Practical aspects and potential risks of intrathecal drug delivery

Jee Bang, MD, MPH
Assistant Professor of Neurology,
Johns Hopkins University School of Medicine
Clinical Director,
Johns Hopkins Huntington Disease Center of Excellence
Disclosures

• Contracted Research: Roche, uniQure, SIGNAL
Outline

- Intrathecal injection
- Contraindications
- Lumbar puncture details
- Troubleshooting
- Complications
- Management of complications
Intrathecal (IT) injection

- Method of drug delivery to the cerebrospinal fluid by injecting the drug into the subarachnoid space via a lumbar puncture (LP)
- Can deliver the drug when it cannot cross the blood brain barrier, e.g. ASOs
Contraindications for an LP

- Signs of increased intracranial pressure
  - Check funduscopy
- Unstable cardiorespiratory status
- Signs of cerebral herniation
- Focal neurological findings
- Chorea severe enough to make the LP impossible
- Susceptibility to prolonged bleeding
  - Check coagulation labs
  - Hold anticoagulants if safe
Check funduscopcy before the LP
Preparation
Position the patient

• Lateral or sitting up
Palpate the landmarks

- L3-L4 or L4-L5
- Use superior iliac crests

*BMJ* 2018;361:k1920

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 располагать пальцы на позвонках:

- L3-L4 или L4-L5
- Использовать верхние подвздошные гребни

*BMJ* 2018;361:k1920
Sterilize with antiseptic sponges

BMJ 2018;361:k1920
Administer local anesthetic

- Pull back before injecting, to make sure you’re not injecting into a vein
- Around 5 ml
- Be generous
- Can use the same path with the spinal needle
Atraumatic needle is preferred

- Reduces the following:
  - Postdural puncture headache
  - Need for epidural blood patch
  - Nerve root irritation
  - Hospital visit for fluids and analgesia

- No differences from conventional:
  - Back pain
  - Failed LP

BMJ 2018;361:k1920
Schmittner et al., 2011
Pirbudak et al., 2019
Use the atraumatic needle (24G) with the introducer needle
Insert the introducer needle
Insert the spinal needle through the introducer needle
Spinal needle through the interspinous ligament
Spinal needle through the ligamentum flavum
Needle enters the dura and the subarachnoid space
Pull out the stylet and let the CSF flow
Attach the tubing to the spinal needle
Attach the syringe to the tubing and apply negative pressure to withdraw CSF
Take the CSF syringe off, then connect the drug syringe to the tubing and inject over 90 seconds.
Pull out the entire apparatus in a single controlled fluid motion; apply sterile dressing
ALMOST TOO EASY
## Troubleshooting

<table>
<thead>
<tr>
<th>Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient reports leg pain</td>
<td>May have gone too lateral and hit a spinal nerve root</td>
</tr>
<tr>
<td>Blood is filling up the needle hilt/hub</td>
<td>Needle may have hit a venous plexus</td>
</tr>
<tr>
<td>Needle is meeting resistance</td>
<td>Needle may have hit a calcified spot</td>
</tr>
</tbody>
</table>

![Diagram of spinal anatomy](image-url)
Different ways of redirecting the spinal needle

- Pull back the spinal needle or push it in further
- Pull back the spinal needle and redirect the introducer without withdrawing it
- Pull back the spinal needle, withdraw the introducer and then redirect it
- Pull out the spinal needle, pull out the introducer, then reinsert the introducer at a different angle or insert in a different spot within the same lumbar level
  - Move caudally, rostrally, medially, or laterally
## Troubleshooting

<table>
<thead>
<tr>
<th>Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF stops flowing</td>
<td>Rotate the needle</td>
</tr>
<tr>
<td>A nerve root may be blocking the needle opening</td>
<td>Loosen the Luer lock connection</td>
</tr>
<tr>
<td></td>
<td>Use a smaller syringe</td>
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</tbody>
</table>

*Roche*
Possible complications of LP

- Post-LP headache/post-dural puncture headache (PDPH)
- Post-LP pain
- Bleeding
- Infection
- CSF leakage
- Brain herniation (in cases of increased ICP)
Post-LP management

• Patient should get up and start moving around right after the procedure is done
  • Brain perfusion is much better when upright\(^1\)
  • Helps promote CSF flow and drug distribution

• Increase fluid intake: also helps when done 24 hours before the LP\(^2\)
  • Minimum of 1500 ml

• No heavy exertion for 24 hours

\(^1\) Klarica et al., 2014
\(^2\) Nowaczewska et al., 2019
Post-LP headache management

• Increase caffeine intake
  • Decreases the proportion of participants with PDPH persistence and those requiring supplementary intervention

• Gabapentin, theophylline and hydrocortisone also proved to be effective, relieving pain better than placebo or conventional treatment alone
  • Conventional treatment = bed rest, hydration, acetaminophen and meperidine or bed rest, hydration, caffeinated beverages, opioid and/or NSAID

*Ona et al., 2015*
No serious AEs in HTT$_{Rx}$-treated patients in Phase I/IIa clinical trial of RG6042

- In the treatment group: PDPH after 10% of LPs
  - no apparent relationship to trial duration or dose
  - no evidence of an increased risk of PDPH with successive LPs
  - All PDPHs resolved within 2 days (median duration)

Tabrizi et al., 2019
Conclusion

• Current ASO therapies are administered through intrathecal injections
• So far, repeated IT injections appear to be safe and well-tolerated
• There are multiple ways to “troubleshoot”
• Post-LP complications are mostly mild and short-lived. They can be managed successfully.
• We continue to gather long-term data on repeated IT injections
Johns Hopkins Huntington Disease Center

www.hopkinsmedicine.org/psychiatry/hd
References


References

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3 or 4</th>
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<tr>
<td></td>
<td>HTTRG Groups (N=14)</td>
<td>Placebo Group (N=12)</td>
<td>HTTRG Groups (N=14)</td>
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<td>Procedural pain</td>
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<td>Post-lumbar-puncture syndrome</td>
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Types of spinal needles

- Conventional
- Atraumatic

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