

Endoscopic ultrasound-guided celiac plexus neurolysis using a reverse phase polymer

Keith L Obstein, Fernanda P Martins, Gloria Fernández-Esparrach, Christopher C Thompson

Keith L Obstein, Christopher C Thompson, Gastroenterology Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, United States

Fernanda P Martins, Federal University of São Paulo, Rua Botucatu, 640 2º andar, São Paulo 04023-062, Brazil

Gloria Fernández-Esparrach, Department of Gastroenterology, Endoscopy Unit, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain

Author contributions: Obstein KL, Martins FP, Fernández-Esparrach G and Thompson CC contributed equally to this work; Obstein KL, Martins FP, Fernández-Esparrach G and Thompson CC performed the research; Obstein KL, Martins FP, Fernández-Esparrach G and Thompson CC analyzed the data; Obstein KL, Martins FP, Fernández-Esparrach G and Thompson CC wrote the paper.

Supported by A grant from Generalitat de Catalunya (AGAUR, BE-100022)

Correspondence to: Christopher C Thompson, MD, MSc, FASGE, Gastroenterology Division, Brigham and Women's Hospital, 75 Francis Street, Thorn 1123, Boston, MA 02115, United States. ccthompson@partners.org

Telephone: +1-617-5258266 Fax: +1-617-2646342

Received: April 25, 2009 Revised: November 4, 2009

Accepted: November 11, 2009

Published online: February 14, 2010

RESULTS: EUS-guided CPN was successfully performed in all 6 pigs without immediate complication. Methylene blue was identified throughout the peritoneal and retroperitoneal cavity in group 1. The blue colored poloxamer was found in the retroperitoneal cavity immediately adjacent to the aorta, in the exact location of the celiac plexus in group 2.

CONCLUSION: EUS-guided CPN using a reverse phase polymer in a non-survival porcine model was technically feasible. The presence of a poloxamer gel at the site of the celiac plexus at necropsy indicates a precise delivery of the neurolytic agent.

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Key words: Celiac plexus neurolysis; Celiac plexus blockade; Endoscopic ultrasound; Polymer

Peer reviewer: Dr. Massimo Raimondo, Division of Gastroenterology and Hepatology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States

Obstein KL, Martins FP, Fernández-Esparrach G, Thompson CC. Endoscopic ultrasound-guided celiac plexus neurolysis using a reverse phase polymer. *World J Gastroenterol* 2010; 16(6): 728-731 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i6/728.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i6.728>

Abstract

AIM: To assess the feasibility of endoscopic ultrasound (EUS)-guided celiac plexus neurolysis (CPN) using a poloxamer.

METHODS: In this prospective evaluation, six Yorkshire pigs underwent EUS-guided CPN. Three received an injection of 10 mL of 0.25% Lidocaine plus methylene blue (group 1) and three received an injection of 10 mL of 0.25% Lidocaine plus blue colored poloxamer (PS137-25) (group 2). Necropsy was performed immediately after the animals were sacrificed. The abdominal and pelvic cavities were examined for the presence of methylene blue and the blue colored poloxamer.

INTRODUCTION

Pancreatic cancer and chronic pancreatitis commonly cause pain that is difficult to control^[1-3]. Opioids are frequently used in an attempt to mitigate pain, however, tolerance, nausea, constipation and other side effects develop^[4,5]. Non-pharmacologic therapies are often employed to improve pain control and quality of life while reducing drug-related side effects. Celiac plexus blockade (CPB) using steroids or celiac plexus neurolysis (CPN) using alco-

hol has been utilized and considered safe. Endoscopic ultrasound (EUS)-guided CPB and CPN have demonstrated safety and efficacy through real-time imaging and anterior access to the celiac plexus from the posterior gastric wall, thereby avoiding complications related to the puncture of spinal nerves, arteries and the diaphragm.

Unfortunately, EUS-guided CPN and CPB provide limited benefit in terms of degree and duration of pain relief^[3]. While benefit duration of EUS CPN diminishes after 8-12 wk, the etiology remains unknown^[6,7]. One theory is that the neurolytic or blockade agent washes away from the celiac plexus injection site due to its liquid free-flowing form and does not remain in the ideal anatomical location. Thus, if a neurolytic or blockade agent could be delivered in an alternate phase (solid or gel), it could offer the potential for enhanced efficacy and safety^[8].

Recently, non-ionic surfactant triblock (ABA) copolymers of polyethylene oxide_a-polypropylene oxide_b-polyethylene oxide_a (PEO_a-PPO_b-PEO_a), also termed as poloxamers, have been widely used in industrial and medical applications^[9-14]. Certain poloxamers have demonstrated rapid reverse phase thermosensitive properties at certain concentrations. Purified poloxamers PS138-25, PS107-20 and PS137-25 (Pluromed Inc., Woburn, MA, USA) are thin liquids at room temperature while at body temperature they are solid gel plugs (Figure 1). Therefore using a neurolytic or blockade agent as an additive in a purified poloxamer will potentially form a solid gel plug at the exact location of injection at the celiac plexus with enhancement of efficacy and safety. This study will assess the feasibility of EUS-guided CPN/CPB using a poloxamer in a non-survival porcine model.

MATERIALS AND METHODS

Six Yorkshire pigs (25-30 kg) were food restricted for 24 h prior to the procedure. Intravenous (iv) Telazol (4.4 mg/kg), Atropine sulfate (0.04 mg/kg) and Xylazine (2.2 mg/kg) were used for anesthesia induction followed by inhaled Isoflurane (1% to 3%) on a semi-closed circuit for anesthesia maintenance after endotracheal intubation.

EUS-guided CPN was then performed using a linear echoendoscope (GF-UC140P, Olympus, Tokyo, Japan). Once the location of the celiac plexus was identified by its position relative to the celiac artery, a 19-gauge needle (Wilson-Cook Medical, Inc., Winston-Salem, NC, USA) was introduced under direct EUS visualization (Figure 2). The needle was flushed with 2 mL normal saline and aspiration was performed to evaluate for vessel penetration prior to additional injections.

Three pigs were randomly assigned to receive a single injection of 10 mL of Lidocaine (0.25%) plus methylene blue (group 1) and three pigs randomly received a single injection of 10 mL of Lidocaine (0.25%) plus blue colored poloxamer PS137-25 (LeGoo-endo™, Pluromed, Inc., Woburn, MA, USA) (group 2). Due to the increased viscosity of the poloxamer, a greater amount of force was required for injection. This was easily overcome with the use of a Controlled Radial Expansion (CRE) balloon dilator inflation hand pump system (Boston

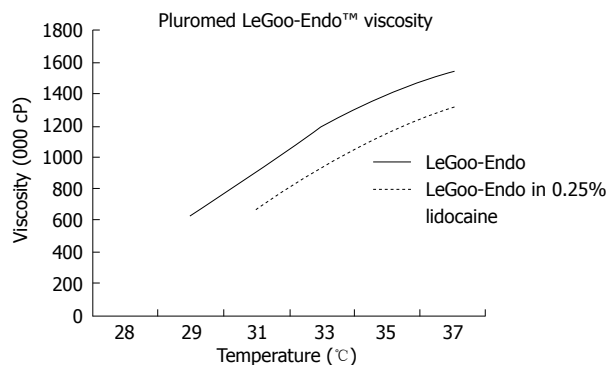


Figure 1 Temperature profile of LeGoo-Endo™ (PS137-25) that transits from liquid to gel at body temperature. The viscosity of LeGoo-Endo™ with Lidocaine is slightly higher than LeGoo-Endo™ at body temperature.



Figure 2 Illustration of endoscopic ultrasound (EUS)-guided celiac plexus neurolysis (CPN). Figure from Arcidiacono PG, Rossi M. Celiac Plexus Neurolysis. *J Pancreas* 2004; 5: 315-321.

Scientific, Natick, MA, USA). During the procedure, the blood pressure, heart rate, temperature, ventilation, and oxygenation status of the pigs were continuously monitored by the professional veterinary team of the Animal Research at Children's Hospital (ARCH) (Boston, MA, USA). The investigators were not blinded to the injection group.

Using Fatal Plus (86 mg/kg), the group 1 pigs were immediately sacrificed after the procedure and the group 2 pigs were sacrificed at 60 min after the procedure. Necropsy was performed immediately upon death of the pigs and close examinations of the peritoneal and retroperitoneal cavities were made. Photographic and video records were obtained. This study was approved by the Animal Research Committee of the ARCH and complied with the National Academy of Sciences Guide for the Care and Use of Laboratory animals.

RESULTS

All the six pigs tolerated the procedure well with no immediate complications. EUS-guided CPN was successfully performed in both groups. An echodense smudge was endosonographically visualized after injection of Lidocaine plus methylene blue and Lidocaine plus blue colored poloxamer PS 137-25 (Figure 3).

At necropsy, methylene blue was identified spread throughout the peritoneal and retroperitoneal cavities in group 1. In group 2, a blue gel plug was identified in the retroperitoneal cavity, adjacent to the aorta, in the exact

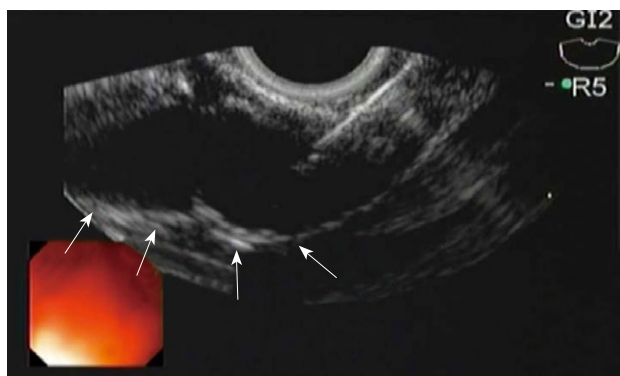


Figure 3 EUS-guided injection of Lidocaine plus blue colored poloxamer PS 137-25. The outer margin of the hypoechoic poloxamer is visualized upon injection into the celiac plexus (arrows).

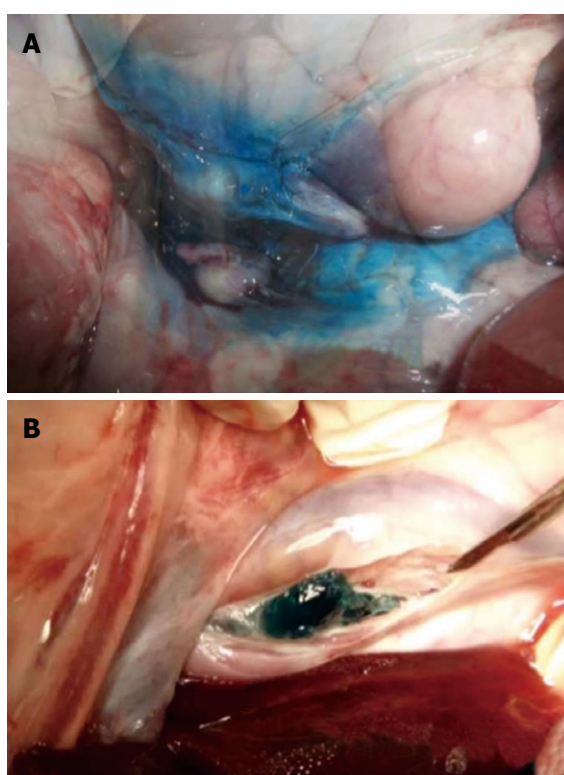


Figure 4 Group 1 (A) and group 2 (B) at necropsy.

location of the celiac plexus without evidence of any blue gel elsewhere in the peritoneal or retroperitoneal cavity (Figure 4).

DISCUSSION

EUS-guided CPN and CPB are safe and effective methods for pain control in patients with pancreatic neoplasms and chronic pancreatitis^[3-6,15-18]. Unfortunately, the degree and duration of therapeutic effect vary. Gress *et al.*^[18] performed EUS-guided CPB in 90 patients with chronic pancreatitis and found that 55% of patients had decreased pain scores at a mean follow-up of 8 wk. This included a reduction in pain medication requirements as reported by the patients in the study. Persistent benefit was found

in 26% of patients at week 12 and in 10% at week 24. Gunaratnam *et al.*^[6] performed EUS-guided CPN in 58 patients with pancreatic cancer, 78% of whom experienced a decline on a continuous 11-point visual analog pain scale 2 wk after the procedure. Only 54% experienced a decline of greater than 2 points after EUS-guided CPN and the efficacy diminished 8-12 wk after the procedure in those not receiving adjuvant therapy. Those authors also found that opioid administration increased throughout the study, however this increase was not statistically significant. Levy *et al.*^[3] administered EUS-guided direct ganglia injection in 33 patients with pancreatic cancer and chronic pancreatitis, 94% and 80% of the patients reported pain relief with alcohol injection at 2-4 wk after the procedure, however long-term follow-up data was not recorded.

In a report in 1996, fluoroscopic evaluation of the abdomen was conducted in patients who underwent EUS-guided CPN. Of those examined, all were noted to have injected material spread in a periaortic distribution with dye spread anterior and lateral to the aorta with extension in both the cranial and caudal direction^[16]. This study supports our findings in group 1 pigs where the injected methylene blue was identified spread throughout the peritoneal and retroperitoneal cavities.

While short-term reduction in pain has been indicated, long-term benefit with this technique is limited. This may be explained by the fact that until recently, the celiac ganglia was unable to be directly visualized, leading to a less precise delivery of therapy^[3,19,20]. Other possibilities include interference with direct visualization due to the echodense smudge and potential alterations in anatomy after injecting one side of the aorta with the therapeutic agent using the double injection technique. Additionally, dispersion of the therapeutic agent away from the desired location may act to influence the efficacy and duration.

The goal of this study was to evaluate the feasibility of EUS-guided CPN using a poloxamer that would potentially remain in the desired target location. This may yield a safer and more durable therapeutic result. In group 2, where the PS137-25 was injected, a gel plug was successfully created at the intended location of the celiac ganglia. The gel maintained the therapeutic agent in the celiac plexus and potentially released the drug slowly over time, thereby optimizing long-term therapeutic results.

A limitation of this study is that it is an acute, non-survival evaluation without long-term follow-up. It is therefore unclear how the injected gel plug interacts with the porcine model over time. Additionally, the study was performed using Lidocaine instead of a steroid or alcohol as it was simpler to integrate into the PS137-25. Steroid or alcohol integration may influence the temperature phase transition point of the poloxamer, however, the formation of a gel at body temperature and liquid at room temperature would remain intact. Lastly, the quantity and rate of drug release from the gel plug was unable to be determined in this current study.

In conclusion, EUS-guided CPN using a reverse phase polymer is feasible in a non-survival porcine model. The formation of a gel plug at the exact location of the celiac ganglia

may avoid dispersion of the injected therapeutic agent and increase the duration of analgesic effect. A survival study is now necessary to determine the duration and breakdown of the gel plug within the body. This would provide useful information on potential complications related to the plugs presence and allow for assessment of the therapy from the gel plug over time. Future studies will also integrate the use of steroids and alcohols into the poloxamer.

COMMENTS

Background

Pancreatic cancer and chronic pancreatitis commonly cause pain that is difficult to control. Nonpharmacologic therapies are often employed to improve pain control and quality of life while reducing drug-related side effects. Endoscopic ultrasound (EUS)-guided celiac plexus blockade (CPB) using steroids or celiac plexus neurolysis (CPN) have demonstrated safety and efficacy. Unfortunately, the neurolytic or blockade agent may wash away from the celiac plexus injection site due to its liquid free-flowing form and does not remain in the ideal anatomical location. Therefore, using a neurolytic or blockade agent as an additive in a reverse thermodynamic phase poloxamer will potentially form a solid gel plug at the exact location of injection at the celiac plexus with enhancement of efficacy and safety.

Research frontiers

Expanded research utilizing reverse phase poloxamers for additional applications in medical practice. Survival studies utilizing reverse phase poloxamers to determine the duration and breakdown of the gel plug within the body. Enhancement of the efficacy and safety of CPB and CPN.

Innovations and breakthroughs

Recently, non-ionic surfactant triblock (ABA) copolymers of polyethylene oxide_n-polypropylene oxide_n-polyethylene oxide_n (PEO_n-PPO_n-PEO_n), also termed as poloxamers, have been widely used in industrial and medical applications. Certain poloxamers have demonstrated rapid reverse phase thermosensitive properties at certain concentrations. Purified poloxamers PS138-25, PS107-20 and PS137-25 (Pluromed Inc., Woburn, MA, USA) are thin liquids at room temperature while at body temperature they are solid gel plugs. Therefore, the novel use of a neurolytic or blockade agent as an additive in a purified poloxamer will potentially form a solid gel plug at the exact location of injection at the celiac plexus.

Applications

EUS-guided CPN using a reverse phase polymer is feasible in a non-survival porcine model. The formation of a gel plug at the exact location of the celiac ganglia may avoid dispersion of the injected therapeutic agent and increase the duration of analgesic effect. A survival study is now necessary to determine the duration and breakdown of the gel plug within the body. Future studies will also integrate the use of steroids and alcohols into the poloxamer.

Terminology

Poloxamer: A non-ionic surfactant triblock (ABA) copolymer of polyethylene oxide_n-polypropylene oxide_n-polyethylene oxide_n (PEO_n-PPO_n-PEO_n). Reverse phase thermosensitivity: When a material or substance is in its liquid phase at cold temperature and in its solid phase at hot temperature.

Peer review

Dr. Thompson *et al* present an animal experience on the use of reverse phase polymer to increase the efficacy of EUS-guided celiac plexus injection for pancreatic pain control. This represent an interesting experiment outlining the possible improvement of the procedure by using a compound which facilitate the retention of the injectate at the local level (celiac plexus).

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