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Research Article

MEAN SIGNAL INTENSITY CURVE ANALYSIS OF BRAIN TUMOR BY DYNAMIC SUSCEPTIBILITY CONTRAST MAGNATIC RESONANCE PERFUSION IMAGING

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A B S T R A C T

The mean signal intensity curve generated from the MR perfusion images and can measure the alteration in capillary leakiness/permeability and vascular shunting of the tumor bed. The aim of this study was to analyze the mean signal intensity curve and evaluated the patterns shown by different brain tumors in dynamic susceptibility contrast enhanced MR Perfusion imaging.

Method: A total 30 patients with histopathological confirmed brain tumor were evaluated the mean perfusion curve. The sloping angle of the signal drop and the percentage of signal recovery were determined from the mean signal intensity curve. Based on these findings the various patterns of the mean perfusion curve were evaluated.

Results: The range of the signal drop angle and signal recovery percentage of meningioma were 3.61^0 to 6.8^0 and 3.99 % to 120% hemangiopericytoma 8.35^0 to 8.4^0 and 45.69% to 64.02%, Schwannoma was 4.62 to 10.2 and 53.87 to 76.02 , high grade glioma 5.6^0 to $9.3^0$and 9.8% to 72.3%, pilocytic astrocytoma was 7.1^0 to 8.75^0 and 9.5% to 100%, low-grade glioma was 6.3^0 and 98.8%, Oligodendroglioma was 5.1 to 6.2 and 44.48% to 91.66%, hemangioblastoma was 4.88^0 to 9.79^0 and 52.05% to 54.16% , meduloblastoma was 4.6^0 to 4.7^0 and 65.28% to 66.18%, central neurocytoma was 5.99^0 and 71.89%, anaplastic Ependymoma 5.53^0 and 71.17%, lymphoma was $6.3^0$and 120 % and metastasis was 6.5^0 to 10.07^0 and 71.17% to 71.92%.

Four types of mean signal intensity curve were observed based on signal drop and signal recovery.

Type I: The signal recovery overshoot above the base line after the first pass of contrast. This pattern was seen in 1 case of primary CNSlymphoma and 1 case of meningioma.

Type II: The signal recovery reach to the baseline after the first pass. This pattern was seen in 1case of low-grade fibrillary astrocytoma, 1 case of oligodendroglioma and 2 cases of pilocytic astrocytomas

Type IIIA: The signal recovery upshot, but which never reached the baseline. This pattern was seen in3 cases of meningioma, 2 cases of high grade gliomas, 1 case of pilocytic astrocytoma, 2 cases of Schwannoma, 2cases of meduloblastomas, 2 cases of oligodendroglioma, 1 case of neurocytoma, one case of hemangioblastoma, 1 case of hemangiopericytoma and 2cases metastasis

Type IIIB: The signal recovery upshot after the dip, but which never reached the baseline was seen in 1 case glioblastoma, 1 case of pilocytic astrocytoma and 1 case of meningioma (case 4), in addition to a metastasis.

Type IV: The signal recovery was flat after the first pass. this type was seen in a case of highgradeglioma and 1 case of meningioma

Conclusion: The MPC along with the with perfusion maps and conventional cross-sectional imaging, can help in the characterization of intracranial tumors

INTRODUCTION

The diagnosis of brain tumors usually involves several systematic steps, which can include detail clinical history of the patients including symptoms and signs, complete neurological examinations, brain scans and/or biopsy.

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of the tumors and also helps in the formulation of initial management strategy for a brain tumor. Magnetic Resonance perfusion imaging used to noninvasively measure cerebral perfusion via assessment of various hemodynamic measurements. The mean signal intensity curve generated from the MR perfusion images consist of signal drop followed by signal recovery. The signal drop is well correlated with rCBV and thus reflects total microvasculature density within the tumor bed. The signal recovery is well correlated with alteration in capillary leakiness/permeability and vascular

shunting of the tumor bed. There is limited data available in the literature on details analysis of the mean perfusion curve for brain tumors. This study is to details analysis of mean signalintensity curve to understand the brain tumor physiology. The aim of this study was to analyze the mean signal intensity curve and evaluated the patterns shown by different brain tumors in dynamic susceptibility contrast enhanced MR Perfusion imaging.

METHOD

Study design

This study was a prospective cross sectional study conducted for 2 years' period from 2014 to 2015. The Study was approved by the Institutional Ethical committee. All the patient histopathologicaly confirmed brain tumor were included in this study. Mass lesions of brain other than tumorswere excluded from the study. All the neoplastic lesions were categorized separately on the basis of histopathological diagnosis and MR perfusion mean curve were analyzed separately for each group.

MR Perfusion Protocol

The DSC MR perfusion study of brain was performed by 1.5T SEIMENS AVANTO MR Scanner. The protocol includes DSC gradient-echo echo-planar perfusion imaging which has long TR (2200.0 ms), TE (40 ms) and small flip angle (30^0). The FOV and slice thickness was 230 x 230 and 5mm respectively. The gadolinium based contrast agent, Gadobenate dimeglumine (Gd-DTPA) was used intravenously at a dose of 0.2 mmol/kg body weight by a MR compatible power injector. The rate of injection was at 3-4 ml/s through antecubital vein via IV cannula followed by 10-20mL continuous saline flush. The first eight time points were ignored to get the base line. The complete perfusion image series included 50 time points and each time point was acquired at every ~2 seconds in MR scanner

Image analysis

For image processing, the source images are first transferred to the offline workstation and inspected for overall image quality and the presence of motion artifacts. The main perfusion series were processed by the perfusion and mean curve analysis applications. The region of interest (ROI) in the most enhancing portion of lesion was selected along with contralateral healthy white matter in the same slice by the use of round free hand tool in the tool taskbar to get the mean signal intensity curve. The sloping angle of the signal drop and the percentage of signal recovery were evaluated from the mean signal intensity curve (Figure 1).

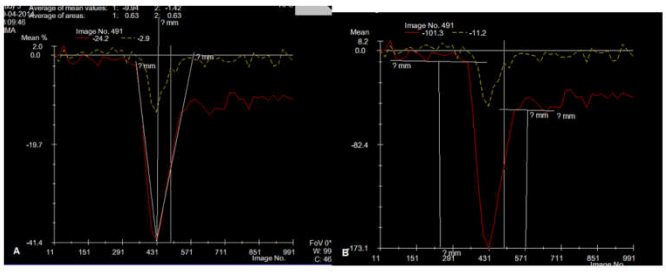

Figure 1 Measurement of signal drop angleand percentage of signal recovery in a mean perfusion curve

A reveal evaluation of signal drop angle (A) and 1B reveal evaluation of percentage of signal recovery (B).

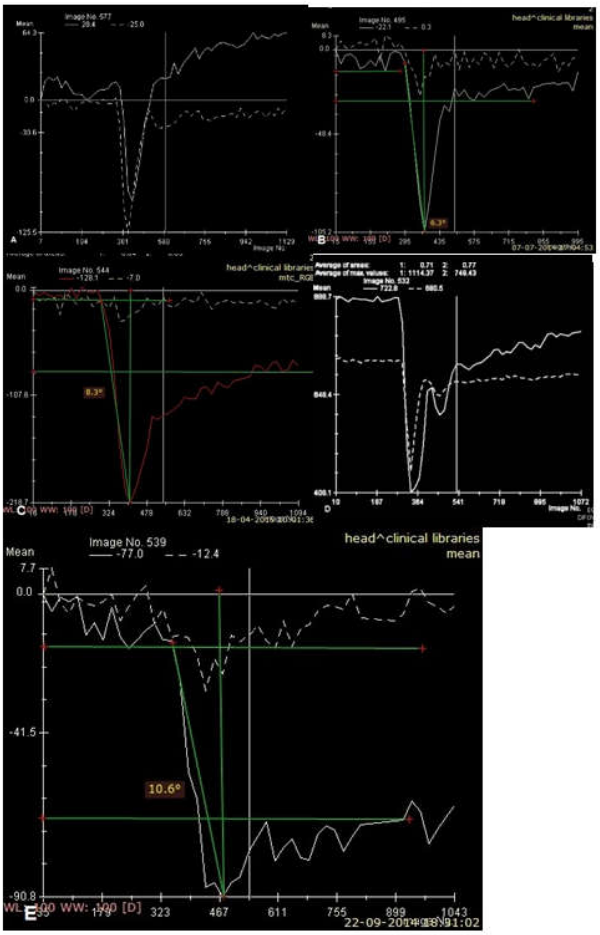

Figure 2 Patterns of mean perfusion curve

Figure 2A Type I mean perfusion curve. The signal recovery overshoot above the base line after the first pass of contrast
Figure 2B Type II mean perfusion curve. The signal recovery reach to the baseline after the first pass.
Figure 2C Type IIIA mean perfusion curve. The signal recovery upshot, but which never reached the baseline
Figure 2D Type IIIB mean perfusion curve. The signal recovery upshot after the dip, but which never reached the baseline
Figure 2E Type IV mean perfusion curve. The signal recovery was flat after the first pass

Based on these findings, patterns of the perfusion curve were determined. Based on these findings the various patterns of the mean perfusion curve were evaluated.

RESULTS

The DSC MR Perfusion imaging was carried in a total of 66 patients with clinically suspicion of having brain neoplasm. Out of them, 30 patients with histopathologically confirmed tumors cases were included in our final analysis of the study. The rest of cases were not included in the study because of lack of histopathological diagnosis or histopathology confirmed other diagnosis or had gross technical errors.

Mean curve analysis

a. Signal drop angle and percentages of signal recovery of each tumor were documented Table 1.
b. Pattern of Mean Curve

Four type of mean signal intensity curve were observed based on signal drop and signal recovery.

Type I: The signal recovery overshoot above the base line after the first pass of contrast (Figure 2A). This pattern was seen in 1 case of primary CNSlymphoma and 1 case of meningioma

Type II: The signal recovery reach to the baseline after the first pass (Figure 2B). This pattern was seen in 1case of

low-grade fibrillary astrocytoma, 1 case of oligodendroglioma and 2 cases of pilocytic astrocytomas.

Type IIIA: The signal recovery upshot, but which never reached the baseline (Figure 2C). This pattern was seen in3 cases of meningioma, 2 cases of high grade gliomas, 1 case of pilocytic astrocytoma, 2 cases of Schwannoma, 2cases of meduloblastomas, 2 cases of oligodendroglioma, 1 case of neurocytoma, one case of hemangioblastoma, 1 case of hemangiopericytoma and 2 cases metastasis.

Type IIIB: The signal recovery upshot after the dip, but which never reached the baseline was seen in 1 case glioblastoma, 1 case of pilocytic astrocytoma and 1 case of meningioma (case 4), in addition to a metastasis (Figure 2D).

Type IV: The signal recovery was flat after the first pass. This type was seen in a case of highgradeglioma and 1 case of meningioma.

Table 1 Signal drop angle and percentages of signal recovery of each tumor

SL No.	Final diagnosis	Signal drop (degree)	Signal recovery (%)
1	Meningioma	5.61	120
2	Meningioma	3.61	75.81
3	Meningioma	4.7	88.28
4	Meningioma	4.54	68.44
5	Meningioma	6.83	66.66
6	Meningioma	10.5	3.99
7	Lymphoma	6.3	120
8	High grade glioma	6.4	72.30
9	High grade glioma	9.03	63.63
10	High grade glioma	5.6	67.25
11	High grade glioma	8.75	9.58
12	Pilocytic astrocytoma	7.1	100
13	Pilocytic astrocytoma	7.68	61.47
14	Pilocytic astrocytoma	8.3	100
15	Low grade astrocytoma	6.3	98.8
16	Schwannoma	4.62	76.02
17	Schwannoma	10.2	53.87
18	Meduloblastoma	4.7	66.18
19	Meduloblastoma	4.6	65.28
20	Oligodendroglioma	5.3	44.48
21	Oligodendroglioma	5.1	93.66
22	Oligodendroglioma	6.2	88.83
23	Central Neurocytoma	5.99	71.89
24	Hemangioblastoma	9.79	54.16
25	Hemangioblastoma	4.88	52.05
26	Hemangipericytoma	8.35	64.02
27	Hemangipericytoma	8.4	45.69
28	Metastatic lung Ca.	6.5	90.47
29	Metastatic lung Ca.	10.07	71.92
30	Anaplastic Ependymoma	5.53	71.17

DISCUSSION

The role of magnetic resonance perfusion mean curve has steadily increased and now it has nearly become the important investigation for the diagnosis of brain tumors, however, there are limited data published in literature. This study was performed to evaluate the signal drop angle and percentage of signal recovery of the brain tumor and also to evaluate the various patterns of mean signal intensity curve.

The high-grade tumor has high cellularity and high cell turnover and thereby it has high metabolic demand that leads to cellular hypoglycemia and hypoxia. It has the ability to synthesized new vessels to fulfill its metabolic demands for oxygen and glucose and to removal of metabolic waste products. The hypoxia and hypoglycemia induce the increased angiogenic cytokines production which is responsible for neoangiogenesis(Jackson *et al*., 2002). These blood vessels are tortuous and immature, consist of large endothelial gap, incomplete basement membrane and absence of smooth muscles(James M Provenzale, Wang, Brenner, Petrella, & Sorensen, 2002).

The T2* MR perfusion imaging represents the dynamic activity of the brain tumor. As the tumor vessels has high leakiness, the contrast agents enter to the tumor bed which result in T2 shortening and signal drop. This is followed by T1 shortening causing increased signal intensity to variable height, depending on the arteriovenous shunting.

The angiographic finding of meningioma ischaracterized by early contrast filling of the lesion which persist late venous phase and slow venous drainage(L.T., J.C., & P.K., 1996). However, in malignant meningioma, early venous drainage is noted due to presence of presence of high arteriovenous shunting. Meningioma is an extra axial tumor with lack of blood brain barrier (BBB) causing sudden contrast intravastation to the tumor bed which appear as sudden signal drop on T2* images and making acute signal drop angle. The signal recovery is depending on the presence of AV shunting. Meningioma with low AV shunting causes relative intravascular contrast stasis due to sluggish venous drainage which also enhance by high endo vascular leakage, results in the T1 shortening, although presence of persistence predominates T2 effect. This results in a curve with little tendency to return to baseline(Chinchure *et al*., 2011). The meningioma has relatively high rCBV values and signal intensity curve upshot after the dip, but never reached the baseline("MR Perfusion Imaging and Intensity- Time Curve Analysis in Cerebral Tumors," 2007), (Zimny & Sasiadek, 2011). In our study, the signal drop angle and signal recovery varies from 3.61^0 to 6.8^0 and %, 33.99% to 120% overshooting the baseline.

Hemangiopericytoma shows hyper perfusion with moderately increase rCBV within tumor bed (Clarençon *et al*., 2011). There is no previous literature on mean signal curve of the above tumors for comparison. In mean signal curve analysis, there is signal drop angle was varying between 8.35^0 to 8.40^0. This suggests moderately increased contrast intravastation to the tumor bed due to extra axial location with corresponding increased hyper perfusion on perfusion study. The signal drop angle and recovery values vary between 8.35^0 to 8.4^0 and 45.69% to 64.02%. The partial signal recovery is suggesting moderate arteriovenous shunting.

Schwannoma has lower rCBV values than in meningioma and the mean signal intensity curve returned to the baseline after signal drop(6). In our study, there was mildly increased rCBV in tumor bed with signal drop varying between 4.62^0 to 10.20^0. This suggests moderately increased microvasculature density within the tumor bed. The signal recovery values varied between 53.87 % to 76.02 %. Because the tumor is outside the BBB, the partial signal recovery suggests high arteriovenous shunting in tumors.

The glioblastoma is highly vascular tumour. It consists of prominent feeding arteries, draining veins with varying degree of arteriovenous shunting (AVS), aberrant vessels, vascular pooling, and mass effect(L.T. *et al*., 1996). The Mean perfusion curve, glioblastoma and other high-grade gliomas shows rapid steep fall due to the leakiness of the BBB. The percentage of the signal recovery variable depending on presence of AV shunting which causes shifting of the contrast

from the tumours bed and thereby causes decreased T1 signal intensity(Cemil, Tun, Polat, Ozen, & Kaptanoglu, 2009). In some glioblastoma the signal rapidly returns to the base line followed by a second smaller dip. This is due to the aberrant vessels, vascular pooling and stasis. In addition, a second dip has been noted in some cases of glioblastoma that represents rapid recirculation of contrast due to AVS, Peak height and signal intensity recovery, as reflected by the MPC, which have been used to differentiate between glioblastoma and single metastases(Soonmee Cha *et al*., 2007).

In our study, allglioblastomas showed moderate to significant increase in vascularity on perfusion map. The signal drop angle varies from 5.6^0 to 9.03^0. The percentage of signal recovery varied between 9.8% to 72.3% in our study. This type of mean signal intensity curve signifies increased microvascular density due to neoangiogenesis within the solid component of the tumor and significant leakiness of blood brain barrier.

The low grade gliomas are WHO grades I/II and they usually show a low rCBVmap(Di Costanzo *et al*., 2008), (Petrella, J.R. and Provenzale, 2000). The perfusion mean curve of these tumours are similar to the MPCof normal appearing white matter. The MPC may appear as moderate to rapid signal intensity drop depending on the degree of BBB leakiness followed by tendency to return towards base line.

The signal recovery of mural nodules of some pilocytic astrocytoma has tendency to overshoot the baseline secondary to a predominance of endovascular leakage and low Arteriovenous shunting. However, some pilocytic astrocytoma are highly vascular like higher-grade gliomas(Petrella, J.R. and Provenzale, 2000), (Bonekamp, Degaonkar, & Barker, 2011). Thomas *et al* studied the potential usefulness of signal intensity in a pilocytic astrocytoma and observed relatively high rCBV with a signal upshot after the dip, but never reached the baseline ("MR Perfusion Imaging and Intensity-Time Curve Analysis in Cerebral Tumors," 2007).

In our study, one case of diffuse astrocytoma was proved on histopathology which showed 6.30^0 signal drop and 98.8 % of signal recovery. This type of signal drop is corresponding to low neovessels density in tumor nodule as compared to high grade astrocytic tumors. The complete recovery is related to very negligible AV shunting of the tumors(Jenkinson *et al*., 2006).

Most oligodendroglia tumors exhibit higher rCBV values than astrocytoma, irrespective of tumoralgrade(S. Cha *et al*., 2001) and difficult to distinguish histology subtype or grade(Covarrubias, Rosen, & Lev, 2004). In our study, out of 3 oligodendroglioma, two were low grade and one was anaplastic variety. Mildly increased vascularity was observed in low grade lesion and moderate vascularity in anaplastic tumor. The signal drop angle varied from 5.1^0 to $6.2^0$and the percentage recovery ranges from 44.48% in anaplastic one to 91.66% in low grade one. The above parameters suggest moderate increase of neoangiogenesis in the tumor bed and leakage of blood brain barrier, more in anaplastic one resulting less signal recovery compared to low grade one. However, one low grade lesion shows sharp signal drop than anaplastic one which are misleading.

Haemangioblastomahas highly vascular mural nodule with high AVS on angiography(L.T. *et al*., 1996) and shows high rCBV as compared with Pilocytic astrocytoma (Bladowska *et al*., 2013). They can show a rapid steep falls in signal intensity with rapid return to baseline. In some hemangioblastoma show a second, smaller dip after first pass. Bing F *et al*. found high value of rCBV in hemangioblastomaand first-pass curve crossing the baseline(Jenkinson *et al*., 2006). SheD.J *et al*. found higher relative peak height and lower relative percentage signal recovery values in hemangioblastoma compared to pilocytic astrocytoma(Kumar, Knopp, & Zagzag, 2010).

In our study, all the lesions are cystic tumors with pial based enhancing mural nodules and prominent flow voids located in cerebellum. On perfusion study, there is increased rCBV. The signal drop varies from 4.8^0 in VHL patient to 9.8^0 in other one. This suggests significant increased neovascularity in tumor nodules which are more than the pilocytic astrocytoma. The recovery of signal varies from 52.05% to 54.16% indicates the high arterio-venous shunting.

Medulloblastomas is a WHO grade IV neoplasm and higher rCBV on perfusion map related to the micro vessel density. Again there were correlation between increasing degree of permeability and increasing tumor grade (J M Provenzale, Mukundan, & Barboriak, 2006). In our study, all meduloblastomas are enhancing with one showing very high rCBV and other showing moderate rCBV on perfusion maps. Low vascular map may be due to susceptibility artefacts resulting from bleed. The signal drop is varying from 4.6^0 to 4.7^0 which indicate high intratumoural neovascularity. The signal recovers were not reaching the baseline with range from 65.28% to 66.18% in our study. The partial signal recovery is due to highly leaky blood brain barriers and intratumoural vascular shunting.

Central neurocytoma is a highly vascular tumor with markedly elevated rCBV on perfusion MRI(She, Xing, Zeng, Shang, & Cao, 2015). In our study, a central neurocytoma showed very high vascularity and rCBV on perfusion map. There is sharp deep of signal (5.9^0) and partial recovery (71.89%) in mean curve analysis.

Yuh EL *et al* had demonstrated markedly elevated rCBV and poor return of mean curve signal to baseline in Ependymoma that may be attributable to fenestrated blood vessels and incomplete BBB (Nabavizadeh *et al*., 2014). In our study, we found a case of supratentorial anaplastic ependymoma showed high relative CBV with sharp deep in signal (5.3^0) and partial signal recovery 71.15%. This indicates high neovascularity in tumor bed with leaky BBB and vascular shunting.

Primary CNS lymphoma has high vascular permeability between as evident by thinned endothelial cells, fenestrations in capillary endothelium, and absence of endothelium between the lumen and basement membrane on electron microscopy(Molnár, O'Neill, Scheithauer, & Groothuis, 1999), (Takeuchi, Matsuda, Kitai, Sato, & Kubota, 2007). At the same time, neovascularization is not a prominent in PCNSL. These causes lower rCBV in lymphoma (Liao *et al*., 2009). MR perfusion mean curve is characterizing by signal recovery goes above the baseline (Hartmann *et al*., 2003). This may to be related to less arterio-venous shunting. On our study, we found a case of lymphoma with similar findings.

The vascularity of the metastatic lesion may depend on the primary malignancy. They are usually highly perfused lesions with high rCBV (Lupo, Cha, Chang, & Nelson, 2005). Two

patterns of MPC are described: a rapid steep fall in signal intensity with little tendency to return to baseline, and a rapid steep fall in SI signal intensity rapid return to baseline.

This study has certain limitation. The biggest challenge to the reliability of the study is due to the small sample size. The study included less number and varieties of brain tumour case as it is a rare tumour. The DSC MR Perfusion study is a semi-quantitative method where absolute value of the parameters cannot be calculated. There is uncertainty about the relationship between tracer concentration and measured reflexivity in the technique. There is difference in perfusions characteristics of large and small vessels within the tumour bed. Variable cardiac output severely affects the perfusion parameters by over and underestimation. Arterial disease like ICA stenosis or occlusion also underestimates the perfusion parameters. Patient's movement during the study distort the mean signal curve. So it is very difficult to get the reliable curve.

CONCLUSION

The signal drop angle and signal intensity recovery followed by pattern of perfusion mean curve give the idea of the tumors dynamics. The Mean perfusion curve along with the with perfusion maps and conventional cross-sectional imaging, can help in the characterization of intracranial tumors.

Conflict of Interest: There is no conflict of interest

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