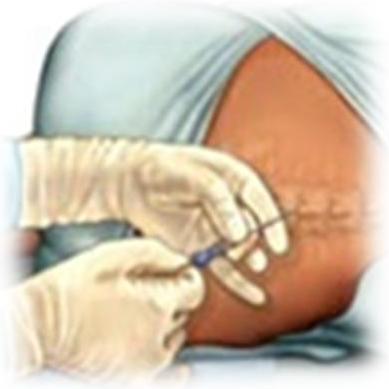
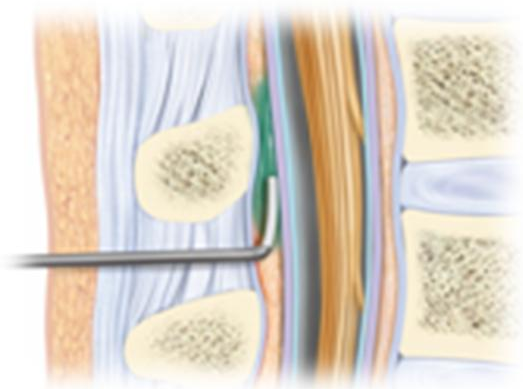
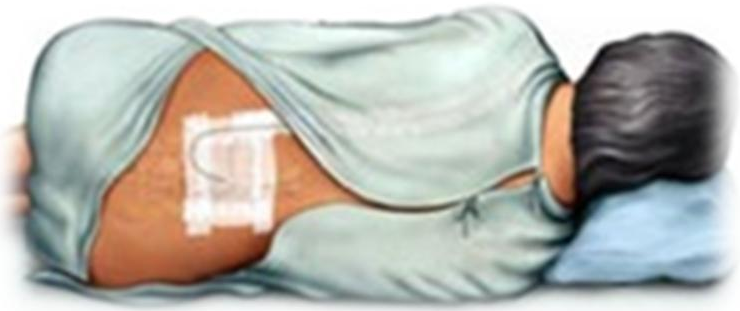
ISSN 2329-5856

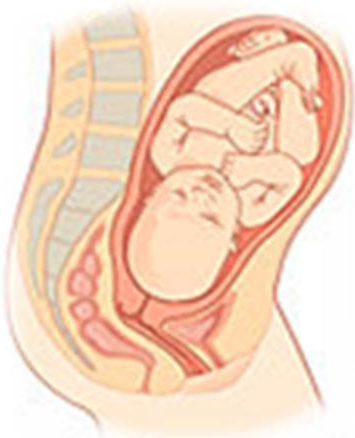
Science INSIGHTS®

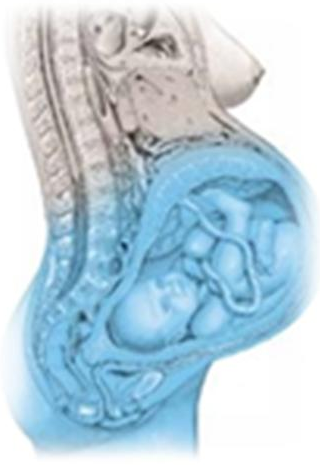
12 APRIL 2014, VOLUME 7, NO 2











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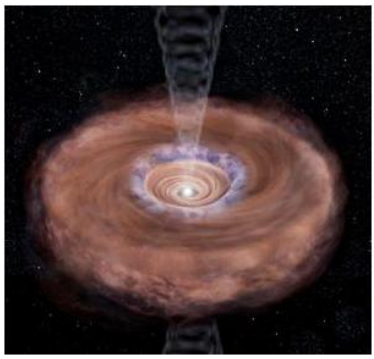
NEWS



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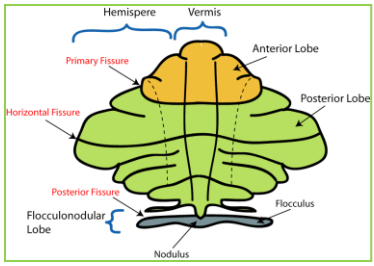
EDITOR'S CHOICE



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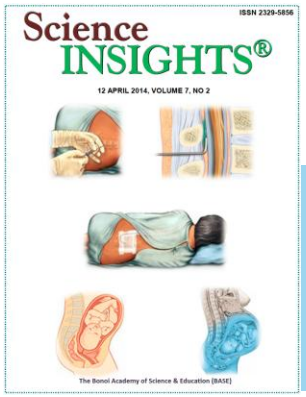
PICTURE STATION

ARTICLE



COVER
Epidural analgesia should be avoided in controlling labor pain at the cervix below 10.0mm due to its influence on the progress of labor resulting in high rate of Cesarean. Maternal characteristics are additional aspects need to be concerned during epidural labor control in nulliparous women. See page 153.

Image: BASE illustrating group

ISSN: 2329-5856

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ISSN: 2329-5856 www.bonoi.org

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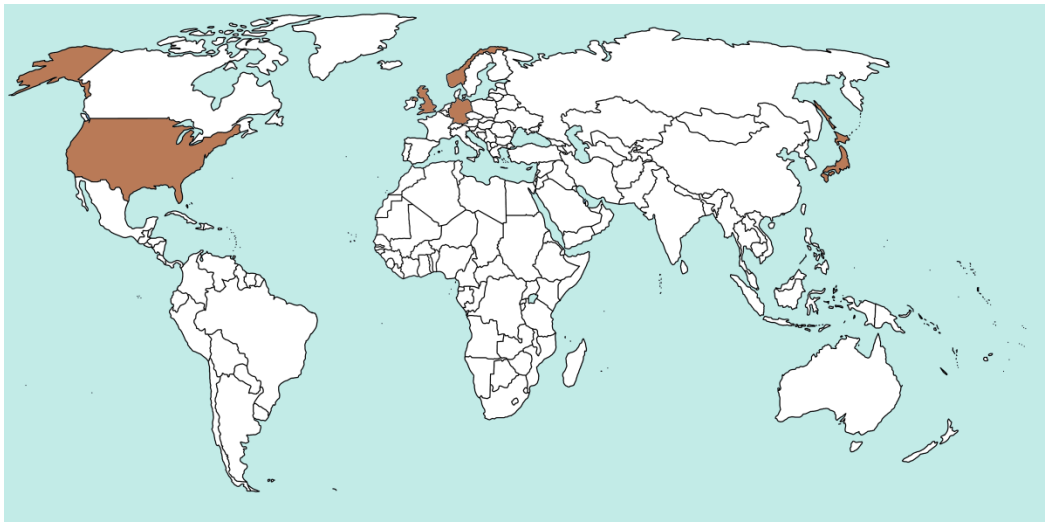
London, UK
Earliest Human Footprints Found in Britain

We human being is looking for the originality of us from some so-called clues of fossils. Is the reality? Recently unearthed footprints left by ancient humans 800,000 years ago have been found in Britain, the earliest evidence of such markings outside Africa. Researchers discovered the footprints, which were left by both adults and children, in ancient estuary mud at Happisburgh in Norfolk, eastern England. The only older footprints found so far are at Laetoli in Tanzania, at about 3.5 million years old, and at Ileret and Koobi Fora in Kenya at about 1.5 million years. The discovery came at an archaeological site that has yielded several previous discoveries of stone tools and fossil bones, including mammoth remains. The researchers found the prints at low tide when waves washed away much of the beach sand to explose the silt below. The group of early humans that left the footprints appeared to have consisted of at least one male and several smaller people believed to be females and youngsters, the researchers said. Analysis of the prints found that they were from a "range of adult and juvenile foot sizes" equating to modern shoe sizes of up to British 7 or 8 (US 8 or 9, European 41 or 42). The researchers estimated that the height of the ancient humans who left the prints varied from about 0.9 meters to over 1.7 meters (2 ft 11 in to 5 ft 6 in), not far off the height of modern humans. They were dated at 800,000 years old partly on the basis of the site's geological position beneath glacial deposits, but also because the fossils there come from now-extinct types of mammoth and horse and early forms of vole that were alive at that time. But the question of exactly what type of ancient humans left their footprints in the sands of time remains a mystery. They may have been related to people of a similar period in history found in Atapuerca in Spain, assigned to the species Homo antecessor, or Pioneer Man. Homo antecessor apparently became extinct in Europe 600,000 years ago and was perhaps replaced by the species Homo heidelbergensis, followed by the Neanderthals from about 400,000 years ago, and eventually modern humans some 40,000 years ago.■



Washington DC, USA
"Turning Point" in Fusion Energy Quest

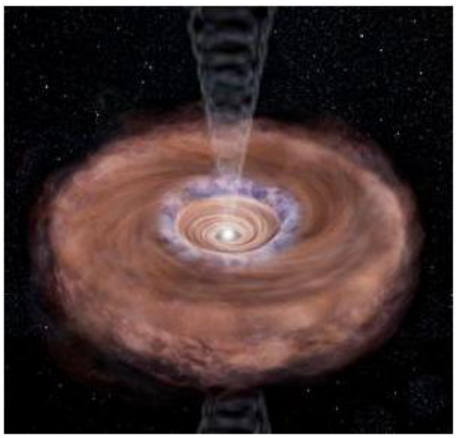
We must face the energy crisis, but we are striving to seek new solution. U.S. scientists announced an important milestone in the costly, decades-old quest to develop fusion energy, which, if harnessed successfully, promises a nearly inexhaustible energy source for future generations. For the first time, experiments have produced more energy from fusion reactions than the amount of energy put into the fusion fuel, scientists at the federally funded Lawrence Livermore National Laboratory in California said. The researchers, led by physicist Omar Hurricane, described the achievement as important but said much more work is needed before fusion can become a viable energy source. They noted that did not produce self-heating nuclear fusion, known as ignition that would be needed for any fusion power plant. Researchers have faced daunting scientific and engineering challenges in trying to develop nuclear fusion - the process that powers stars including our sun - for use by humankind. "Really for the first time anywhere, we've gotten more energy out of this fuel than was put into the fuel. And that's quite unique. And that's kind of a major turning point, in a lot of our minds,"

Hurricane told reporters. "I think a lot of people are jazzed." Unlike fossil fuels or the fission process in nuclear power plants, fusion offers the prospect of abundant energy without pollution, radioactive waste or greenhouse gases. Unlike the current nuclear fission energy that is derived from splitting atoms, fusion energy is produced by fusing atoms together. Experts believe it still will be many years or decades before fusion can become a practical energy source. "I wish I could put a date on it," said Hurricane. "But it really is (just) research. And, you know, although we're doing pretty good, we'd be lying to you if we told you a date." Of the uncertain path ahead in fusion research, Hurricane compared it to "climbing half way up a mountain, but the top of the mountain is hidden in clouds. You cannot see it. You don't have a map". The research was conducted at the laboratory's National Ignition Facility (NIF), which was completed in 2009. The scientists used 192 laser beams to zap a tiny target containing a capsule less than a tenth of an inch (about 2 mm) in diameter filled with fusion fuel, consisting of plasma of deuterium and tritium, which are two isotopes, or forms, of hydrogen. The fuel was coated on the inside of the capsule in a frozen layer less than the width of a human hair. At very high temperatures, the nucleus of the deuterium and the nucleus of the tritium fuse, a neutron and something known as an "alpha particle" emerge, and energy is released. The experiments, published in the journal Nature, created conditions up to three times the density of the sun. In two experiments described by the researchers that took place in September and November of last year, more energy came out of the fusion fuel than was deposited into it, but it was still less than the total amount deposited into the target. The deuterium-tritium implosions were more stable than previously achieved. The researchers did so by doubling the laser power earlier in the laser pulse than in earlier tries. The fusion-energy yield was increased by about tenfold from past experiments, in a series that started last May. One of the experiments produced more than half of the so-called Lawson criteria needed to reach ignition - but only about one-100th of the energy needed for ignition. Lawrence Livermore National Laboratory, located about 45 miles (70 km) east of San Francisco, is overseen by the National Nuclear Security Administration, an agency of the U.S. Department of Energy. Eager to exploit the potential this type of energy offers to reduce dependence on oil and other fossil fuels, the United States and other nations have invested many millions of dollars into fusion research, often with uneven results. There are two main approaches. This team focuses on what's known as inertial confinement fusion energy - using lasers to compress fuel pellets, which triggers fusion reactions. Other labs like the Culham Centre for Fusion Energy, which is the British national laboratory for fusion research, and the Princeton Plasma Physics Laboratory in New Jersey focus on magnetic confinement fusion energy - putting plasma in a magnetic container and heating it up until nuclei fuse. Steve Cowley, director of the Culham Centre, called new findings "truly excellent" but said different measures of success make it hard to compare with his type of research. "We have waited 60 years to get close to controlled fusion, and we are now close in both magnetic and inertial confinement research. We must keep at it," Cowley said in a statement. Mark Herrmann, a fusion researcher at Sandia National Laboratories in New Mexico which is also overseen by the U.S. National Nuclear Security Administration, called the new findings important, but sees a "very long road to assessing the viability of fusion as a long-term energy source". "I believe a compact carbon-free energy source is very important for humankind in the long term," he said by email. "Fusion is one bet. If it pays off, the return will be big."■

Tokyo, JAPAN

Strange Star Chemistry May Reveal Secrets of Planetary Disks

A dusty gas cloud around a young sun-like star is surprising astronomers with its strange chemistry, suggesting that such planet-forming disks may be more complicated than previously thought. An international team of scientists used the giant ALMA radio telescope in Chile's Atacama Desert to detect significant chemical changes in the star's dust cloud along a region known as the centrifugal barrier, where the pull of gravity no longer overcomes the centrifugal force rotating the gas. "Spectral lines of these minor [chemical] species are faint, because of their low abundances," lead scientist Nami Sakai of the University of Tokyo told Space.com in an email. Sakai led the team of scientists that studied the young star and its gas cloud about 450 light-years from Earth. "But we were able to observe them, thanks to the high sensitivity of ALMA, and succeeded in discovering the drastic chemical change at the centrifugal barrier. No such exploration has been done before." Gravity draws clouds of gas in space together to form new stars at their center. The gas left behind after the stellar birth continues to rotate around the new star, forming a disk that is further surrounded by an envelope of gas. Using the changing chemistry that exists at the border, the team could precisely mark the boundary of the two. Scientists can probe these regions by studying the spectral lines emitted by sim



ple molecules such as carbon monoxide. As technology has improved, other simple gases have been observed within such clouds, and the completion of ALMA and its high sensitivity and spatial resolution is expected to result in even more molecules, such as the cyclic-cyclopropenylidene (C3H2) and sulfur monoxide (SO) detected by Sakai's team. Cyclic-C3H2 has been detected in a variety of regions of space, where it plays a key role in producing other hydrocarbons, but the highly-reactive molecule can only be found on laboratories on Earth. It survives in environments like interstellar clouds because the density and temperatures are lower than those of Earth. Sakai had previously studied the young star, which is located in the Taurus molecular cloud. The dense cloud is about 450 light-years from the sun, making it the closest large star-forming region to Earth. Her team had previously found rich carbon-chain molecules, and was eager to use ALMA to explore their origin and fate. The rotation that helped birth the young star continues after its formation. Gravity pulls the gas toward the star, but distance limits its reach. At the centrifugal barrier, the force of rotation outweighs the force of gravity, and the star can longer fall inward. Gas containing cyclic-C3H2 piles up at the outer edge of the barrier, increasing the density. Temperatures of the jammed up gas spike suddenly from minus 243 degrees Celsius (minus 405 degrees Fahrenheit) to temperatures of minus 213 C (minus 351 F) or higher. The heat increase allowed the particles of SO to jump directly from the solid to gas phase in a process known as sublimation. The complex chemicals only exist outside of the barrier; inside, both would be frozen out on dust grains, causing their spectral lines to disappear and marking the boundary between the disk and the envelope.■

Santa Monica, USA

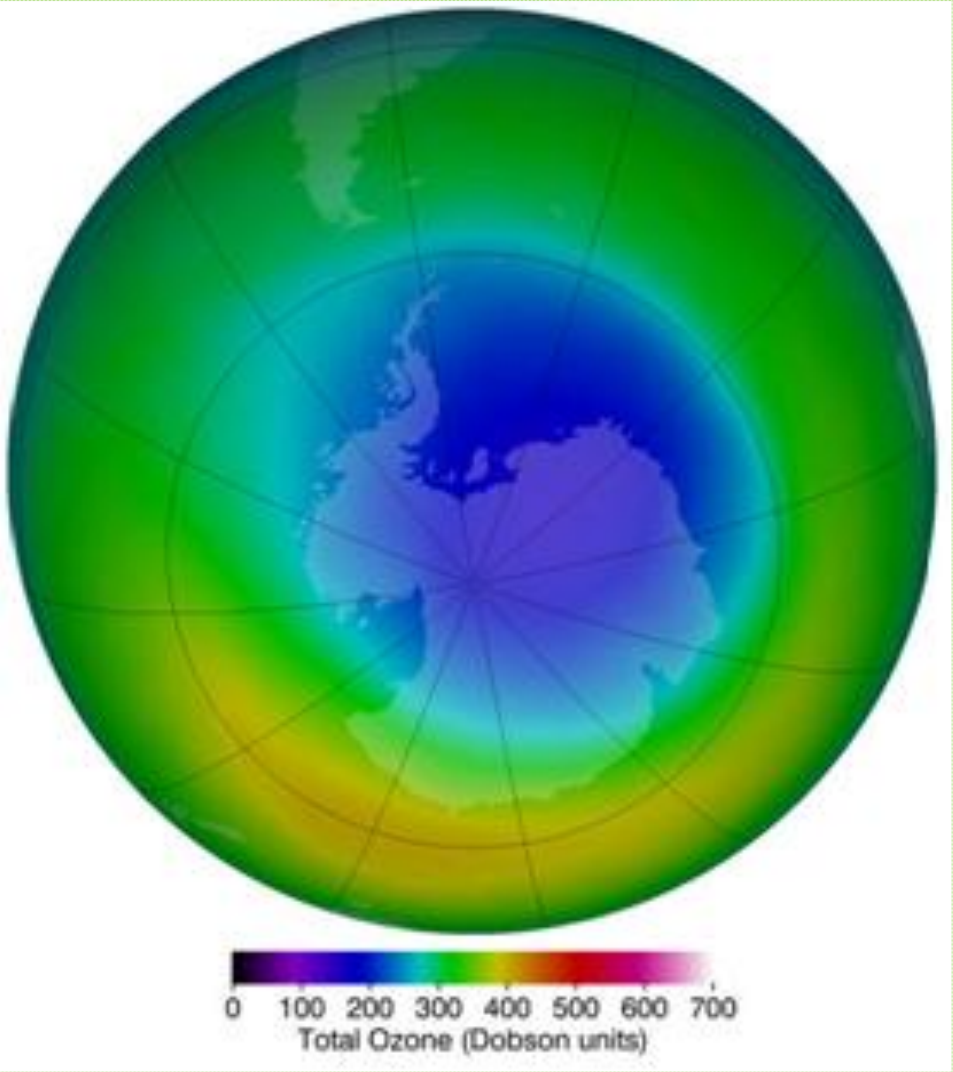
Lymph Node Test a Good Strategy for Melanoma: Study

We fight diseases and seeking novel therapeutics using modern science. Testing a key lymph node in patients with the most dangerous form of skin cancer is the best approach to determine if the cancer has spread, new late-stage clinical research indicates. The test could significantly improve survival among those whose affected lymph nodes are then removed. Culminating nearly two decades of international research, the study provides the first long-term evidence affirming the value of a procedure known as "sentinel node biopsy" for intermediate and thick melanoma lesions, the study authors said. The study compared melanoma patients during a 10-year period. Among people with intermediate-thickness lesions, those whose lymph nodes were removed after their sentinel node biopsy tested positive for cancer were 44 % more likely to survive their melanoma, said study author Dr. Mark Faries. The other "watchful waiting" group of patients didn't have their nodes removed until the disease was later found to have spread. According to the American Cancer Society, lymph nodes are small structures that work as filters for harmful substances in the body. They contain immune cells that can help fight infection by attacking and destroying germs in lymph fluid. Melanoma is diagnosed in about 120,000 Americans each year and kills about 9,000 annually, according to the Skin Cancer Foundation. The strongest risk factor for the disease is intense, periodic exposure to ultraviolet light from sunshine or tanning beds, but other risk factors include fair skin and family history. Initiated in 1994, the study randomly assigned about 2,000 patients with melanoma to two groups. The observation group had their lesion removed and their lymph nodes observed for recurrence, at which time they were removed. The biopsy group underwent lesion removal and a sentinel node biopsy, with immediate lymph node removal for patients whose cancer had spread to the sentinel node. In melanoma, a sentinel node biopsy removes the lymph node nearest a lesion and tests it for evidence of cancer. If the sentinel node is unaffected, the cancer is highly unlikely to have spread to surrounding lymph nodes or distant sites in the body. The biopsy procedure is also used in other malignancies, particularly breast cancer. In the new study's biopsy group, sentinel node results were the most important predictor for 10-year survival of melanoma among patients with lesions considered intermediate or thick. Disease-free survival rates over 10 years were significantly better in the biopsy group among patients with intermediate melanoma (about 71 % compared with 65 %) and thick melanoma (nearly 51 % versus about 41 %). Among patients whose cancer spread to the lymph nodes from an intermediate-thickness melanoma, biopsy yielded better 10-year disease-free survival to distant organs as well as better overall survival from melanoma. Removing all lymph nodes from an area of the body can trigger painful, chronic tissue swelling known as lymphedema. But this risk for melanoma patients can be supported by the survival-rate improvements documented in the new study.■

Oslo, NORWAY

Four New Gases That Harm Ozone Layer Found

We have only one earth, and we need take care of it. Scientists have detected four new man-made gases that damage the Earth's protective ozone layer, despite bans on almost all production of similar gases under a 1987 treaty. The experts were trying to pinpoint industrial sources of tiny traces of the new gases, perhaps used in making pesticides or refrigerants that were found in Greenland's ice and in air samples in Tasmania, Australia. The ozone layer shields the planet from damaging ultra-violet rays,



which can cause skin cancer and eye cataracts, and has been recovering after a phase-out of damaging chemicals under the U.N.'s 1987 Montreal Protocol. In total, the scientists estimated more than 74,000 metric tons of the four had been released to the atmosphere. None was present before the 1960s in Greenland's ice cores, according to the study in the journal Nature Geoscience. That is only a small fraction of the million metric tons of CFCs (chlorofluorocarbon) produced every year at a 1980s peak, according to the team of scientists in Britain, Germany, Australia, France, the Netherlands and Switzerland. HCFCs (hydrochlorofluorocarbon) have often been used to replace more damaging CFCs. One of the newly discovered CFCs was worrying since concentrations were rising fast. Such emission increases had not been spotted for other CFCs since the 1990s. The gases were detected earlier in Greenland than Tasmania, indicating they were produced in the northern hemisphere and then blown south. Research planes, taking air samples around the world, may be able to find the sources. Four new man-made, ozone-destroying chemicals have been discovered in the upper atmosphere, and appear to be slowing the recovery of the ozone hole, according to a new report. The ozone hole over Antarctica has been gradually healing ever since an international treaty known as the Montreal Protocol began limiting the production of ozone-depleting chemicals in 1989. These chemicals, known as chlorofluorocarbons (CFCs), were commonly used in refrigerators, air conditioners and aerosols until they were found to react with and break down ozone molecules in the Earth's protective ozone layer. The treaty was created to significantly cut CFC emissions and allow the ozone hole to completely close, potentially by 2050. In 2010, a total ban on CFCs was put in place, but certain loopholes still exist in the Montreal Protocol that allow trace amounts of the chemicals to be used in the production of certain products, including some types of insecticides and solvents used to clean electronic equipment. Now, researchers based at the University of East Anglia in the United Kingdom have calculated that these loopholes - previously thought to be relatively insignificant - have actually allowed more than 74,000 metric tons (about 82,000 tons) of three previously unknown CFCs, and one related compound known as an HCFC, to be released into the atmosphere. While this quantity is far smaller than peak CFC emissions in the 1980s, it is still a significant quantity that could slow the recovery of the ozone hole.■

Potsdam, GERMANY
Why West Africa Did Not Follow South America

South America nearly carried off Northwest Africa when the world's last supercontinent fell apart 130 million years ago. Now, a new model helps explain why the Sahara settled east of the Atlantic instead of sailing off with South America – it's all about the angles. Back before the Atlantic Ocean formed, Africa and South America nestled together in a massive supercontinent called Gondwana. When this landmass started to split, gashes in Earth's crust called rifts opened up along pre-existing weaknesses. One of these gashes, called the West Africa Rift System, started to tear apart the future Sahara desert. Two more rifts formed along the future boundaries of South America and Africa. Imagine three rift zones, two lined up essentially north-south and one pointing east-west. These alignments are key to explaining why the continents broke apart the way they did, according to a study published March 6 in the journal Geology. The planet's plate tectonic forces could more easily pull apart the

two continents at the east-west–oriented rift than at the north-south–oriented rift in the Sahara desert, the researchers found. "The direction in which the continents break apart heavily influences the success of the rift system," said study co-author Sascha Brune, a geophysicist at GFZ Potsdam in Germany. "Because the rift system was at a very low angle to the extension direction, this rift won out in the end," he told Live Science's Our Amazing Planet. At that time, South America was heading westward. "Plates are pulled apart by large-scale geological forces that come from the plate boundary or the mantle, but for the rift, it's not important where these forces come from," Brune said. "If you pull more in the direction of the rift, you need two times less force to get the rift going." The mantle is the hotter layer of rock beneath Earth's crust. The crust often breaks apart at three-pronged junctions, such as the triple rift that formed between Africa-South America, and it's not uncommon for one rift to fail to develop. The model developed by Brune and his co-authors suggests that the angle between the rift and the plate tectonic forces plays an important role in determining which rifts will fail.■

New York, USA
How Pterosaurs Ruled the Skies Above the Dinosaurs

Before birds really took off, the skies of prehistoric Earth belonged to the pterosaurs. These winged reptiles soared around the planet during the time of their relatives, the dinosaurs. Pterosaurs first appear in the fossil record about 220 million years ago, making them the first vertebrates, or animals with backbones, to evolve the ability to fly on their own power. These creatures also rank as the largest flying animals, ever. Fossils suggest the biggest pterosaur, *Quetzalcoatlus northropi*, had a wingspan stretching about 33 feet (10 meters), longer than that of a small airplane. Of course, not all were giants. Of the more than 150 known species, some attained birdlike sizes, along the lines of sparrows or seagulls. With size comes weight. Michael Habib, who studies biomechanics at the University of Southern California, has calculated that one particular group of pterosaurs may have weighed more than 661 pounds (300 kilograms), a weight they managed to consistently foist into the air and keep aloft. "Flapping flight is one of the more challenging things you can do," Habib said during a panel discussion for a preview of a new pterosaur exhibition here at the American Museum of Natural History. In addition to displaying real pterosaur fossils, including one German specimen known as the Dark Wing, the exhibition includes a motion-sensor-based demonstration where visitors can virtually 'pilot' two species of pterosaurs. Insects were the first organisms to take to the air using their own power. Among vertebrates, or animals with a backbone, pterosaurs, birds and bats each independently evolved the ability to fly by flapping wings derived from forelimbs. Each of these animals devised different means to accomplish the same lofty feat. "One of the advantages of the pterosaur body plan in terms of flying animals are you can get bigger," Habib told Live Science. So, not surprisingly, pterosaurs massively outgrew bats and birds. (Among living birds, the wandering albatross has the largest wingspan, measuring up to about 11 feet, or 3.4 m.) Three anatomical requirements set the stage for large size in flying animals: wing anatomy that generates a large amount of lift per unit speed, hollow bones with a high ratio of stiffness to weight, and the muscle power to launch into the air, Habib said. "Bats have the right launch system, but they don't have pneumatic [air-filled] bones. Birds have pneumatized bones, but they don't have the right launch system, and they don't have as high a lift coefficient [for their] wings," Habib said. "Pterosaurs are the only ones by happenstance that ended up with those three things." The flying reptiles could also walk on all fours, and they most likely

leaped into the air for takeoff, Habib said. An exhibition panel at the museum demonstrates how bats, birds and pterosaurs created wings from the same bones humans have in their arms, hands and fingers. But among pterosaurs, a considerable portion of the wingspan comes from a long fourth finger, which corresponds to the human ring finger. Birds took to the skies during pterosaurs' reign, but they were a little behind the reptiles, said exhibition curator Mark Norell, chair of the museum's paleontology department. Bats, which are mammals, evolved more recently; the earliest known fossil of an insect-eating bat dates back about 50 million years.■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EVOLUTION AND GENETICS

Skin, Hair, and Eye Pigmentation in Europeans

Natural selection determines our specific traits. Yes, we believe so from the scientific point. Pigmentation is a particularly conspicuous human phenotypic variation. Eye, hair, and skin pigmentation are highly variable in humans, particularly in western Eurasian populations. What are the underlying determinants for these different types' colors in our body? A new study led by Dr. Mark G. Thomas from the University College London, UK reported their findings on this phenomenon in the journal of *Proceedings of the National Academy of Sciences of the United States of America*, and revealed that three key genes known to be involved in human pigmentation pathways - *HERC2*, *SLC45A2*, and *TYR* - using allele frequency estimates from Eneolithic, Bronze Age, and modern Eastern European samples and forward simulations. Neutrality was overwhelmingly rejected for all alleles studied, with point estimates of selection ranging from around 2–10 percent per generation. Our results provide direct evidence that strong selection favoring lighter skin, hair, and eye pigmentation has been operating in European populations over the last 5,000 y. As the authors summarized that a combination of selective pressures associated with living in northern latitudes, the adoption of an agriculturalist diet, and assortative mating may sufficiently explain the observed change from a darker phenotype during the Eneolithic/Early Bronze age to a generally lighter one in modern Eastern Europeans, although other selective factors cannot be discounted. The selection coefficients inferred directly from serially sampled data at these pigmentation loci range from 2 to 10% and are among the strongest signals of recent selection in humans.■

PNAS 2014;111:4832

ECONOMIC PSYCHOLOGY

Behavioral Dynamics of Tax Evasion

The yearly-round taxes report just completed. For this, what should we do and what do we need to do? What kind of behaviors we have upon it? Let us have a look on the newly released report on the behavioral dynamics of tax evasion, but not compliance. This survey was conducted by Dr, Aloys Prinz from University of Münster, Germany, and colleague Dr. Michael Pickhardt (deceased) from Brandenburg University of Technology Cottbus, Germany, reported that Although personal traits of taxpayers are more or less unchangeable, personal and social norms as well as rationalizations can be influenced by interactions with others. For instance, if tax evasion becomes a widely spread phenomenon, it will be difficult to enforce tax laws. This means that interactions between taxpayers, taxpayers and tax authorities as well as taxpayers and tax practitioners are crucial for the dynamics of personal attitudes, norms and rationalizations. As the authors summarized that surveying the recent literature with respect to these interaction dynamics revealed a multiplicity of approaches from (i) economic theory to psychological research to (ii) empirical and experimental results and, finally, to (iii) agent-based modeling by methods from economics and econophysics. The multiplicity of approaches is not incidental. The reason is that it is rather difficult to shed light on such a complex phenomena like tax evasion and compliance. The approaches are found to be complementary, although they compete among each other for relevance. However, from the viewpoint of tax enforcement policy the most import lessons to be learned from recent research are as follows: (a) Tax enforcement by considering all taxpayers as potential tax cheaters and, hence, employing mainly instruments to deter tax evasion by audits and punishment, seems no longer adequate since it might decrease voluntary tax compliance. The reason is that many citizens pay their share of the public good without force. This source of compliance might be eroded if these citizens are treated as potential tax evaders. (b) Although a certain number of audits and punishment is required to deter tax fraud, measures to encourage people to pay taxes voluntarily are needed. To this end, simpler tax codes, more service-oriented tax authorities and a kinder attitude of tax authorities to taxpayers seem very

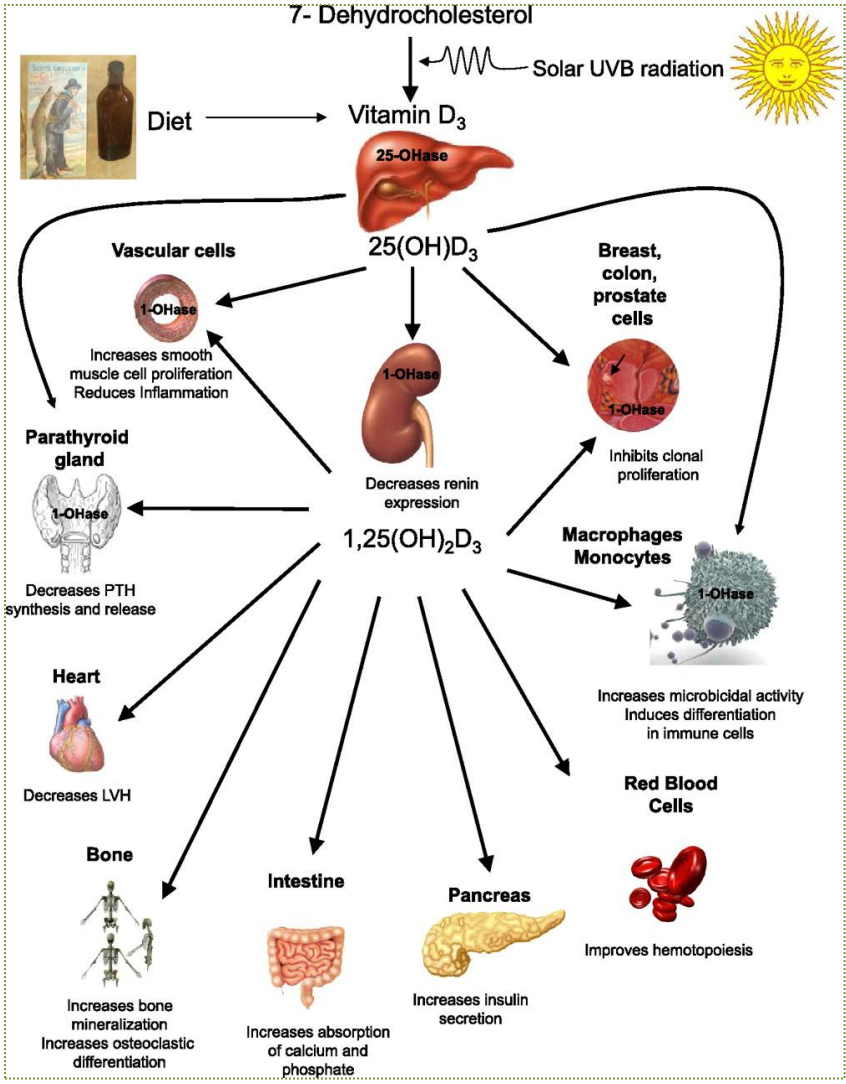
helpful. Trust is the main ingredient for cooperative tax behavior. (c) If tax authorities distrust people, taxpayers seem to mirror this attitude and start to distrust tax authorities, too. In such a climate, voluntary tax compliance will suffer. To restore it is a difficult and perhaps expensive business.■

J Econ Psychol 2014; 40:1

HEALTH AND MEDICINE

Vitamin D and Multiple Health Outcomes

Does vitamin D only is beneficial for our health? Multiple studies gave different results on this issue. In an umbrella review study led by Dr. Evropi Theodoratou from University of Edinburgh, UK, reported their findings that although vitamin D has been extensively studied in relation to a range of outcomes and some indications exist that low plasma vitamin D concentrations might be linked to several diseases, firm universal conclusions about its benefits cannot be drawn. Observational studies have identified links with several diseases, but these have either not been evaluated or not been replicated in randomized controlled trials. Randomized controlled trials for autoimmune and cancer related outcomes are clearly lacking. In addition, earlier evidence from randomized controlled trials that vitamin D supplementation (with or without calcium) increases bone mineral density and reduces the risk of fractures in older people is not seen in clinical trials that examine vitamin D only supplementation. On the basis of the results of this review, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions. In their study, the authors analyzed 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomized controlled trials of vitamin D supplementation were identified. The relation between vitamin D and 137 outcomes has been explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. Ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomized controlled trials, but the direction of the effect and level of statistical significance was concordant only for birth weight (maternal vitamin D status or supplementation). On the basis of the available evidence, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic



kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions. In contrast to previous reports, evidence does not support the argument that vitamin D only supplementation increases bone mineral density or reduces the risk of fractures or falls in older people. As concluded that despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.■

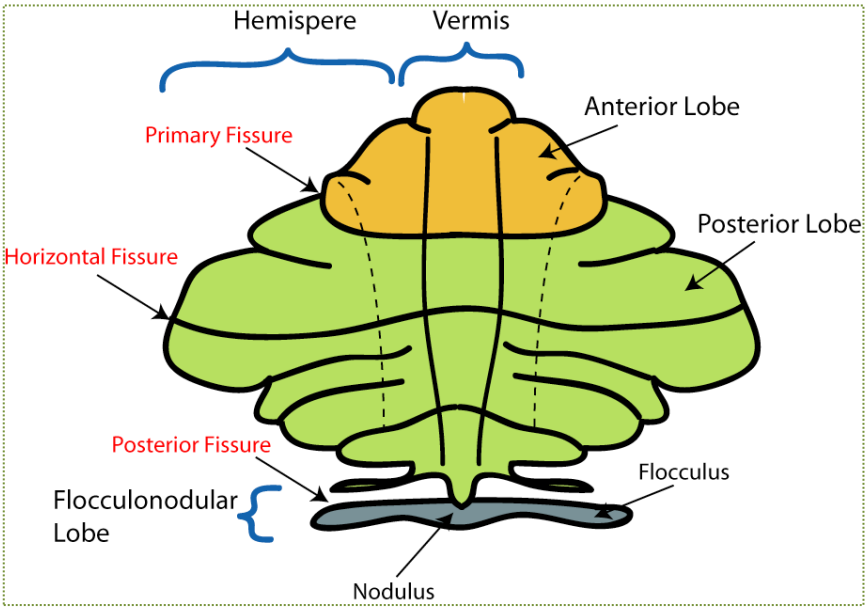
BMJ 2014;348:g2035

NEUROSCIENCE

α2-Adrenergic Regulation of Noradrenergic Synaptic Facilitation at Cerebellar GABAergic Synapses

Adrenergic system in the central nervous system plays its role by combining with other types of neurotransmitters in facilitating or inhibiting the synaptic function. A new study headed by Dr. M. Hirono from RIKEN Brain Science Institute, Japan, reported that noradrenaline (NA) acts as a neurotrophic factor that strengthens GABAergic synaptic transmission in the developing cerebellar cortex and that α2-ARs temporally restrain the noradrenergic facilitation of sIPSCs after GABAergic synaptogenesis. In their study, the authors investigated the effects of α2-AR activation by NA on cerebellar GABAergic synaptic transmission that is accompanied by the activation of other AR subtypes, α1- and β-ARs. They developmentally examined the roles of α2-AR activation in the noradrenergic facilitation of sIPSCs in cerebellar PCs. Until the second postnatal week, when substantial inhibitory effects of α2-ARs are absent, NA potentiated sIPSCs and maintained the increased sIPSC frequency, suggesting that NA causes long-lasting facilitation of GABAergic synaptic transmission through α1- and β-AR activation. After the second postnatal week, NA transiently increased the sIPSC frequency, whereas blocking α2-ARs sustained the noradrenergic sIPSC facilitation and increase in the firing rate of MLIs, suggesting that α2-AR activation suppresses the noradrenergic facilitation of GABAergic synaptic transmission. The simultaneous activation of α1- and β-ARs by their specific agonists mimicked the persistent facilitation of sIPSC frequency, which required extracellular signal-regulated kinase 1/2 activation.■

Neuroscience 2014; 256:242




Who feeds us?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Stop wasting foods

Milky Way Galaxy

By Erwin Matys and Karoline Mrazek

Milky Way Galaxy: Green airglow shimmers atop translucent clouds as the Milky Way rises over a remote island off the northwest coast of Africa in a majestic photo recently sent to Space.com. Erwin Matys and Karoline Mrazek captured this spectacular image on June 6, 2013 from the southern part of La Palma Island, Canary Islands. They took the image as part of Project Nightflight, an astrophotography project aimed at "capturing the beauty of the night sky." “Just after we finished our shots the whole sky was suddenly covered with thick clouds and all the magic was gone,” Matys told Space.com via email. The foreground features the characteristic volcanic landscape of the Canary Islands. The faint lights are from neighboring islands, La Gomera toward the left and El Hierro. Tiny top-lights from a small wind park on the shore give off the fait red glow visible in the foreground. The photographers digitally combined two exposures of four minutes, one for the Milky Way (tracked), the second for the landscape (untracked). They used a 16mm fisheye lens at f/5.6 on an EOS 350D body with an ISO setting of 1600.


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Impact of Epidural Analgesia at Different Cervical Dilation on the Rate of Cesarean Delivery

Shiqin Xu, Fuzhou Wang, Yusheng Liu, Shanwu Feng, Qingsong Zhao, Xirong Guo, Rong Shen, Hongmei Yuan, Ru Liu, Hua Tong, Xiaoqi Gu, Dongying Fu, Qinfen Pan, Xiaofeng Shen

Science Insights 2014; 7(2):153-166
Science Insights is published by The Bonoi Academy of Science & Education, Chapel Hill, NC 27510, USA

ISSN: 2329-5856

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Impact of Epidural Analgesia at Different Cervical Dilation on the Rate of Cesarean Delivery

Shiqin Xu,[*,1] Fuzhou Wang,[*,†,1] Yusheng Liu,[*,1] Shanwu Feng,[*,1] Qingsong Zhao,[*,‡] Xirong Guo,[¶] Rong Shen,[§] Hongmei Yuan,[*] Ru Liu,[‖,¦] Hua Tong,[§] Xiaoqi Gu,[¶] Dongying Fu,[**] Qinfen Pan,[**] Xiaofeng Shen[*,Δ]

BACKGROUND: Epidural analgesia is the optimal means in controlling labor pain, whereas the correlation between epidural analgesia at different cervix dilation and corresponding risk of operative delivery remains unclear.

OBJECTIVE: The aim of this study was to investigate the association between the epidural analgesia at different cervix and the rate of Cesarean in nulliparous women.

METHODS: This is a perspective controlled trial conducted in a University affiliated tertiary women's health care hospital. After approval by the Institutional Ethical Committee, 780 nulliparous women who underwent spontaneous vaginal delivery at term requesting labor analgesia were screened and 596 of them were assigned into interventions. Subjects were allocated into one of four groups received epidural analgesia initiated at different cervical dilation, i.e. from the onset of painful uterine contraction to the cervix 50.0 mm or greater. The primary outcome was the rate of Cesarean delivery. Others included maternal and neonatal outcomes due to epidural analgesia and drug delivery.

RESULTS: Five hundred and thirty three subjects completed the study. Significant difference in the rate of Cesarean delivery was observed amongst the four groups (98.9% at cervix ≤ 10.0mm, 30.2% at cervix 11.0 – 30.0mm, 24.2% at cervix 31.0 – 50.0mm and 18.1% at cervix ≥ 51.0mm, $P < 0.0001$). The major reason led to high Cesarean rate at cervix ≤ 10.0 mm was poor labor progression (75.2%). No significant differences were expressed in variables of non-reassuring fetal status.

CONCLUSIONS: Epidural analgesia should be avoided in controlling labor pain at the cervix below 10.0mm due to its influence on the progress of labor resulting in high rate of Cesarean. Maternal characteristics are additional aspects need to be concerned during epidural labor control in nulliparous women.

TRIAL REGISTRATION: Epidural Analgesia in Different Cervix Diameter and the Rate of Cesarean Delivery (EACDRCD). ClinicalTrials.gov ID, NCT00677274. http://clinicaltrials.gov/ct2/show/NCT00677274.■

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Submitted: 15 November 2013
Revised: 12 February 2014
Accepted: 28 February 2014

SCIENCE INSIGHTS 2014; 7(2):153-166.

How to Cite This Paper: Xu S, Wang F, Liu Y, Feng S, Zhao Q, Guo X, Shen R, Yuan H, Liu R, Tong H, Gu X, Fu D, Pan Q, Shen X. Impact of epidural analgesia at different cervical dilation on the rate of Cesarean delivery. Science Insights 2014;7(2):153-166.

Keywords: Epidural analgesia – Labor pain – Cesarean – Cervix

WHILE different people hold different point on how women might cope with the pain from labor, the fundamental is that they should be treated individually. In North America and West Europe (1-4), as well as in China (5-8), epidural analgesia (EA) hitherto is the only available consistently effective technique of pain relief during labor and delivery, and is a preferable method because it can provide more effective pain control compared with non-epidural pharmacological analgesia. However, the timing of EA is a controversial issue. Prior to 2002, clinical guidelines and practitioners considered that the administration of EA in nulliparous women should be delayed until the cervical dilatation reaches at least 4.0 to 5.0 cm and that other forms of analgesia should be used until that time (9). In 2005, Wong and colleagues published a high-level evidenced paper clarified that pain relief early in labor with neuraxial analgesia at the cervix dilated ~2.0 cm does not increase the risk of Cesarean delivery (10), and following this is the change in guideline recommendation on EA in labor pain control (11).

The current available evidence, in nulliparous women at term with singleton fetus in vertex presentation, supports that EA is safe in "laboring" women with cervix dilated 2 cm or more (10). Our previous findings showed that epidural analgesia at the cervix of 1.0 cm or more is safe for nulliparous women without oxytocin induction (12). In further, systematic reviews on this topic suggest to better define dystocia and non-reassuring fetal status (NRFS) diagnoses by precise and repeatable criteria (13-15). The National Institute for Health and Clinical Excellence (NICE) guidelines (16, 17) suggest that "women in labor who desire regional analgesia should not be denied it, including women in severe pain in the latent first stage of labor – a period of time begins from painful contractions and some cervical change including cervical effacement and dilatation up to 4 cm".

When parturients at the cervix below 2.0 cm request EA, generally, the obstetric care should be integrated with regular and effective uterine contractions, cervical effacement (%) and rupture of membranes (ROM) timing, and with a favorable cervix evaluated with Bishop Score for an induction or augmentation of labor. Nevertheless, ample evidence from both randomized controlled trials (RCT) and well-designed observational studies suggest pregnant women with induced labor are at higher risk for Cesarean delivery, of which predominantly related to an unfavorable Bishop Score at admission (18-20). Under such circumstances, an interdisciplinary team approach and quality assessment is required for successful delivery care. A national wide survey in the United States unraveled that large differences exist in obstetricians' approach to medical decision making with similar patient, and disclosed a real risk for nonevidence-based practice (21). Therefore, written evidence-based protocols are crucial for improving obstetric care outcomes.

Therefore, abundant evidence suggested that early placement of EA at the cervical dilation of 1.0 cm or more does not increase the risk of Cesarean delivery, but whether the EA performed at cervix below 1.0 cm could increase the risk of Cesarean or not is yet to be verified, and no study hitherto systematically investigate the influence of EA at different cervix on the rate of operative deliveries. The present study was designed to clarify the relationship between patient-controlled epidural analgesia (PCEA) administered at different cervical dilation from the onset of labor to the cervix 5.0 cm or greater and the rate of Cesarean delivery in nulliparous women.

Materials and Methods

After approval by the Institutional Ethics Examining Committee of Human Research, 780 nulliparous women who underwent vaginal delivery at term requesting labor analgesia at daytime (from 08:00 AM to 16:00 PM) were screened for eligibility after admission to the labor and delivery unit. A total of 596 subjects met the criteria were assigned to this single-blind and controlled study. All these participants signed an informed consent before initiation of analgesia. Given the potential restriction of cervical dilation, analgesia request and grouping assignment, this study did not do randomization in subjects' enrollment.

A full explanation was given about the technique of epidural puncture and catheterization, the narcotics and local anesthetics used in this study and the linear Visual Analog Scale (VAS) of pain and satisfaction with analgesia. The data were collected from the subjects admitted to the University affiliated tertiary teaching hospital from May to September 2008. Hospital teaching status was ascertained from the Council of Teaching Hospitals of Chinese Medical Colleges.

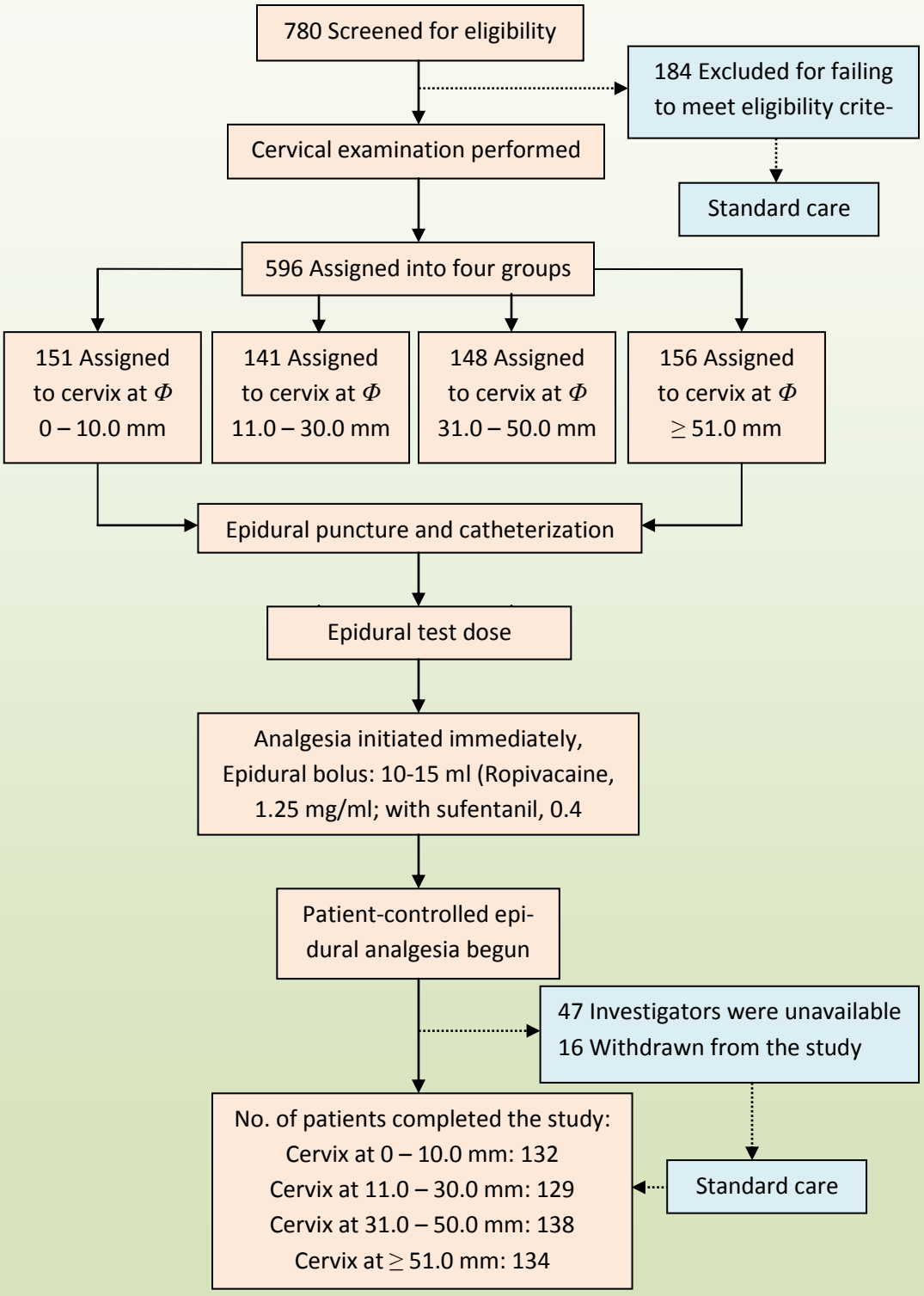
Parturients were excluded from the analysis if any of the following criteria were met: a) Allergy to opioids, a history of the use of centrally-acting drugs of any sort, chronic pain and psychiatric diseases records; b) Participants younger than 18 years or older than 45 years; c) Those who were not willing to or could not finish the whole study at any time; d) Parturients with spinal abnormalities, bleeding tendency, infection and anxiety to epidural puncture were not enrolled; e) Alcohol addictive or narcotinum dependent patients were excluded for their influence on the analgesic efficacy of the epidural analgesics; f) Subjects with a nonvertex presentation; g) Diagnosed diabetes mellitus and pregnancy-induced hypertension; h) Twin gestation.

Once subjects were eligible for inclusion, all demographic and clinical data were recorded including age at delivery, weight, height, gestational age of fetus, current status of smoking, VAS rating of pain intensity and vital signs before analgesia, and whether spontaneous rupture of the membrane > 12 h before oxytocin infusion (see Appendix 1).

Subjects did not request analgesia or excluded from the study were treated with standard obstetric care procedures according to clinical indications by guideline recommendations (see Appendix 2) (16). The analgesia option was based on individual request and systemic or epidural technique was available to them.

Face Box

Figure 1. Study Flowchart of the Analgesia Intervention.



Nulliparous women who underwent vaginal delivery at term requesting labor analgesia were screened for eligibility after admission to the labor and delivery unit. The technique of epidural puncture and catheterization was performed. The test dose of 3.0 ml lidocaine 1.5% (45mg) plus epinephrine 5 μg/ml was given. After delivering test dose, an epidural bolus of analgesic mixture 10-15ml of ropivacaine 0.125% with sufentanil, 0.4 μg/ml, followed by patient-controlled analgesic (PCA) pump with a 5 ml patient-controlled bolus without background infusion, a lockout interval of 15 min and hourly limit 30ml. 184 subjects were screened out from the trial, and the major reasons for exclusion were presented in the result part of the text.

Table 1. Baseline characteristics of the subjects.*

Characteristic	Cervical Dilation (mm)				
	0 – 10.0 (n=151)	11.0 – 30.0 (n=141)	31.0 – 50.0 (n=148)	≥ 51.0 (n=156)	P Value
Age at delivery – yr	25.5 ± 3.2	25.0 ± 5.6	24.9 ± 4.7	26.1 ± 5.2	0.97
Weight – kg	74 ± 11	77 ± 17	69 ± 10	75 ± 16	0.91
Height – cm	163 ± 5	159 ± 9	164 ± 11	161 ± 6	0.88
Gestational age of fetus – week					0.85
Median	39	38	40	39	
Interquartile interval	38 – 41	37 – 40	37 – 41	37 – 40	
Current smoker – n (%)	22 (14.6)	24 (17.0)	17 (11.5)	19 (12.2)	0.51
Spontaneous ROM > 12 h before oxytocin infusion – n (%)	31 (20.5)	36 (25.5)	28 (18.9)	24 (15.4)	0.18
Use of oxytocin prior to analgesia – n (%)	23 (15.2)	27 (19.1)	17 (11.5)	22 (14.1)	0.33
Reasons for oxytocin					
Induction of labor after prelabor ROM – n (%)	14 (60.9)	18 (66.7)	11 (64.7)	15 (68.2)	0.96
Augmentation of labor – n (%)	7 (30.4)	5 (18.5)	4 (23.5)	4 (18.2)	0.72
Maternal request – n (%)	2 (8.7)	4 (14.8)	2 (11.8)	3 (13.6)	0.92
Pain ratings before analgesia with VAS†					0.17
Median	63	85	87	88	
Interquartile interval	52 – 77	67 – 90	70 – 93	75 – 97	
Vital signs prior to analgesia					
Blood pressure					
Systolic pressure – mmHg	116 ± 13	120 ± 13	109 ± 12	113 ± 13	0.76
Diastolic pressure – mmHg	65 ± 7	68 ± 8	62 ± 7	73 ± 9	0.41
Heart rate – beats per minute	72 ± 10	71 ± 5	77 ± 8	68 ± 9	0.62
Respiratory rate – breaths per minute	22 ± 7	19 ± 8	23 ± 5	19 ± 7	0.84
Oral temperature – ℃	37.3 ± 0.1	36.9 ± 0.4	36.8 ± 0.2	37.0 ± 0.2	0.16

* Plus-minus values indicate the means ± standard deviation (SD). P values were calculated with ANOVA or the Chi-square test, as appropriate.
† The Visual Analog Scale (VAS) ratings of pain intensity is a 100-point linear gauge in which 0 = no pain, 100 = worst pain imaginable.
ROM: rupture of membranes.

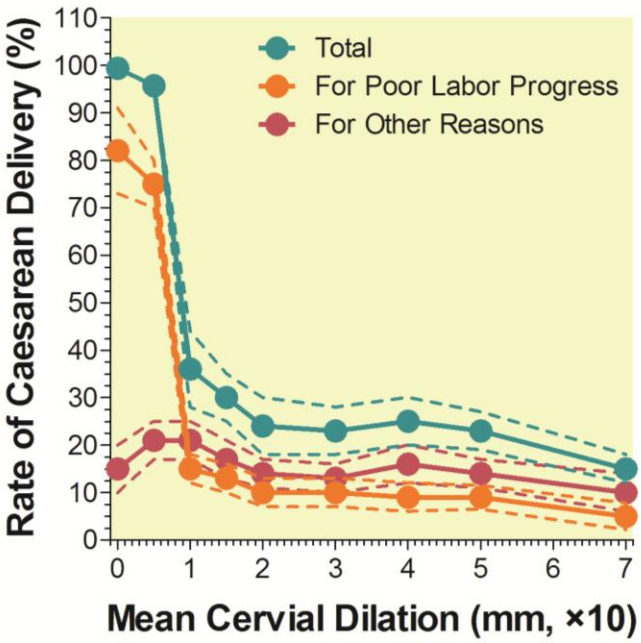
Even the standard epidural analgesia can be used, yet it was performed by non-study-members, and the corresponding data were not included in analysis.

In our study, we adapted following definitions according to the National Institute for Health and Clinical Excellence (NICE) guidelines on intrapartum care (16): 1) first stage of labor, this consists of latent and active phases in temporal sequence. Latent phase of labor refers to a period of time begins from painful contractions and some cervical change including cervical effacement and dilatation up to 4 cm, and active phase of labor refers to that there are regular painful contractions and progressive cervical dilatation from 4 cm to fully dilated; 2) second stage of labor, this period begins when the cervix becomes fully dilated (~10.0 cm) and ends with the complete birth of the infant (22).

All condition-matching subjects underwent cervical examination and then were assigned into one of four groups: group 1 (at cervix 0-10.0 mm), group 2 (at cervix 11.0-30.0 mm), group 3 (at cervix 31.0-50.0 mm) and group 4 (at cervix ≥ 51.0 mm). Parturients and healthcare providers who did not involve in this trial as study members were kept from group allocation. Study investigators were opened to group assignment, data collection and results analyses. The technique of epidural puncture and catheterization was performed to all participants. The test dose of 3.0 ml lidocaine 1.5% (45 mg) plus epinephrine 5 μg/ml was given to patients. After delivering test dose, all participants immediately received an epidural bolus of analgesic mixture 10-15ml of ropivacaine 0.125% (1.25 mg/ml) with sufentanil, 0.4 μg/ml, followed by patient-controlled analgesic (PCA) pump with a 5 ml patient-controlled bolus without background infusion, a lockout interval of 15 min and hourly limit 30ml.

The maternal parameters monitored during the whole study from before the analgesic procedures to the completion of the labor including the heart rate by 5-lead electrocardiograph, respiratory rate, noninvasive systolic and diastolic blood pressure,

Figure 2: Rate of Cesarean Delivery in Relation to the Absolute Cervical Dilation during Epidural Analgesia.



Data are presented as mean ± SD of the Cesarean delivery.

mean arterial pressure and fingertip pulse oximetry.

A catheter was inserted in a right or left antecubital vein for fluid and drug administration. Ringer's solution 8 ml/kg was titrated 15 minutes prior to initiation of EA. Intrapartum fluid management included replacement of preexisting fluid deficits, normal losses (maintenance requirements), the amount of urine collected via a measurable basin-like container, and hemodynamic variables.

The intrauterine pressure sensor, if necessary, was placed to show the intensity of uterine contraction. Oxytocin was infused by the nursing staff set by the obstetricians according to clinical guidelines (detailed criteria and procedures see Appendix 1). A decision whether an operative delivery need to be proceeded to was made by the obstetrical team who did not involved in this study depending upon maternal and fetal indications (see Appendix 2).

During the whole process of study, the patient-derived VAS scores of pain at rest were measured hourly with the 100-mm gauge (based on a 0-100 linear VAS, 0 = no pain; 100 = worst pain imaginable). Global pain to each patient, namely the pain intensity on average the patient felt during labor, was scored. In addition, the maternal satisfaction with analgesia was assessed via the VAS system (a 1-100 mm linear VAS used, 1 = dissatisfaction; 100 = fully satisfied). Finally, the incidence of the side effects, such as nausea, vomiting, pruritus, shivering and urinary incontinence or retention throughout the study were recorded by the follow-up physicians according to the maternal reports; maternal oral temperature and hypotension were measured by caregiver intermittently.

A continuous external electronic fetal heart-rate monitoring and tocodynamometry were made. Apgar scores were rated by the pediatric personnel according to the standard assessment. Umbilical-cord blood gas analysis was performed by the investigators.

The rate of operative delivery was selected as the primary outcome. In addition, the Odds Ratios of the interventional variables were calculated and recorded as supplementary data to the primary outcome. The following measures were selected as the secondary outcomes: the indication for Cesarean delivery; the rate of instrumental delivery; the time from the randomly allocation of groups to performing EA procedures; the interval from the initiation of EA to the time of a decision of CS was made; the time from the onset of painful uterine contraction to completion of vaginal delivery; the duration of EA; the verbal ratings of VAS pain and satisfaction with analgesia; oxytocin requirements; the maternal oral temperature; the incidence of side effects from epidural puncture and drug administration; infant outcomes, such as the body weight, Apgar scorings, umbilical-cord blood gas measurement and antibiotic treatment.

Neonatal sepsis evaluation was performed as previously reported (23). In brief, a blood culture and a complete blood count of the neonate suspected for sepsis possibility performed and followed by a lumbar puncture if one major or two minor criteria presented at the time of the study. Major criteria included rupture of membranes for > 24 h or a sustained fetal heart rate of > 160 beats per minute lasted up to 15 minutes or longer. Minor criteria included a low-grade maternal temperature of 37.5℃ to 38℃, rupture of membranes for 12 to 24 h, maternal admission white blood cell count of > 15,000 cells/ml^3, or five-minute Apgar score < 7.

Statistical analyses

Analyses were performed using GraphPad Prism v5.0 (GraphPad Software Inc., San Diego, CA, USA). Values are expressed as the mean, standard deviation (SD), median, interquartile interval, Odds Ratio (OR) or numbers. A pre-study power table where δ (the mean difference in Ce-

Table 2. Primary and secondary outcomes.*

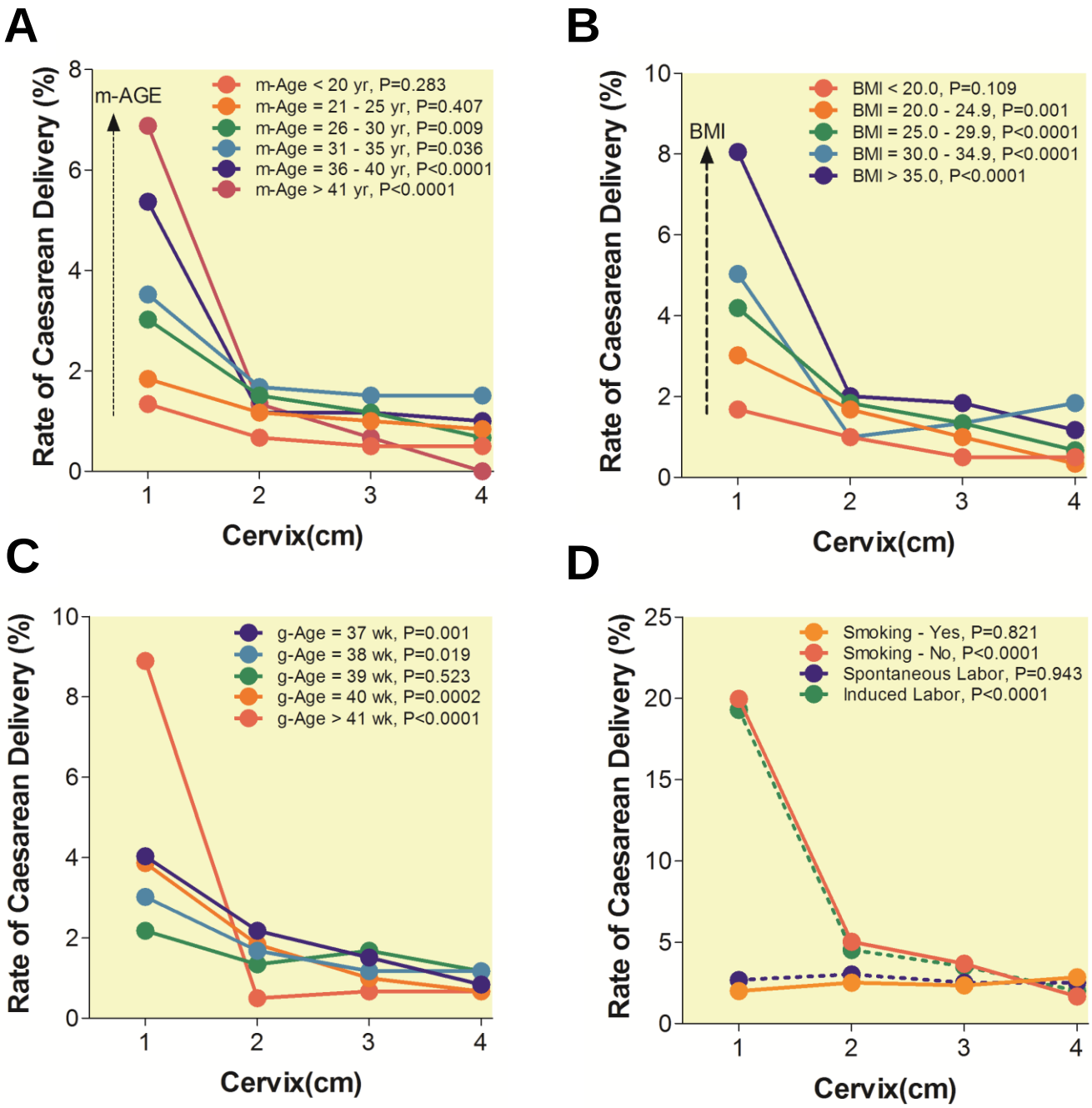
Outcome	Cervical Dilation (mm) 0 – 10.0 (n_a=132; N_i=149)	11.0 – 30.0 (n_a=130; N_i=149)	31.0 – 50.0 (n_a=137; N_i=149)	≥ 51.0 (n_a=134; N_i=149)	P Value
Maternal outcomes					
Method of delivery					
Cesarean – n (%)	115 (77.2)	45 (30.2)	36 (24.2)	27 (18.1)	< 0.0001
Instrument-assisted vaginal – n (%)†	7 (4.7)	21 (14.1)	17 (11.4)	13 (8.7)	0.21
Indications for Cesarean‡					
Arrest of dilatation – n (%)	102 (88.7)	11 (24.5)	8 (22.2)	6 (22.2)	< 0.0001
Arrest of descent – n (%)	10 (8.7)	5 (11.1)	6 (16.7)	5 (18.5)	0.43
Other fetal status – n (%)	3 (2.6)	29 (64.4)	22 (61.1)	16 (29.3)	< 0.0001
Other outcomes					
Time interval to performing EA – min§	33 ± 19	57 ± 22	64 ± 33	75 ± 38	0.40
Time interval to CS – min¶	217 ± 52	239 ± 74	196 ± 53	201 ± 68	0.84
Cervix at the time of CS decision – mm	47 ± 12	61 ± 19	65 ± 25	70 ± 31	0.66
Length of labor – hr (Vaginal deliveries only)‖	9.1 ± 4.3	8.2 ± 5.5	8.8 ± 5.2	7.8 ± 4.6	0.83
Duration of first stage – min	431 ± 56	419 ± 52	401 ± 63	385 ± 55	0.72
Duration of second stage – min	69 ± 11	53 ± 15	64 ± 19	57 ± 26	0.83
Average VAS pain ratings (0 – 100 mm) Δ					
First stage of labor					0.72
Median	37	28	32	33	
Interquartile interval	26 – 45	21 – 37	22 – 43	26 – 46	
Second stage of labor					0.83
Median	33	25	23	24	
Interquartile interval	25 – 48	16 – 37	11 – 33	15 – 42	
Use of oxytocin after analgesia – n (%)	107 (71.8)	36 (24.2)	31 (20.8)	23 (15.4)	< 0.0001
Maximal oxytocin dose – mU/min					0.17
Median	25	12	13	9	
Interquartile interval	19 – 36	8 – 23	10 – 28	7 – 17	
Duration of analgesia – hr					0.086
Median	12.1	10.7	7.6	4.7	
Interquartile interval	10.3 – 14.6	9.1 – 13.5	5.7 – 11.1	2.6 – 6.8	
Oral temperature during labor – ℃	37.1 ± 0.2	37.4 ± 0.6	37.2 ± 0.3	36.8 ± 0.5	0.54
Temperature > 38℃ – n (%)	13 (8.7)	23 (15.4)	12 (8.1)	6 (4.0)	0.007
Nausea – n (%)					0.008
Mild	13 (8.7)	9 (6.0)	7 (4.7)	8 (5.4)	
Moderate	15 (10.1)	7 (4.7)	7 (4.7)	5 (3.3)	
Severe	2 (1.3)	0	0	0	
Vomiting – n (%)	6 (4.0)	5 (3.3)	5 (3.3)	3 (2.0)	0.79
Pruritus (Itching) – n (%)	7 (4.7)	14 (9.4)	8 (5.4)	5 (3.3)	0.13

(Continued)

Urinary retention – n (%)	2 (1.3)	3 (2.0)	1 (0.7)	0	0.11
Urinary incontinence – n (%)	0	1 (0.7)	0	0	0.39
Shivering – n (%)	11 (7.4)	17 (11.4)	6 (4.0)	4 (2.7)	0.01
Hypotension – n (%)	0	1 (0.7)	0	0	0.39
Motor block – n (%)	1 (0.7)	1 (0.7)	0	0	0.57
Highest sensory block	T8 (T7 – T12)	T9 (T8 – T11)	T9 (T8 – T12)	T8 (T7 – T12)	0.90
Maternal overall satisfaction score with analgesia (VAS, 1 – 100mm) **					0.085
Median	46	85	74	61	
Interquartile interval	35 – 58	63 – 95	52 – 83	43 – 72	
Non-reassuring fetal status (NRFS) birthed vaginally ††					
Weight – g	3 500 ± 336	3 455 ± 352	3 568 ± 476	3 469 ± 445	0.93
1 – min Apgar < 7 – n (%)	4 (23.5)	19 (22.3)	15 (14.8)	12 (11.2)	0.19
5 – min Apgar < 7 – n (%)	0	0	0	0	–
Umbilical – cord gases measured – n (%)	15 (88.2)	77 (90.6)	81 (80.2)	84 (78.5)	0.12
Umbilical – vein pH	7.32 ± 0.03	7.30 ± 0.04	7.28 ± 0.05	7.27 ± 0.06	0.72
Umbilical – artery pH	7.22 ± 0.04	7.20 ± 0.03	7.21 ± 0.05	7.22 ± 0.03	0.88
Low umbilical cord pH (artery < 7.20) – n (%)	10 (58.8)	46 (54.1)	32 (31.7)	26 (24.3)	< 0.0001
Neonatal sepsis evaluation – n (%)	2 (11.7)	5 (5.9)	6 (5.9)	5 (4.7)	0.72
Neonatal antibiotic treatment – n (%)	3 (17.6)	16 (18.8)	15 (14.8)	11 (10.3)	0.39

* Plus-minus values are means ± standard deviation (SD). P values were calculated with ANOVA, the Kruskal – Wallis test or the Chi-square test, as appropriate.
† The percentage was calculated with the number of subjects need instrumental delivery to the intent-to-treat number of participants.
‡ The percentage was calculated with the number of subjects indicating to need Cesarean section to the total number of participants had Cesarean delivery.
§ Time interval to performing EA refers to the period from the randomly allocation of group to performing EA procedures.
¶ Time interval to CS refers to the period from the initiation of EA to the time of a decision of CS was made.
‖The length of labor indicates the time period from the onset of regular uterine contraction to the 1 hr after delivery of placenta.
Δ The VAS system of pain is a 0 to 100 mm linear gauge in which 0 = no pain, 100 = worst pain imaginable.
** The VAS system of satisfaction with analgesia is a 1 to 100 mm linear gauge in which 1 = dissatisfaction, 100 = fully satisfied.
†† The percentage was calculated through the number of neonates with positive outcomes to all babies birthed vaginally.
n_a: The actual number of patients who completed the study; N_i: the intention-to-treat number of patients; EA: epidural analgesia; CS: Cesarean section.

Figure 3: Proportion of Cesarean Delivery in Relation to Overall Outcome Characteristics in Different Cervical Dilation during Epidural Analgesia.



The correlation amongst the maternal characteristics and the rate of Cesarean section was analyzed. Panel A is the maternal age at delivery, in which the arrow denotes the CS rate at the cervix ≤ 10.0 mm group increased with the increase of maternal age. Panel B is the maternal body-mass index (BMI), in which the arrow denotes the CS rate at the cervix ≤ 10.0 mm group increased with the increase of maternal BMI. Panel C is the gestational age at birth, in which the gestational age > 40 weeks or < 39 weeks is risk factor for the CS. Panel D is the smoking status and means of labor, in which smoking during pregnancy does not increase the rate of CS, but the induced labor are one confounder influencing the rate of CS.

sarean delivery about 41 percent in four groups recorded in a pilot study), the rate of CS was 71% in the group at cervix ≤ 10.0 mm, and 30% in other groups at cervix ≥ 11.0 mm; expected SD was 1; two-sided α= 0.05, one-sided β = 0.10 and the power of test = 0.90, resulted in the need for a minimum of 125 subjects in each group to detect this difference. In preventing potential missing data during following-up, therefore, the intention-to-treat number of patients was increased to 149 to each group. However, our early observation showed that round thirty per cent patients would be dropped-out during the screening period, so we increased the screening size of patients to 195 to each group to account for potential drop-outs.

All categorical data were analyzed with a Chi-square test or Fisher's exact test to indicate the trend. Continuous variables like as the effects of the epidural analgesia on patient's self-rated VAS of pain and satisfaction, the duration of labor and each stage of delivery, and the highest sensory block level were summarized by calculating the median and interquartile interval, and compared with the Kruskal-Wallis test. The demographic data and background characteristics were presented as mean ± SD and analyzed with one-way analysis of variance (ANOVA). The ANOVA tests were always followed by the Bonferroni *post hoc* tests. To identify the characteristics associated with the Cesarean delivery, the binary logistic regression analysis was used for the primary outcome. All reported P values are two-sided and a P value of equal or less than 0.05 was considered to indicate statistical significance.

Results

Seven hundred and eighty gravidas were screened for eligibility (Fig. 1). Five hundred ninety six subjects were assigned to the four groups and followed up. The intention-to-treat number of patients was one hundred forty nine in each group. Finally, forty seven (7.9%) were excluded after group assignment because follow-up physician's unavailable and consequently this investigator was ruled out from the study group, and sixteen patients (2.7%) withdrawn from the trial without clear reasons. Finally, five hundred thirty three subjects totally completed the whole study. As a result, the data from these sixty three women enrolled but not completed the study after assignment was unable to be evaluated in the same fashion as the other participants. They were not included in the analysis of completed patients' data but in the intention-to-treat analysis. We excluded one hundred and eighty four records during screening period because of the following reasons of which are likely to overlap each other: 88 (47.8%) were nonvertex presentation; 47 (25.5%) diagnosed with diabetes and pregnancy-induced hypertension; 17 (9.2%) were twin gestation; 16 (8.7%) were not in the inclusion range of age (18 to 45 years) at delivery; 11 (5.9%) refused to participation; 9 (4.9%) were alcohol addictive; 3 (1.6%) had history of the use of centrally-acting drugs.

The material from all subjects underwent assignment was analyzed for baseline characteristics. There were no significant differences in the demographic and background data amongst the four groups (Table 1). Vital signs all were within the physiological ranges throughout the analgesic period and not significantly different among the groups. In this trial, the average duration of performing EA procedures was 8 ± 3 min in all participants. There was no statistically significant difference observed in EA performing duration among the four groups.

The results were displayed by analyzing the material depending on the intention-to-treat number of patients, but not the actual number of patients completed the study. Big difference in the rate of Cesarean delivery was shown in the four groups, the difference in the CS rate at the cervix ≤ 10.0 mm compared with other three groups was at least 57.7 percentage points or greater (P < 0.0001, Table 2, Fig. 2). The indications of Cesarean delivery showed big differences amongst groups, especially in the arrest of cervical dilation (P < 0.0001, Table 2). In addition, the percentages of subjects who obtained oxytocin infusion after analgesia still expressed significant difference (P < 0.0001, Table 2). If took the analgesia at cervix 11.0-30.0 mm as the referent of CS, the ORs were 16.82, 0.71 and 0.51 in the cervix ≤ 10.0 mm, 31.0-50.0 mm and ≥ 51.0 mm groups, respectively (Table 3).

We analyzed the data via a multivariate regression to assess the association between the baseline variables and the rate of Cesarean deliveries, and to clarify the confounders related with the CS rate during epidural analgesia. Maternal age at delivery and body-mass index (BMI), gestational age at labor, smoking status and onset of labor were evaluated, and found that maternal age and BMI are two confounders positively associated with the increase of CS rate at the cervix ≤ 10.0 mm. Moreover, gestational age > 40 weeks or < 39 weeks and induced labor are risk confounders for CS rate during EA at the cervix ≤ 10.0 mm. But smoking status is not in association with the increased rate of CS (Table 3, Fig. 3).

There were no significant differences in the length of vaginal labor, the time to the first and second stages of labor (Table 2). The average VAS ratings of pain prior to analgesia were similar, P = 0.17. There were no significant differences in the VAS pain scorings after analgesia (Table 2). The duration of analgesia in both groups was calculated from the bolus injection of the drug mixture into epidural space to the disappearance of the sensory block. The analgesic time shortened with the delayed beginning of EA at different cervical dilation, but no significant difference was observed, P = 0.086 (Table 2).

The intrapartum nausea, shivering and oral temperature > 38℃ ex

Table 3: Odds ratios for caesarean delivery.*

Variable	Odds Ratio (95% CI)	P Value
Cervical dilation – mm		
0 – 10.0	16.82 (9.19 – 30.78)	< 0.0001
11.0 – 30.0 (Referent)	1.0	
31.0 – 50.0	0.74 (0.44 – 1.23)	0.24
≥ 51.0	0.51 (0.29 – 0.88)	0.015
Age at delivery – yr		
≤ 20	0.46 (0.26 – 0.81)	0.006
21 – 25	0.75 (0.45 – 1.23)	0.26
26 – 30 (Referent)	1.0	
31 – 35	1.31 (0.84 – 2.04)	0.22
36 – 40	1.40 (0.91 – 2.17)	0.12
> 40	1.43 (0.93 – 2.21)	0.10
Body-mass index (BMI)		
< 20.0	0.59 (0.35 – 1.03)	0.059
20.0 – 24.9 (Referent)	1.0	
25.0 – 29.9	1.36 (0.87 – 2.13)	0.17
30.0 – 34.9	1.58 (1.02 – 2.44)	0.038
> 35.0	2.34 (1.55 – 3.54)	< 0.0001
Gestational age at birth – week		
37	1.17 (0.77 – 1.78)	0.45
38	0.95 (0.61 – 1.47)	0.82
39	0.85 (0.54 – 1.34)	0.49
40 (Referent)	1.0	
> 41	1.51 (1.01 – 2.25)	0.044
Current smoker		
Yes	0.25 (0.18 – 0.34)	< 0.0001
No (Referent)	1.0	
Onset of labor		
Spontaneous (Referent)	1.0	
Induced	3.45 (2.52 – 4.73)	< 0.0001

* Calculated according to the global outcome characteristics.

pressed significant differences amongst the groups. No significant difference was observed in the other side effects like as vomiting, pruritus, urinary incontinence and retention, hypotension as well as motor block (Table 2).

There were no significant differences in Apgar scorings, umbilical-cord pHs, incidence of sepsis and antibiotic use. The occurrence of umbilical artery pH < 7.20 increased when the EA was performed in the earlier labor (P < 0.0001, Table 2).

We got similar results in actual per patient analyses as well as the intention-to-treat analyses presented as the above ones.

Discussion

The data of this trial demonstrate that epidural labor analgesia at the cervical dilation ≤ 10.0 mm is a risk in resulting in intrapartum Cesarean delivery, during which the maternal age at delivery and BMI, gestational age at labor and induced labor are confounding factors in influencing the CS rate. Nevertheless, the EA technique at the cervix > 10.0 mm is an effective and safety means in controlling labor pain without increasing the rate of Cesarean delivery in nulliparous women (12).

We systematically investigated the correlation between the EA performed at different cervix dilation and the rate of CS, and the results extended current knowledge with respect to the minimal cervix needed to get epidural labor control. Wong and colleagues have compared the risk of Cesarean delivery after early neuraxial analgesia (CSEA) *vs.* systemic analgesia given at the cervix <4.0 cm, in which the cervical dilation reached ~2.0 cm (10). Chestnut's studies actually belonged to the active phase analgesia intervention (24, 25). In the present study, we performed EA from the onset of painful uterine contraction to the cervical dilation > 50.0 mm, and big difference in the CS rate was found when the cervix ≤ 10.0 mm. As thus the interventional window of epidural labor analgesia in nulliparous women can be enlarged from 20.0 mm to 10.0 mm of cervical dilation as presented by our previous study (12).

While Wong found that intrathecal opioid use significantly shortened the first stage of labor compared with the systemic opioid administration (10), in the present trial, no significant difference was gotten in the duration of vaginal labor, the time to first and second stage of delivery, which was

likely to be the reason that the data from the group at cervix ≤ 10.0 mm were excluded in data analyses. It suggests the earlier initiation of epidural analgesia at cervix > 10.0 mm in nulliparous women is not a risk factor for prolonging the progress of labor. Nonetheless, one major finding in this study is that the increased rate of CS in at the cervix ≤ 10.0 mm patients was mainly because of the influence of EA on the progression of labor, and correspondingly, more oxytocin was prescribed to them for poor labor progress. These are in agreement with other reports that an association existed between EA and intrapartum oxytocin infusion (26), and the EA combined with oxytocin infusion would increase the rate of CS (27).

Our results are consistent with previous studies the rate of instrumental deliveries would be increased if the epidural infusion of local anesthetics lasted longer (28, 29).When the EA performed at the cervical dilation >10.0 mm, the rate of instrumental deliveries was decreased in accompanying with the shortening of the analgesic duration at different cervical groupings.

The oral temperature was detected during analgesia recommended by Banerjee that oral temperature is a preferred routine detection of maternal pyrexia in labor for its positive correlation with intrauterine temperature (30). Our data are in line with other published results that women receiving EA had a significant increase in temperature after about five hours of analgesia (31). The longer the analgesia lasted, the more women experienced high oral temperature > 38 Celsius degree.

Nausea and vomiting are main side effects of gastrointestinal tract influenced by the pregnancy (32). In the present study the subjects evidenced more incidences of nausea and pruritus while the EA delivered at smaller cervical dilation, during which longer analgesia lasted. This is likely to be from a longer epidural analgesia results in a relative larger dose of lipophilic opioid was absorbed into blood.

Given only one infant was delivered in at the cervix ≤ 10.0 mm group, so the analyses were processed in the infant outcomes statistics with the exclusion of this group. The one-minute and five-minute Apgar scores were similar amongst the other three groups. This expressed EA does not exert significant influence on neonatal Apgar ratings. The results of umbilical-cord blood gases measurement were in agreement with Wong's data (10). Goetzl et al. found EA could increase the rate of neonatal sepsis in afebrile women, in which the rate was 20.4% (23). Nonetheless, we did not find convincing evidence that EA performed early or late in labor increase the rate of neonatal sepsis. According to the report of Fisler et al., neonates received more diagnostic or therapeutic administration of antibiotics in those whose mothers received EA for pain relief during labor than infants born after an elective CS (33). The neonatal antibiotic treatment, in the present study, was similar to aforementioned report (approximately 10 %).

Additional analyses were performed to clarify the correlation amongst maternal characteristics and the risk of CS. Our results were consistent that maternal age at delivery, BMI, gestational age at birth and induced labor are significantly associated with the risk of Cesarean delivery (10, 34), but the smoking status is not related with the CS rate. These indicate that maternal characteristics are additional predictors for Cesarean during EA in labor.

Limitations

The study merely investigated the nulliparous women with single and vertex presentation, but whether such results could be applied to other populations were not guaranteed. Another question is the difficulty in blinding the study groupings from the obstetricians who ultimately made the decision for Cesarean delivery. We monitored the fetal heart-rate as a possible indicator for emergency CS, though; the association amongst EA, fetal heart-rate variability and Cesarean delivery was not analyzed. In our study, the occurrence of an unfavorable fetal heart-rate in studying groups are similar (data are not shown). During enrolling subjects, we did not randomly assign the patients into groups; this is a methodological drawback of this trial.

Conclusions

When the EA was used in controlling labor pain, cervical dilation is a major aspect needed to be concerned. Cervical dilation ≤ 10.0 mm is a risk threshold in resulting in intrapartum Cesarean delivery, but the cervix > 10.0 mm is safety window for epidural placement without increasing the rate of Cesarean delivery in nulliparous women at term with vertex presentation. In addition, the maternal age at delivery and BMI, gestational age at labor and induced labor are confounding factors in influencing the CS rate while using EA. Further research is required to determine whether other patient groups are also likely to fit in such treatment.■

Acknowledgement

We are indebted to all obstetricians, midwives, pediatricians, nurses and anesthesiologists who participated in collecting the data in our hospital.

Funding

This work was supported in part by the grants of National Natural Scientific Foundation of China (NSFC, 81271242 and 81371248), Nanjing Municipal Outstanding Young Scientist Grant, China (JQX12009) and Nanjing Municipal Youth Grants of Medical Science (QYK11139).

Conflict of Interests

None

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APPENDIX I

Obstetric Oxytocin Infusion

1. **Prerequisites for oxytocin:**
   With one-to-one chaperonage to parturients;
   Adequate intravenous solution;
   Available of micro-infusion pump for precise administration of oxytocin;
   Fetal-heart monitor at least 20 min prior to oxytocin;
   Gestational age ≥ 41^{+0} weeks;
   With favorable cervical dilation assessed with Bishop Score.
2. **Indications for oxytocin infusion:**
   Pemature rupture of membranes;
   Postterm pregnancy;
   Significant fetal growth restriction;
   Non-reassuring fetal surveillance;
   Maternal conditions including diabetes, renal disease, significant pulmonary disease, hypertension-gestational, etc.;
   Suspected or proven chorioamnionitis, abruption, and fetal death;
   Patients' request (in special conditions).
3. **Procedures for oxcytocin use:**
   Initial dose of oxytocin 0.5 – 1.0 mU/min;
   Increscent gradually 1.0 – 2.0 mU/min every 30 – 60 min till a maximal dose 20mU/min reached or to ideal uterine contraction (3 – 4 contractions in ten minutes, and lasting 90 sec or less with an interval of 30 sec);
   Generally, oxytocin 10U dissolved into 1,000 ml Ringer's solution, and titrated with the rate of 1.0mU/min.
4. **Matters need attention during oxytocin infusion:**
   Continuous monitors of fetal-heart rate and uterine contraction;
   Maintained if contraction reached ideal state;
   If excessive uterine activity occurs (i.e. more than six contractions in two consecutive 10 min or contractions lasting longer than 120 sec), then:
   1) Stop oxytocin use further;
   2) Reposition the women in right or left lateral side;
   3) Oxygen 10 l/min by face mask;
   4) Maternal circulation evaluation;
   5) Increase in intravenous hydration if appropriate;
   6) Pelvic examination to rule out cord prolapsed;
   7) Cervical dilation assessment;
   8) Cesarean preparation if without recovery of fetal-heart rate;
   If intrauterine resuscitation successes, oxytocin can be reused at the initial dose of half the last dosage before resuscitation;
   In preventing postpartum uterine inertia, additional oxytocin 10 U administered intramuscularly or 20 U in 1,000 ml Ringer's solution titrated with the rate of 100 – 125 ml/h at least one hour.

APPENDIX II

Standard Obstetric Care Procedures

1. **Procedures on parturients care in delivery suite:**
   Cervical examination at an interval of 30 – 60 min;
   Monitoring the fetal heart rate;
   Maternal vital signs and uterine contraction monitor;
   Maternal fluid management;
   Oxygen provided with a nasal cannula;
   Oxytocin titrated as appropriate with a favorable cervix condition;
   Doula support;
   Measuring the pain intensity with Visual Analog Scale (VAS) system;
   Labor pain control at request including systemic or neuraxial analgesia;
   Timely instrumental or Cesarean deliveries.
2. **Indications for Cesarean section:**
   Malpresentation or malposition;
   Fetal distress or premature rupture of membrane;
   Placenta previa or placental abruption;
   Uterine atony or metryperkinesis;
   Abnormal amniotic fluid;
   Mother-to-child transmission of maternal infections;
   Abnormality of parturient canal including pelvic and genital tract;
   Abnormality of umbilical cord including presentation, prolapse, torsion and entanglement;
   Without any improvement after careful treatment of the abnormality of fetus and force of labor;
   Severe obstetric complications (Hemorrhage, Convulsions, etc.);
   Cessation of cervical dilation;
   Arrest of fetal descent.
3. **Indications for instrument-assisted delivery:**
   Fetal distress;
   Delay in the second stage of labor;
   Suspicion of immediate or potential fetal compromise in the second stage of labor;
   Maternal indications include exhaustion, bleeding, cardiac or pulmonary disease, and history of spontaneous pneumothorax;
   Fetal malposition including the after-coming head in breech vaginal delivery.
4. **Prerequisites for instrumental delivery:**
   Fully dilated and retracted cervix;
   Engaged head;
   Ascertained position of the head;
   No cephalopelvic disproportion beforehand assessment;
   With ruptured membranes;
   Adequate maternal analgesia;
   Available facilities and supportive elements;
   With competent operator.

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