



The first national survey of anesthesia techniques for fetal therapies in Japan

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Abstract

Purpose The aim of this study was to survey the frequency of various anesthetic techniques used in the anesthetic management of both the mother and fetus during fetal therapies in Japan.

Methods We sent a postal survey to the institutions with physicians who held membership of the Japan Society of Fetal Therapy to describe maternal and fetal anesthetic management during fetal therapies performed from January 2016 to March 2017. The therapies included were thoracoamniotic shunting (TAS), intrauterine transfusion (IUT), radiofrequency ablation (RFA), fetoscopic laser photocoagulation (FLP), fetoscopic endotracheal occlusion (FETO), and ex utero intrapartum treatment (EXIT). Survey respondents were asked to specify the standard anesthetic technique used in each of these procedures done during the study period.

Results The most common anesthetic techniques used in each therapy were sedation/analgesia with local anesthesia in TAS (31%), local anesthesia alone in IUT (47%), neuraxial anesthesia in RFA (50%), FLP (66%) and FETO (100%), and general endotracheal anesthesia in EXIT. Fetal analgesia was utilized in 61% of TAS, 33% of IUT, 10% of RFA, 22% of FLP, 100% of FETO, and 50% of EXIT. In all fetal therapies, the most common route of administration for fetal anesthesia was maternal administration.

Conclusion In this first published description of the frequency of various anesthetic techniques used during fetal therapies in Japan, we found that anesthetic techniques varied depending on the degree of invasiveness to the mother and fetus. Fetal anesthesia was not always performed, and the most common route for fetal anesthesia was maternal administration.

Keywords Fetal therapy · Fetal anesthesia · Maternal anesthesia for fetal therapies

Introduction

Currently, a variety of fetal therapies are performed in limited numbers of institutions in Japan. For example, thoracoamniotic shunting (TAS), intrauterine transfusion (IUT), and radiofrequency ablation (RFA) are performed as fetal image-guided surgery (FIGS), and these procedures are covered by national health insurance now. Fetoscopic laser photocoagulation (FLP) and fetoscopic tracheal occlusion (FETO) are performed as fetoscopic surgery in registered

institutions. Fetal surgery with hysterotomy for myelomeningocele repair has not been performed in Japan, but ex utero intrapartum treatment (EXIT), involving hysterotomy during cesarean delivery, has been reported from many institutions mostly for securing fetal airway before cord clamping.

A unique characteristic of anesthesia during fetal therapy is that both the mother and the fetus are the recipients of anesthesia. In performing anesthesia for the mother, the anesthesiologist must consider not only the duration and invasiveness of the procedure, but also the influence of the anesthetic agents on the fetus. The fetus's ability to perceive pain can arise after thalamocortical pathways start to function, which occurs in the third trimester around 29–30 weeks of gestational age [1]. For example, during intrauterine blood transfusion via the fetal intrahepatic vein by direct needling, the middle cerebral artery pulsatility index and fetal plasma concentrations of cortisol and endorphins respond during blood transfusion into the intrahepatic vein to a greater

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degree than during the transfusion into the umbilical vein. These responses are inhibited by fetal intravenous administration of fentanyl [2]. For the fetus, analgesia is needed during potentially noxious stimuli such as TAS and FETO. In addition, fetal immobilization can facilitate the correct completion of the intrauterine procedure.

The effectiveness of each fetal therapy has been reported and reviewed by the Japan Fetal Therapy Group [3–6]. However, there are only a few reports on each method of anesthetic management for fetal therapies in Japan [7–9]. We have no data on the frequency of use of anesthetic procedures such as general anesthesia, neuraxial anesthesia, and local anesthesia during fetal therapies. We likewise lack detailed data about fetal-specific administration of anesthesia. In this study, we sought to provide the first description of the frequency of various anesthetic techniques used in the anesthetic management of both the mother and the fetus during fetal therapies in Japan.

Methods

We sent a postal survey to the institutions with physicians who held membership of the Japan Society of Fetal Therapy. Surveys were posted to each of the ninety-seven institutions of the Society. Survey respondents were asked to specify the type of standard anesthetic techniques used in each of fetal therapies performed from January 2016 to March 2017. If a respondent did not perform a fetal therapy during the period, we asked to specify the current standard anesthetic techniques. The therapies included in the survey were TAS, IUT, RFA, FLP, FETO, and EXIT. We investigated the anesthetic methods, the need of fetal analgesia and/or immobilization, the fetal anesthetic agents used, and the providers of anesthesia for each fetal therapy.

Ethical approval for this survey was obtained from the Saitama Medical Center Clinical Research Ethics Committee (1691) and from the Japan Society of Fetal Therapy. All investigations were conducted in accordance with the Declaration of Helsinki.

Results

Of the 97 institutions included, 57 (59%) responded to the survey. Of these 57 institutions, 36 institutions (63%) had performed at least one kind of fetal therapy. Twenty-three institutions (40%) had performed TAS, 21 (37%) had performed IUT, 14 (25%) had performed EXIT, 10 (18%) had performed RFA, 9 (16%) had performed FLP, and 1 (2%) had performed FETO during the study period.

In the majority of institutions, the anesthesia providers were anesthesiologists (58%), followed by obstetricians

(31%), either anesthesiologist or obstetrician depending on the situation (6%), and unknown (5%).

Anesthetic techniques varied depending on the fetal therapies. When all the techniques for FIGS and fetoscopic surgery were combined, maternal anesthesia methods used included local anesthesia alone (27%), sedation/analgesia (S/A) with local anesthesia (22%), combined spinal epidural anesthesia (CSEA) (20%), general endotracheal anesthesia (GETA) (13%), epidural anesthesia with S/A (8%), epidural anesthesia alone (5%), and spinal anesthesia (5%). Fetal analgesia and immobilization were provided in 39% of the techniques. The routes of administration for the fetus were maternal intravenous or inhalational anesthesia (IV/IH) (80%), maternal IV/IH and fetal intramuscular injection of anesthetic agent(s) (IM) (8%), fetal IM anesthesia alone (4%), maternal IV/IH and umbilical vein injection of anesthetic agent(s) (UV) (4%), and UV anesthesia alone (4%).

The detailed results on each fetal therapy are shown in Table 1 and summarized below.

TAS The most common anesthetic technique was S/A with local anesthesia. Fetal analgesia was utilized in 61% of institutions. The most common route of administration was maternal IV/IH. The fetal analgesia agents used were quite variable. The anesthesia providers in these institutions were anesthesiologists (56%), obstetricians (35%), and either anesthesiologist or obstetrician depending on the situation (9%).

IUT The most common anesthetic technique was local anesthesia alone. Fetal analgesia was utilized in 33% of institutions. The most common route of administration was maternal IV/IH. The fetal analgesia agents used were variable. The anesthesia providers in these institutions were obstetricians (62%), anesthesiologists (24%), either anesthesiologist or obstetrician depending on the situation (5%), and unknown (9%).

RFA Neuraxial anesthesia was used in 50% of institutions. Fetal analgesia was utilized at only one institution, in which remifentanyl was administered via a maternal IV route. The anesthesia providers in these institutions were anesthesiologists (80%), obstetricians (10%), and either anesthesiologist or obstetrician depending on the situation (10%).

FLP The most common anesthetic technique was neuraxial anesthesia. Fetal analgesia was utilized at two institutions (22%). The two institutions used maternal IV route, and the fetal analgesia agents used were either remifentanyl alone or dexmedetomidine and midazolam in combination. The anesthesia providers in these institutions were anesthesiologists (88%), obstetricians (11%), and both (11%).

FETO FETO was performed at only one institution, and anesthesia was provided by anesthesiologists who performed S/A with remifentanyl and CSEA. Fetal analgesia involved maternal intravenous remifentanyl and direct fetal intramuscular administration of fentanyl and rocuronium.

Table 1 Description of the anesthetic techniques and drugs utilized during fetal therapies in Japan

Fetal therapies	FIGS							Fetoscopic surgery				EXIT	
	TAS	n = 23	IUT	n = 21	RFA	n = 10	FLP	n = 9	FETO	n = 1	EXIT	n = 14	
Anesthetic techniques (n, %)	LA + S/A	8 (31)	LA	10 (47)	CSEA	4 (40)	CSEA	3 (33)	CSEA + S/A	1 (100)	GETA + Regional	5 (36)	
	CSEA	5 (19)	LA + S/A	5 (24)	LA	2 (20)	EA + S/A	2 (22)			GETA	5 (36)	
	GETA	4 (15)	CSEA	1 (5)	GETA	2 (20)	SA	1 (11)			CSEA	2 (14)	
	LA	4 (15)	EA	1 (5)	EA + S/A	1 (10)	LA + S/A	1 (11)			Unknown	2 (14)	
	SA	2 (8)	GETA	1 (5)	Unknown	1 (10)	LA	1 (11)					
	EA	2 (8)	Unknown	3 (14)	GETA	1 (11)							
Fetal analgesia (n, %)	Utilized	14 (61)	Utilized	7 (33)	Utilized	1 (10)	Utilized	2 (22)	Utilized	1 (100)	Utilized	7 (50)	
	Not utilized	9 (39)	Not utilized	10 (48)	Not utilized	8 (80)	Not utilized	7 (77)	Not utilized	0	Not utilized	5 (36)	
Routes of fetal analgesia (n, %)	Maternal	12 (86)	Maternal	5 (71)	Maternal	1 (100)	Maternal	2 (100)	Maternal + fetal IM	1 (100)	Maternal	5 (71)	
	Fetal IM	1 (7)	UV	1 (14)							Maternal + fetal IM	2 (29)	
Drugs used for fetal analgesia (n)	Maternal	1 (7)	Maternal + UV	1 (14)									
	Maternal	4	Maternal	Remifentanyl	1	Remifentanyl	1	Maternal			Maternal		
	Diazepam	4	Fentanyl	3	Remifentanyl	1	MDZ + DEX	1	Remifentanyl	1	Sevoflurane	6	
	Fentanyl	3	Diazepam	2			Fetal IM		Fetal IM		Propofol	2	
	Remifentanyl	3	Propofol	1			Fentanyl + rocuronium	1	Fentanyl	1	Fentanyl	2	
	Propofol	2	Sevoflurane	1							Remifentanyl	2	
	Sevoflurane	2	Dexmedetomidine	1							Nitrous oxide	1	
	Pentazocine	1	UV								Fetal IM		
	Dexmedetomidine	1	Vecuronium	1							Fentanyl + muscle Relaxants	1	
	Fetal IM		Midazolam	1							Relaxants		
Fentanyl + Vb	1									Muscle relaxants	1		
Fentanyl + Vb + Atr	1												

FIGS fetal image-guided surgery, EXIT ex utero intrapartum treatment, TAS thoracoamniotic shunting, IUT intrauterine transfusion, RFA radiofrequency ablation, FLP fetoscopic laser photocoagulation, FETO fetoscopic endotracheal occlusion, LA local anesthesia, SA sedation and analgesia, CSEA combined spinal epidural anesthesia, GETA general endotracheal anesthesia, SA subarachnoid anesthesia, EA epidural anesthesia, IM intramuscular, UV umbilical vein, Vb vecuronium bromide, Atr atropine, MDZ midazolam, DEX dexmedetomidine

EXIT The most common anesthetic techniques used were GETA with CSEA or GETA alone. Fetal analgesia was utilized in 50% of institutions, and the main route of administration was maternal IV/IH. The fetal analgesia agents used were variable. The anesthesia providers in these institutions were anesthesiologists (79%), obstetricians (7%), and either anesthesiologist or obstetrician depending on the situation (14%).

Discussion

In our survey, anesthetic techniques varied depending on the type of fetal therapy and the different degrees of invasiveness for the mother and the fetus. We show the operative time, degree of invasiveness, and needs of fetal anesthesia for each fetal therapy in Table 2. For the mother, the degree of invasiveness depends on the size and number of percutaneous instruments inserted (such as needles or fetoscopes) and on the length of the operation. In FIGS, as surgeons use only needles from 22 gauge to 16 gauge in size, local anesthesia alone can be used. In this study, local anesthesia with or without S/A was used in TAS (46%) and in IUT (71%). In previous reports, local anesthesia was most commonly selected for minimally invasive fetal surgery [10, 11]. While local anesthesia has almost no risk to the mother, it cannot provide fetal analgesia and lacks uterine relaxant effect. Local anesthesia can also be used for fetoscopic procedures, but neuraxial anesthesia may be more comfortable for the patient [11–13]. In this study, neuraxial anesthesia was used especially in RFA and fetoscopic surgery. CSEA was most commonly selected during RFA (40%) and fetoscopic surgery (FLP: 33%; FETO: 100%). Neuraxial anesthesia has advantages when multiple insertion sites are required due to effective sensory blockade, thus avoiding larger local

anesthetic dose from multiple local anesthetic injections, as well as providing maternal immobility with motor blockade, and covering lengthy procedures. Disadvantages of neuraxial anesthesia for fetal procedure include maternal risks such as the possibility of a failed block, high spinal block leading hemodynamic instability and respiratory compromise, systemic toxicity from the local anesthetic, and neural injury. Also, neuraxial anesthesia does not provide fetal anesthesia and lacks a uterine relaxant effect. In this study, GETA was used even in some of FIGS and fetoscopic surgeries. GETA can provide anesthesia for both the mother and the fetus and can cause uterine relaxation with inhalational agents. However, for mothers, GETA involves a substantial risk of intubation failure. As EXIT is performed via laparotomy and requires continuous uterine relaxation, it requires GETA and/or neuraxial anesthesia. We found that in EXIT, GETA with or without neuraxial anesthesia was often used (72%).

In this survey, the most common route of administration for fetal analgesia and immobility was via maternal intravenous administration or inhalation. For the fetus, TAS and FETO involve potentially noxious stimulation, and fetal immobilization can facilitate correct shunt placement or enhance ease of tracheoscopy. IUT, RFA, and FLP are procedures performed on the umbilical cord, an acardiac twin, and the placenta, respectively. These procedures do not require direct contact with the fetus, but fetal movement might cause displacement of the needle or laser beam, potentially leading to fetal trauma, bleeding, and other complications. Direct fetal intramuscular administration of fentanyl and muscle relaxant is useful for complete fetal immobilization and analgesia [11–13]. Maternal administration of anesthetic agents is also used for fetal immobilization and analgesia, even if to a lesser degree than direct fetal administration, and in Japan, it is the most common route of administration for fetal anesthesia. Some obstetricians responded that direct fetal

Table 2 Operative time, degree of invasiveness, and fetal anesthesia used in various fetal therapies

	FIGS	Fetoscopic surgery	EXIT
Fetal therapies	TAS, IUT, RFA	FLP, FETO	EXIT
Operative Time	15–60 min	30–90 min	60–120 min
Invasiveness	Single or multiple insertions of 22 gauge to 16 gauge needles (0.7–1.7 mm) into the lower abdomen of the mother	Single insertion into the lower abdomen of the mother 2.5–4 mm	Laparotomy Hysterotomy Continuous uterine atony
Fetal anesthesia	TAS: fetal analgesia and immobilization can be effective IUT: fetal immobilization can be effective RFA: fetal immobilization can be effective	FLP: fetal immobilization can be effective FETO: fetal analgesia and immobilization can be effective	Fetal analgesia may be necessary depending on the degree of invasiveness to the fetus Fetal immobilization can be effective

FIGS fetal image-guided surgery, EXIT ex utero intrapartum treatment, TAS thoracoamniotic shunting, IUT intrauterine transfusion, RFA radiofrequency ablation, FLP fetoscopic laser photocoagulation, FETO fetoscopic endotracheal occlusion

drug administration involved the insertion of a needle into the uterus separate from those needed for fetal therapy itself. Consequently, the insertion of multiple needles may cause uterine contractions or increase the risk of premature rupture of membranes, so they preferred maternal routes of drug administration. In addition, whether fetal immobilization is necessary may depend on the obstetrician's skill, because an experienced obstetrician can complete the procedure in a shorter time. This may be the reason maternal routes of administration with limited degree of fetal immobilization were most commonly used for fetal analgesia or immobilization in Japan, where fetal procedures are offered in limited institutions by experienced practitioners.

The fetal anesthetic agents used were quite varied in our survey. One reason for this could be that there are only a few randomized controlled trials investigating standard fetal anesthetic techniques. Van de Velde et al. showed that maternal intravenous infusion of remifentanyl for fetoscopic procedures was effective to prevent fetal movement and improved operating conditions [11]. In studies from Japan, the combination of maternal administration of fentanyl and diazepam was effective for fetal immobilization and for maternal sedation and analgesia during FLP [8, 9] and TAS [7]. This difference of remifentanyl use may be due to delayed approval of remifentanyl in Japan compared to other countries.

This study provides the first published description of the frequency and methods of various anesthetic techniques used during fetal therapies in Japan. Our work could be useful for planning new studies for safe and effective fetal anesthesia in Japan. However, our study contains several limitations. One is that there are a limited number of institutions where fetal therapy is performed, as the prevalence of fetal diseases requiring surgery is low. Of these institutions that do perform fetal therapy, the response rate in the postal survey we employed was only 59%; however, the responses did include almost all of the main institutions that perform fetal therapy in Japan. Of the 57 institutions that responded, 36 institutions had performed at least one kind of fetal therapy, in which 23 institutions had performed TAS, 10 had performed RFA, 9 had performed FLP and 1 had performed FETO. The Japan Fetal Therapy Group, which is a research group leading clinical research of Japanese fetal therapy, recognizes 11 registered TAS institutions, 6 registered RFA institutions, 9 registered FLP institutions and 1 registered FETO institution as of 2018. Thus, it is likely that the responses to our survey included the majority of the main institutions that perform fetal therapy in Japan.

In conclusion, we found that anesthesia methods varied depending on the degree of invasiveness to the mother and the fetus in this survey. In addition, the survey showed fetal

anesthesia was not always performed, and the most common route of administration for fetal anesthesia was maternal administration in Japan.

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References

1. Lee SJ, Ralston HJ, Drey EA, Partridge JC, Rosen MA. Fetal pain: a systematic multidisciplinary review of the evidence. *JAMA*. 2005;294(8):947–54.
2. Fisk NM, Gitau R, Teixeira JM, Giannakouloupoulos X, Cameron AD, Glover VA. Effect of direct fetal opioid analgesia on fetal hormonal and hemodynamic stress response to intrauterine needling. *Anesthesiology*. 2001;95(4):828–35.
3. Sago H, Hayashi S, Saito M, Hasegawa H, Kawamoto H, Kato N, Nanba Y, Ito Y, Takahashi Y, Murotsuki J, Nakata M, Ishii K, Murakoshi T. The outcome and prognostic factors of twin-twin transfusion syndrome following fetoscopic laser surgery. *Prenat Diagn*. 2010;30(12–13):1185–91.
4. Ishii K, Saito M, Nakata M, Takahashi Y, Hayashi S, Murakoshi T, Murotsuki J, Kawamoto H, Sago H. Ultrasound prognostic factors after laser surgery for twin-twin transfusion syndrome to predict survival at 6 months. *Prenat Diagn*. 2011;31(11):1097–100.
5. Takahashi Y, Kawabata I, Sumie M, Nakata M, Ishii K, Murakoshi T, Katsuragi S, Ikeda T, Saito M, Kawamoto H, Hayashi S, Sago H. Thoracoamniotic shunting for fetal pleural effusions using a double-basket shunt. *Prenat Diagn*. 2012;32(13):1282–7.
6. Wagata M, Murakoshi T, Ishii K, Muromoto J, Sasahara J, Murotsuki J. Radiofrequency ablation with an internally cooled electrode for twin reversed arterial perfusion sequence. *Fetal Diagn Ther*. 2016;40(2):110–5.
7. Ohashi Y, Terui K, Tamura K, Tanaka M, Baba K. Success rate and challenges of fetal anesthesia for ultrasound guided fetal intervention by maternal opioid and benzodiazepine administration. *J Matern Fetal Neonatal Med*. 2013;26(2):158–60.
8. Morimoto Y, Yoshimura M, Orita H, Matayoshi H, Nagamizo D, Sakabe T, Nakata M. Anesthesia management for fetoscopic treatment of twin-to-twin transfusion syndrome (in Japanese). *Masui (Jpn J Anesthesiol)*. 2008;57(6):719–24.
9. Yoshimura M, Murakami Y, Matsumoto Y, Torumi T, Nakata M. Comparison between dexmedetomidine and fentanyl infusion during fetoscopic laser photocoagulation for twin to twin transfusion syndrome (in Japanese). *Masui (Jpn J Anesthesiol)*. 2017;66(3):291–7.
10. Tran KM. Anesthesia for fetal surgery. *Semin Fetal Neonatal Med*. 2010;15(1):40–5.
11. Van de Velde M, De Buck F. Fetal and maternal analgesia/anesthesia for fetal procedures. *Fetal Diagn Ther*. 2012;31(4):201–9.
12. Sviggum HP, Kodali BS. Maternal anesthesia for fetal surgery. *Clin Perinatol*. 2013;40(3):413–27.
13. Lin EE, Tran KM. Anesthesia for fetal surgery. *Semin Pediatr Surg*. 2013;22(1):50–5.

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