateral brain injury. However, the ensuing cavity permits targeted therapeutic intervention, especially for cell transplantation and bioengineered matrices.

Limitations

To date, most studies using fluid percussion injury have used a moderate level of injury. Concerns about injury variability are based on the extent of damaged tissue and range of physiological responses among animals. The number of variables that influence the response to brain injury produces a range that can necessitate large group sizes to detect significant effects.

Complications

Air Bubbles

Air bubbles in the FPI device can prevent an accurate measurement of the injury magnitude. When air is present in the device, the oscilloscope reading will have many jagged peaks instead of a smooth curve with one peak. The syringe ports can be used to remove any air that enters the device. One way for

air to become trapped in the fluid cylinder is after cleaning of the cylinder. This can be minimized by rinsing with a spot remover solution for the dishwasher (e.g., Jet Dry).

Compromised Surgery

During the cranial surgery, the dura can be compromised by the trephination or removal of the bone. When the injury is induced, pressure from the fluid pulse will cause the dura to tear and the brain will herniate through the craniectomy. If the dura is compromised, the injury becomes inconsistent and should be classified as a technical failure. A dura breach will extend the opening of the blood brain barrier and displace neural tissue. Animals with a dura breach should be excluded from any study.

When placing the injury hub over the craniectomy, cyanoacrylate gel can spread on to the dura. If the cyanoacrylate incompletely forms a seal, then methyl methacrylate can spread under the injury hub and on to the dura. These substances on the dura will change mechanical properties and alter the injury. Visual inspection is necessary to identify cyanoacrylate gel or methyl methacrylate on the dura, as well as any other obstruction over the injury site, such as a blood clot.

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