REVIEW ARTICLE

Cerebral microdialysis

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Abstract

Cerebral microdialysis is one of the latest neuromonitoring modalities introduced to clinical practice. It is a bedside monitor used to assess brain tissue biochemistry. The principle of this technique is closely related to brain metabolism and dialysis. Microdialysis helps monitoring different metabolites related to energy and metabolic cascades (glucose, lactate and pyruvate), amino acids (glutamate) and markers of cell membrane degradation (glycerol). Its role has been established in conditions such as traumatic brain injury, subarachnoid haemorrhage, ischaemic stroke, etc. However, it is yet to be included in routine neuromonitoring as the technique is very expensive, needs technical expertise and the measurement is not continuous with a lag period in-between two readings. Till date, it is mostly used as a research tool, even though it is a very promising technique in certain clinical conditions.

Key words: Brain metabolism, cerebral microdialysis, multimodal monitoring, subarachnoid haemorrhage, traumatic brain injury

INTRODUCTION

Cerebral microdialysis (CMD) forms an integral part of multimodal monitoring for neurologically-injured patients. It helps in studying the brain tissue biochemistry and understanding the pathophysiology of both primary and secondary brain injuries. Based on the results of MD, the treatment strategy can be altered in order to optimise the cerebral physiology. It may also help predict outcome in different clinical scenarios. This technique has been used in patients with traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), brain tumours, ischaemic stroke, epilepsy and other neurological diseases.

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HISTORY

Delgado *et al*. developed first primitive version of the current MD probe, known as 'dialytrode'.[1] It consisted of two tubes soldered together making a push-pull cannula, with a small polysulfone membrane (permeable) bag glued to its tip. Delgado *et al*. were first to continuously perfuse dialysis membrane, *in vivo*, in monkeys; and this technique is since then known as 'MD'. Ungerstedt and Pycock improved the design of the probe and made it suitable for human use.[2] The first human CMD was performed in 1987, in a patient with Parkinson disease.[3] MD technique has also been used in several organ systems other than brain.

PRINCIPLES OF MICRODIALYSIS

MD is a minimally invasive neuromonitoring technique which works on the principle of dialysis. The substances present in an area of higher concentration diffuse across a semipermeable membrane, present in the tip

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of the MD probe to an area of lower concentration. The microdialysate collected from the brain is then analysed for different endogenous compounds (analyte). This direction of movement can be controlled, by altering the strength of perfusate either to sample a substance or to deliver a substance into the brain (retrodialysis).

THE PROCESS OF MICRODIALYSIS

The MD catheter constitutes of a shaft, semipermeable end, an inlet and outlet tubing [Figure 1]. The catheter, except the distal end, is made up of polyurethane, and has a maximum outer diameter of 0.9–1 mm. The distal end of the catheter has a 10–30 mm long semipermeable membrane having a diameter of 0.6 mm. Through the inlet tubing, a solution simulating cerebrospinal fluid (CSF) (artificial CSF or perfusate) is infused continuously with the help of a miniature pump (MD pump). The artificial CSF is isotonic, similar in composition and pH as brain interstitial fluid. Adequate amount of cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) are present in artificial CSF that prevents their depletion from the surrounding tissue. However, artificial CSF lacks proteins and neurotransmitters, which actually enable these substances to be retrieved from brain tissue via microdialysate. The semipermeable membrane permits substances with molecular weight <20 kDa. Newer types of MD catheters (CMA 71) enable the collection of larger molecules having molecular weight up to 100 kDa. The flow rate of perfusate varies from 0.1 to 3.0 µl/min. The perfusate reaches the distal end of the probe which is placed in the brain tissue [Figure 2]. Here, diffusion of molecules occurs along the concentration gradient across the semipermeable membrane. After the diffusion process, the collected fluid is known as 'microdialysate' which moves along the outlet tube; finally into special type of collecting chambers called 'microvial'. These microvials are then placed in the bedside monitor for biochemical analysis. In common clinical practice, catheters having 10 mm long semipermeable membrane are often used with perfusate flow rate of 0.3 µl/min.

FACTORS AFFECTING RELATIVE RECOVERY

The factors affecting the recovery of substance under study during MD are:

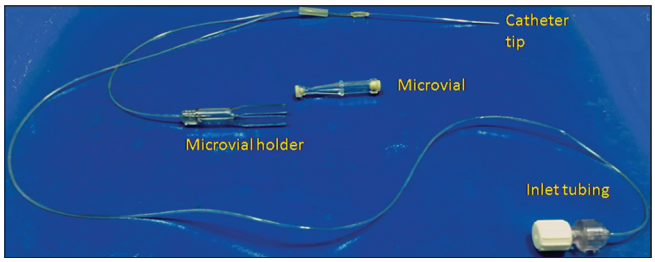

Figure 1: Microdialysis catheter and its parts

Flow rate of perfusate

At low perfusion rates, the relative recovery of a substance increases proportionally. Lower is the perfusion rate; more time is available for the substance to move across the semipermeable membrane and be detectable in microdialysate. The diffusibility of the substance, characteristics of the semipermeable membrane and its length, all determine the recovery of the substance. Flow rate of 0.1 µl/min through a 30 mm long semipermeable membrane enables almost 100% recovery. For practical reasons, slowing the flow rate also decreases the volume of the sample obtained in a stipulated time and thus, longer times are required for adequate sample volume to collect. A rate of 0.3 µl/min allows sufficient detectable concentration of the analyte to be obtained in microdialysate. For intraoperative CMD, a higher flow rate of 1–2 µl/min is usually employed to quicken the recovery of microdialysate and shorten the event detection time.

Characteristics of semipermeable membrane

Higher the surface area of the semipermeable membrane more is the recovery rate. The length of the membrane is usually 10 mm but by using a longer membrane of 30 mm, 100% recovery may be achieved. The materials commonly used for the semipermeable membrane are regenerated cellulose, polyacrylonitrile, polycarbonate-ether or polyarylethersulphone.

Characteristics of analyte

The diffusion of substances decreases proportionally with higher molecular weight substances. Hydrophobic substances have less diffusibility, and hence lower rate of recovery.

Temperature

For every, 1° increase in temperature, about 1–2% increase in the diffusion coefficient is seen. Hence, the

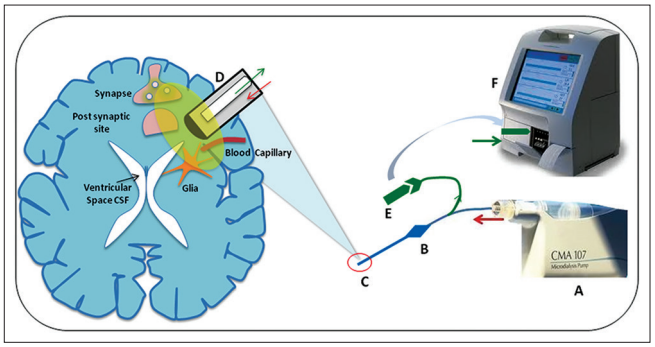

Figure 2: The procedure of cerebral microdialysis with infusion of perfusate by the microdialysis pump (A) through a microdialysis catheter (B), the distal end containing semipermeable membrane (C) is placed in the brain interstitium (D). Depending on the concentration gradient across the semi-permeable membrane, molecules pass into centrally located tube from where it is collected into microvials (E). It is taken out of holder and is placed in the bedside monitor/analyser (F)

temperature should be maintained at 37°C for all MD procedures.

Tissue factors

Generally, aqueous medium offers less resistance to diffusion than tissues. Diffusion in tissues may be slowed by increased diffusion path, and binding of the analyte to cell proteins. This may be responsible for the difference between *in vitro* and *in vivo* recovery rate.

METABOLITES COMMONLY MEASURED BY CEREBRAL MICRODIALYSIS

Glycolysis takes place in cytoplasm wherein glucose is converted anaerobically to pyruvate producing two molecules of ATP per glucose molecule. Under aerobic conditions, pyruvate dehydrogenase converts pyruvate into acetyl coenzyme A. This in turn enters into a citric acid cycle where mitochondrial respiratory chain uses oxygen to finally produce 36 molecules of ATP for each molecule of glucose oxidised. In the absence of oxygen, lactate dehydrogenase converts pyruvate to lactate [Figure 3]. Increase in lactate and decrease in pyruvate indicates decreased oxygen availability, which may be due to ischaemia or hypoxia [Table 1]. However, increase in extracellular lactate levels in patients with acute brain injury is not only seen in ischaemic conditions but also in cases of hyperglycolysis.[4] Lactate and ketones are considered as an alternative glucose sparing energy substrates.[5,6] Lactate has also been found to help in axonal regeneration.[7] Increase in its uptake by brain has been seen to be associated with better outcome.[8] This possible neuroprotective effect of lactate has even led to exogenous supplementation of lactate in the form of sodium lactate.[9,10] Values of lactate and pyruvate obtained at a flow rate of 0.3 µl/min from the uninjured human brain are 2.9 ± 0.9 mmol/L and 166 ± 47 µmol/L, respectively.[11,12] The normal lactate-pyruvate ratio (LPR) is approximately 20 and a value more than 25 signifies the onset of the metabolic crisis.[13] Increase in LPR can be categorised into two types.[14] Type 1 indicates ischaemia in which lactate is increased and pyruvate is decreased. Type 2 is non-ischaemic, raised LPR seen in glycolysis failure or shunting of glucose to alternative metabolic pathways resulting in primarily decreased pyruvate level. Estimation of other markers of cell damage in conjunction with lactate is, thus important for identification of ischaemic state.

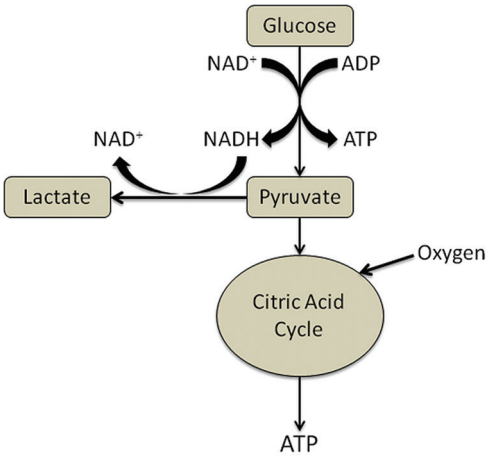

Figure 3: Glucose metabolism in brain

In the absence of oxygen and ATP, failure of ionic pumps leads to calcium influx into cells and activation of several enzymes resulting in cell membrane damage. Glycerol is one of the constituents of triglycerides forming the cell membranes, and normal levels are taken as 82 ± 4 µmol/L that signifies cell damage.[11] Oral administration of glycerol may also lead to increased level in microdialysate and should be kept in mind.[15]

Glutamate opens calcium channels, increases the intracellular concentration of calcium resulting in cell damage. It is a marker of excitotoxicity, and its normal microdialysate level is 16 ± 16 µmol/L.[11]

The microdialysate glucose levels may be affected by ischaemia, hyperaemia, hyperglycaemia, hypermetabolism or hypometabolism. If brain glucose increases or decreases disproportionally to blood sugar levels, then changes in blood flow or metabolism may be the reasons responsible for it. The normal microdialysate value of glucose is taken as 1.7 ± 0.9 mmol/L when 10 mm dialysis membrane and 0.3 ul/min of perfusate flow are used.[11]

INSERTION OF MICRODIALYSIS CATHETER

The MD catheter may be placed either during open surgery, percutaneously, or via a cranial bolt.[13] Multi-lumen bolts help in inserting one or more probes like of intracranial pressure (ICP) or brain tissue oxygenation. The probe has a gold tip, which enables its localisation on computed tomographic (CT) scan. A post-implantation CT should be always done to confirm its site of placement and to rule out any induced trauma. The catheter is placed in penumbra region to help determine the metabolic state of 'at–risk area'.[16] Area of

Table 1: Conditions with increased extracellular lactate

Conditions	Lactate	Pyruvate	LPR
Ischaemia	↑	↓	↑
Hyperglycolysis	↑	↑	Normal
Mitochondrial dysfunction	↑↑	Normal to ↑	↑

LPR = Lactate-pyruvate ratio

brain tissue covered by the catheter is only 1.5 cm^2 which necessitates its proper placement. Timely manipulation of cerebral perfusion pressure (CPP), oxygenation and glucose may help in salvaging this region. However, a second catheter may be placed in the normal brain to have control values for comparison. In cases of SAH, MD catheter is placed in the vascular territory affected by vasospasm. In patients with diffuse axonal injury, the catheter is placed in the non-dominant hemisphere, that is, right frontal region.[16] The micro-trauma induced during catheter insertion and the perfusate flush used at the start of monitoring makes the values during 1st h unreliable.[13,16]

METHOD OF MONITORING

Monitoring is carried out by 'LTC' method[13] - check the levels, trend and comparison.

Levels - whether the level of the substance under study is within normal range or not?

Trends - whether these values are improving or worsening over time? The trend is more important than the absolute values at a given moment.

Comparison - what is neuro-biochemistry in relation to other clinical variables such as CPP, ICP and brain tissue oxygenation?

CLINICAL APPLICATIONS OF MICRODIALYSIS

Traumatic brain injury

Head trauma induces primary brain injury, which cannot be reverted, but it is the secondary injury, which may be prevented or treated. MD catheter placed in this recoverable area not only helps in understanding the pathophysiology of injury but also guides in the therapeutic interventions. Multimodal monitoring in Intensive Care Unit incorporating MD along with brain tissue oxygenation, jugular venous oximetry and CPP can be helpful in optimising therapy. In case of worsening neurochemistry, increasing the blood pressure or fraction of inspired oxygen or interventions to decrease the ICP can salvage the vulnerable tissue.

Injured brain tissue has impaired oxidative metabolism which can be studied by CMD.[17] After TBI, there is an increase in anaerobic glucose metabolism via glycolysis and pentose pyruvate pathway (PPP). To study this cerebral energy metabolism in patients with TBI, CMD has been recently used to deliver (13) C-labelled substrates into brain followed by analysis of the recovered (13) C-labelled metabolites. The labelled lactate recovered in microdialysate helped in comparing the amount of lactate produced by glycolysis and PPP in TBI patients and also demonstrated that brain can utilise lactate via tricarboxylic acid pathway.[18,19] Timofeev *et al*. prospectively collected neuromonitoring data from 97 TBI patients admitted to the neurointensive care unit.[20] In the perilesional tissue, it was observed that the relationship between CPP and neurochemistry variables depended on the state of pressure reactivity index (PRx). Impaired PRx, decrease in cerebral perfusion and oxygenation were found to be associated with worsening neurochemistry. Metabolic markers measured by CMD were found to be independently associated with the neurologic outcome.[21]

Sanchez *et al*. studied 1260 MD samples from 12 TBI patients and analysed them for glucose, lactate, pyruvate, LPR and lactate/glucose ratio.[22] High extracellular lactate and low glucose were found to be indicators of severe neurological damage and poor outcome, because of impaired brain metabolism. Concentration of lactate and LPR both should be taken into consideration to distinguish between anaerobic metabolism and aerobic hyperglycolysis.[23,24] Similarly, the outcome has been found to be worse in patients with high levels of dialysate excitatory amino acids (27 ± 22 μmol/l). Sustained high ICP and poor outcome were significantly correlated to glutamate level more than 20 μmol/l.[25]

Hyperglycaemia and hypoglycaemia both harm the already injured brain. However, the relation between blood and brain glucose is not linear. MD catheter placement can elucidate this relationship and help in the management of hypoglycaemic or hyperglycaemic episodes.[26]

Tight glycaemic control (80–120 mg/dl) after severe brain injury is associated with decreased cerebral glucose availability, increased prevalence of brain energy crisis (CMD glucose <0.7 mmol/l and LPR >40) and increased mortality.[27]

MD may even predict long-term anatomical alteration in head-injured patients. Marcoux *et al*. studied the metabolic state of 15 patients having moderate-severe TBI and assessed their anatomical outcome by volumetric MRI at 6 months after injury.[28] Metabolites were collected for first 96 h after injury via MD catheter placed in normal appearing frontal lobe. Persistently elevated LPR more than 40 was predictive of the extent of frontal lobe atrophy, at 6 months. This effect was independent of age, GCS and volume of frontal lobe contusion.

SUBARACHNOID HAEMORRHAGE

MD applications in SAH patients range from intraoperative to post-operative period. Kett-White *et al*. studied the cerebral oxygenation and neurobiochemical changes during arterial temporary clipping in patients with large, complicated aneurysms. Intermittent occlusion of less than total of 30 min did not affect

neuro-biochemistry.[29] Although the cerebral oxygenation enabled continuous monitoring, MD readings were available at event-detection delay of at least 30 min which being a major limitation for the intraoperative application. A rapid-sampling MD technique for the early detection of adverse metabolic changes has been introduced. A flow rate of 2 µl/min was employed to have a balance between acceptable recovery and rapid microdialysate turn-over. This technique detects changes 9 min after intraoperative events occur (limited only by probe-to-sensor tubing length and dialysate flow rate).[30]

Aneurysmal SAH is often complicated by vasospasm resulting in poor outcome of patients. If only onset of vasospasm can be detected early enough for therapeutic alterations, the course may be modified for better. With the catheter placed into tissue at risk of vasospasm, MD has been found to be highly specific for confirming delayed ischaemic neurological deficit (DIND).[31] However, placing the catheter at the probable place of vasospasm may not always be accurate, and the actual site of occurrence of vasospasm may vary.[32] DIND patients have significantly higher lactate and glutamate concentrations on days 1–8 and a higher LPR on days 3–8 post-SAH, compared with asymptomatic patients. In 83% of the DIND patients, the changes in metabolites indicative of cerebral ischaemia precede the onset of symptomatic vasospasm.[33] It has been observed that the ischaemic pattern preceded the occurrence of a DIND by a mean interval of 11 h.[34]

Similar to TBI patients, several studies have found CMD to be helpful in prognostication of SAH patients. In a prospective study conducted in 149 SAH patients, the LPR was found to be a best prognostic marker of the 12-month outcome.[35] A low level of glucose <0.7 mmol/L and high LPR >45 indicated metabolic crisis and were associated with poor outcome.[36]

Hyperglycaemia has been found to be associated with poor outcome in several studies. In patients with SAH, Zetterling *et al*. found a positive correlation between plasma and microdialysate glucose with a high degree of individual variation, while another study found no relation between hyperglycaemia and cerebral glucose.[37,38] Probably this non-linear relationship between cerebral and plasma glucose makes cerebral glucose monitoring nonetheless important. Insulin therapy decreases cerebral glucose levels independent of blood glucose levels. This may result in decreased cerebral glucose though blood glucose remains normal.[39]

CMD has also been used in SAH to study various extracellular or CSF markers for secondary brain injuries such as S100 B, tau, taurine, interleukins and even potassium.[40-42]

ACUTE ISCHAEMIC STROKE

Patients with acute ischaemic stroke require careful monitoring to detect any deterioration due to the development of oedema of the infarcted tissue. In one of the earliest reports of the use of MD in a patient with middle cerebral artery (MCA) infarction, neurochemical alterations were seen to precede clinical signs of neurological worsening.[43]

It has also been used for monitoring the therapeutic effects of hemicraniectomy and hypothermia. Glutamate, glycerol and LPR are lower in the patients receiving hypothermia or undergoing decompressive craniectomy than patients who were managed conservatively.[44] Hypothermia decreases glutamate, glycerol, lactate, and pyruvate in the 'tissue at risk' area of the infarct.[45]

BRAIN TUMOURS

CMD helps in studying the neuro-biochemistry of brain tumours and associated changes in response to treatment. The levels of extracellular amino acids, proteases, and adenosine have been seen to vary between normal brain and tumour tissue. Intratumoural MD when carried out to study the metabolism of high-grade astrocytomas showed low glucose and high lactate values. Necrotic tissue showed higher levels of glutamate and glycerol.[46] Brain retraction during surgery causes tissue injury and even development of oedema. It presents as a picture of incomplete cerebral ischaemia evident on CMD as raised glycerol, lactate, glutamate and LPR. CMD can be a valuable tool in studying and developing optimal retraction techniques.[47]

Blood-brain, blood-CSF and blood tumour barrier determine the passage of systemically administered drugs. The delivered drug reaches the tumour tissue in varied concentration depending on its molecular weight, lipid solubility, protein binding and state of these barriers. MD has been used to study the drug concentration present in tumour tissue and interstitial space surrounding the brain tumours. Thus, CMD has been used for analysis of drug pharmacokinetics, monitoring the therapeutic effect and even for the development of new therapeutic options.[48]

Delivery of chemotherapy drugs directly into brain tumour tissue by means of MD (retrodialysis) has been carried out in few brain tumour patients.[49,50] The primary advantage is a restriction of the neurochemical effects to the tumourous tissue only.

EPILEPSY

MD has also been used to study the neurochemical milieu of epileptic foci. An imbalance between excitatory

and inhibitory neurotransmitters may lead to epileptic discharges, and this delicate balance has been studied CMD. Aspartate, glutamate, glycine and serine increase in association with both spontaneous and electrically induced seizures.[51]

OTHER APPLICATIONS OF CEREBRAL MICRODIALYSIS

In patients with intracerebral haemorrhage (ICH), CMD has been used to study the perihaemorrhagic zone. A transient increase in glutamate and other amino acids has been observed in perihaematoma region.[52] In an experimentally induced ICH, volume dependent changes were observed in cerebral blood flow, oxygenation and ischaemic CMD markers.[53]

Neurodegenerative diseases such as Parkinson and Alzheimer's disease and various psychiatric disorders involve an imbalance of acetylcholine, dopamine, norepinephrine and serotonin. CMD makes it possible not only to study their level but also the effect of therapeutic drugs on these neurotransmitters.

Hepatic encephalopathy is a complication of liver disease in which high ammonia levels and other factors lead to the development of central nervous symptoms. CMD helps in understanding the mechanisms that induce hepatic encephalopathy and also the effect of various therapeutic treatments.[54]

LIMITATIONS OF MICRODIALYSIS

- The cost of MD catheter and reagents involved makes this monitoring modality expensive
- It requires technical expertise for monitoring. Interpretation of data is also difficult and requires careful understanding of MD values
- The monitoring is not continuous and 'event detection time' is prolonged which delays diagnosis and subsequent management. There is a lag period in-between two recordings; hence, there is always a chance of lost opportunity for therapeutic interventions
- The 1st h readings are usually not reliable as the first sample is often diluted and provides erroneous data
- The catheter can monitor the metabolic state of a small area of the brain (approximately 1.5 cm^2)
- It is an invasive procedure, not free from complications such as infection. Microscopic bleeding and oedema of brain parenchyma can occur around the insertion site. Local cellular reaction (gliosis) to the implanted probe has also been observed; more, with its longstanding use.

FUTURE APPLICATIONS

Various metabolites, aminoacids, neurotransmitters, biomarkers and drugs, and their disposition can be studied by MD. The success of this technique is limited by finding the right biomarkers and their sensitivity and specificity for identifying the brain injury or disease processes. Further improvisation of the technique to shorten the event detection time may result in early management and hence, better outcome. Targeted drug delivery into the brain is still in its infancy and requires further research to establish its impact on survival, if any.

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Conflicts of interest
There are no conflicts of interest.

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