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Review Article

Fetal Pain and Fetal Anesthesia Techniques

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Abstract

The 20 or more week after fertilization the fetuses can feel the pain so after these stage all of the invasive procedures requires the fetal anesthesia. Fetal anesthesia can be applied in several ways such as maternal general anesthesia, administration directly to the fetuses by intramuscular or by umblical cord, and intraamniotic approaches. In recent years, fetal anesthesia before the abortion issue is being discussed but there are different views.

Keywords: Fetus; Pain; Anesthesia; Analgesia; Fetal surgery; Abortion

Introduction

Pain is one of the vital functions of the nervous system that generates signals to stimulate our body against a possible tissue damage [1,2]. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [3-6]. Pain is defined as a protection mechanism [2].

Pain consists of two components such as nociception (sensation of the stimulus) and emotional reaction, which is the unpleasant feeling due to a noxious stimulus [7,8].

Nociception is a sensory activity, which is induced by a noxious stimulus. It is the physiological process underlying the sensation of pain. It is a reflex movement in response to a noxious stimulus, without cortical involvement or conscious pain perception [9]. Pain and nociception are not same. Pain is a perception of nociception. All nociceptors mediated stimulus creates pain but all pains do not result from nociception.

Nociception is a process that includes stages as follows: transduction, transmission, modulation and perception, respectively. Transduction is a process of converting noxious stimulus to action potentials. Transmission involves the nerve fibers from the skin to the spinal cord or brainstem and then into the brain. Modulation is the modification of the nociceptive transmission through a number of humoral and neural effects. Perception is the central processing of nociceptive impulses in order to interpret pain. Perception results in a subjective and emotional pain sensation [10].

The structures which are necessary for pain formation and perception can be listed as nociceptors, nerve fibers, noxious stimulation, thalamus and cerebral cortex, respectively. Nociceptors are free nerve endings in the skin and internal organs [11]. In another saying pain receptors are called nociceptors. Nerve fibers are necessary situations for the transmission of signals between damaged tissue and the central nervous system [10]. Noxious stimulation is an actual or potential tissue damaging event. Pain is commonly associated with physical noxious stimuli. This stimulus activates free nerve endings in the skin [10]. Thalamus is a large mass of brain tissue seated deep within the forebrain. It coordinates sensory information and communicates messages from other parts of the brain to the cortex [10]. Cerebral cortex is the sheet of neural tissue overlaying the cerebrum or forebrain and it plays a key role in attention, memory, language, and perceptual awareness. An intact cortical system is necessary for pain experience [12,13].

Pain Formation in Fetuses

Anatomic and physiological neural connections and cognitive, sensory, affective components are necessary for pain experience. But limited neural system of fetuses suggesting that the fetuses cannot feel pain but many studies showed that fetuses feel pain [14,15].

Transduction in fetus

Nociceptors first appear at 10 weeks in the skin and at 13 weeks in the internal organs in early fetal life and mature over the next 6–8 weeks. But at this stage, these structures are not sufficient for the experience of pain. The electrical activity required which is conducted from the receptors into the spinal cord and to the brain [11]. These are present all over the body by the 20th week [16].

Transmission in fetus

In fetuses, pain transmission is possible from 16 weeks gestation and completely developed from 26 weeks gestation [3]. But at this stage, it is not sufficient to support pain awareness. For this conduction, nerve fibers must reach to either spinal cord or brainstem from the skin firstly, then after to the brain:

Connections between damaged tissue and the spinal cord and brainstem: Postmortem studies showed that nerve fibers grow into the fetal spinal cord from 8 weeks [11]. During the first 8 weeks of pregnancy, fetal spontaneous movements are present. But these movements cannot be termed reflex movements because when sensory nerves have reached the skin, mechanical stimulation of the body can produce reflex movements [11]. The first motor reflexive head movements appear about 7.5 weeks into gestation, hands become sensitive about 10.5 weeks into gestation and at 14 weeks the legs began to show reflex movements and these reactions are called spinal cord reflexes [17-20]. This shows that the information is carried to spinal cord, and as the development of cerebral cortex is much later, these reflex movements are far from the fetal awareness. At this stage, the nervous system is not fully mature [21,22].

Connections between damaged tissue and cortical regions of the brain: Transmission of the sensory information to the thalamus,

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the major sub cortical sensory nucleus and then to cortex, is essential for perception or awareness.

At 18th week, information about tissue damage reaches the midbrain. For the pain awareness, a complete track between the skin, spinal cord, and brain is required [11].

Evolution of Necessary Anatomical Structures for Pain

Pain pathways from the periphery to the thalamus (Spinothalamic pathways)

The development of pain pathways in the fetal nervous system begins early. The synapses with sensory neurons begin at 6 weeks gestation [23,24]. The development of the connection between afferent fibers and peripheral receptors starts at 8 weeks gestation [23]. The afferent system development starts from the 13th week of pregnancy [23]. The myelination starts in the human spinal cord at 12 weeks of gestational age [25], and in the telencephalon around 14 week of gestational age [26]. Spinothalamic connections start to develop from 14 weeks and are complete at 20 weeks gestation [27].

The suplate zon

It is a transient layer of fetal cerebral wall which was develops by 13 weeks of gestation and disappears after 32-34 weeks [28,29,31]. But individual subplate-like neurons remain until adulthood [30]. This structure is the main synaptic or neuronal connection zone in the fetal cortex [32]. It is a site of spontaneous electrical activity [33], organization of cortical connections, to process the thalamocortical information [34-36] and to contribute to the early and transient cortical neuronal circuits involved in the generation of fetal behavior [37]. The projections from the thalamus to the subplate zone reaches between 12 and 18 weeks [29,38,39] and wait for the overlying cortical plate to mature [40].

The most of the development of subplate zone completed at 28 weeks gestation and after this stage subplate fibers starts to enter into the cortical plate so the cortical plate volume increased by 50% [28]. After 30 weeks' the cortical plate matures but the subplate disappears [29,31,41].

Thalamocortical fibers

Talamus is the main source of sensory input to the cortex [21,22]. Thalamocortical connections are present from 17 weeks gestation and completely developed at 26- 30 weeks gestation [27].

The cortex

Cortical processes occur only after thalamocortical connections and pathways have been completed at the 26th gestational week. The migration takes place from the early phases of brain development and it peaks between the third and fifth month of gestation [42,43].

The settling of the neurons in the cortex layers occurs in an inside-out order and fetal neocortex has a full complement of cells by 20 weeks [37].

Fetal Brain

The fetal brain is profoundly immature and its surface layer, the cerebral cortex, is smooth, with no indication of the folds and no cellular connections with the thalamus at 8 weeks [44]. The external surface of the brain is about 1 mm thick and consists of an inner and outer layer with no cortical plate [38]. At 13 weeks, a furrow or groove appears on each side of the brain, which becomes part of the insular cortex around 15 weeks, a key region involved in the experience of external stimuli, including pain [44]. In spite of this, the fetal brain is still largely smooth at 26 weeks. Massive growth of the brain after 34 weeks rapidly results in the characteristic folds and surface features of the more mature brain [37].

Modulation and perception in fetus

This step occurs in neonates and infants.

In conclusion; important neurobiological developments occur at 7, 18, and 26 weeks' gestation and are the proposed periods for when a fetus can feel pain. The developmental changes during these periods are remarkable but insufficient for pain experience. The sub cortical mechanisms, stress responses, mature thalamocortical pathways and other cortical activations are necessary for pain experience. Most authors declared that the cortex is required for pain perception, and it is known that neuronal connections between peripheral nervous system and the cortex are established in 26th week of gestation, which is suggestive of that fetus cannot feel pain before this time.

Fetal Anesthesia Techniques

The invasive diagnostic or therapeutic procedures and open surgeries are required in the practice of fetal medicine. In these situations, the procedure will be associated with a stress response in the fetus and the need for analgesia.

The available anesthetic agents which are commonly used to reduce pain and discomfort include halogenated agents, opioids and benzodiazepines. Essentially, the mode of administration and drug of choice depend on the type of intervention planned.

The anesthetic techniques which are use for fetal surgery includes; maternal general anesthesia, regional anesthesia, and administration of medications for placental transfer to the fetus. The fetal anesthesia provides to inhibit fetal movement during a procedure [46], to achieve uterine atony for facilitate the surgical procedure [20,47-50], to prevent possible adverse effects on long-term neurodevelopment and behavioral responses to pain [53-55], respectively.

We know that the fetus can feel pain after the 26 weeks of gestation so after this time fetal anesthesia is essential for invasive surgical procedures.

Fetal anesthesia and analgesia can perform in various intrauterine invasive therapeutic or diagnostic situations such as blood transfusions, shunt installation, laser coagulation of vascular anastomoses in twin to twin syndromes, endotracheal occlusion for congenital diaphragmatic hernia, surgery for conditions such as urinary tract obstruction, hydrothorax, cystic adenomatous malformation, sacrococcygeal teratomas [56,57]. Otherwise, some authors advised that to perform analgesia during late termination of pregnancy [57].

There are several ways to administer analgesics to the fetus including transplacentally [57], directly to the fetus (intravenous, intramuscular, intracardiac application) [58,59] and intraamniotic administration [57].

Transplacentally Administration (After Maternal Oral or Parenteral Administration)

It is known that when a woman is under general anaesthesia, the fetus is also anaesthetised. When to administering opiates such as morphine, fentanyl and benzodiazepines to the woman intravenously or via epidural, these agents cross the placenta and it causes changes in fetal heart rate and neonatal respiratory depression [60]. Similarly, inhaled volatile anaesthetic gases can cross the placenta. It should be considered that the fetuses are more sensitive to the effects of anaesthetic agents [15].

Directly to the Fetus

One of the way of administer opioids to the fetus into the umbilical cord or by intramuscular injection [57,63]. Some researchers recommend to administer 20μg/kg of intramuscular fentanyl to the fetus prior to the procedure [64,65] while others, recommend the administration to the mother of a continuous infusion rate of remifentanil 0.1μg kg−1min−1, to achieve fetal immobilization and maternal sedation, though they do not exclude to directly administer analgesics to the fetus.

In the literature Fisk et al. showed that the effects of analgesics administered directly to human fetuses during minimally invasive procedures [61]. They showed that intramuscular administration of 10μg/ kg of fentanyl to the fetus, blunts fetal stress response to intrauterine needling at 20–35 weeks of age; the magnitude of fetal β-endorphin and cortisol response to pain after these doses of fentanyl is halved, and the cerebral doppler response was ablated. This is an indirect sign of a certain form of pain that would be antagonized by opioid administration [61]. Fentanyl significantly attenuates the endorphin and cerebrovascular response, but not the cortisol response [61]. Even in preterm babies the same dose of intravenous fentanyl ablated most of the stress responses to surgery, with the exception of cortisol response, and is considered sufficient for analgesia [52].

Intra-amniotic Approach

Intra-amniotic injection is technically simpler than direct fetal injection. In these techniques the drugs can be absorbed from fetal membranes and skin [62]. Strümper et al. recently suggested that the intra-amniotic administration of analgesics might provide a simple and effective means of reassuring good and prolonged fetal analgesia [62].

Open Fetal Surgery

Fetal conditions treated with this approach include congenital diaphragmatic hernia and spina bifida. Open fetal surgeries require a maternal laparotomy with transverse incision. Then the fetus is exposed, but only the necessary anatomy is delivered via the hysterotomy. So these procedures requires significant uterine relaxation. After the surgery warmed Ringer's lactate is infused to restore amniotic volume. Antibiotics are also instilled into the amniotic fluid. The flap of the omentum is sewn over the uterine closure to prevent amniotic fluid leakage. Maternal general anesthesia is often used in open surgery. The advantages of maternal general anesthesia can be listed as to provide adequate fetal anesthesia and produce uterine relaxation which was essential for easier fetal manipulation and successful surgery. Desflurane because of its low solubility allows for rapid emergence from deep anesthesia can be used. Intravenous nitroglycerin can also be used to augment uterine relaxation. Direct fetal administration of fentanyl and pancuronium is reserved for cases where the fetus moves during the procedure [63]. During open surgery procedure an arterial catheter is placed because small changes in maternal blood pressure may have dramatic effects on fetal perfusion, heart rate and function [63]. The risk of fetal distress caused by placental separation, cord compression, maternal hypotension, hypoxia or anemia should be considered in this procedure. In open cases, emergency medications such as atropine and epinephrine are given by intravenously or even intracardiac [66].

Minimally Invasive Procedures

Minimally invasive interventions are the most frequently performed fetal surgical procedures include blood transfusions, shunt installation, laser coagulation of vascular anastomoses in twin to twin syndromes, endotracheal occlusion for congenital diaphragmatic hernia, surgery for conditions such as urinary tract obstruction, hydrothorax, cystic adenomatous malformation, sacrococcygeal teratomas [56,57]. In this technique, the uterine cavity is accessed percutaneously with needles and small sheaths. Ultrasound or fetoscopes which are inserted through the sheets used for visualization. The anesthesia options for this procedure are maternal anesthesia or administer opioids directly to the fetus [57,63]. Immobilization of the fetus is essential for the procedure and multiple regimens have been used successfully, including combinations of opioids and other sedatives such as benzodiazepines or propofol [46]. In Van de Velde M. et al study, they compared diazepam and remifentanil and they showed that the remifentanil group had significantly less fetal movement [67].

Pain Relief before Abortion

It is known that fetus cannot feel pain before 26 week of gestation, fetal anesthesia requirements for abortions before these week is controversial and should not be recommended [9]. But conversely some authors concluded that in the context of abortion, fetal analgesia would be used solely for beneficence toward the fetus, assuming fetal pain exists [9]. But it is known that general anesthesia increases abortion morbidity and mortality for women and substantially increases the cost of abortion. For surgical termination in the United Kingdom, general anaesthesia is usually administered for dilatation and this will result in transfer of anaesthetic agents to the fetus [11].

Avoiding a discussion of fetal pain with women requesting abortions is not misguided paternalism but a sound policy based on good evidence that fetuses cannot experience pain [68].

Conclusion

The 20 or more week after fertilization the fetuses can feel the pain so after these stage all of the invasive procedures requires the fetal anesthesia. Fetal anesthesia for abortions before these week is not recommended.

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