Imaging of mild traumatic brain injury using \(^{57}\)Co and \(^{99m}\)Tc HMPAO SPECT as compared to other diagnostic procedures

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Source of support: This work was supported by a grant from the HersenStichting Nederland and UCB Pharma, Belgium (Dr Betty van Vleymen).

Summary

Background: Traumatic brain injury (TBI) is usually assessed with the Glasgow Coma Scale (GCS), CT and EEG. TBI can result from either the primary mechanical impact or secondary (ischemic) brain damage, in which calcium (Ca) plays a pivotal role. This study was undertaken to compare the applicability of SPECT using \(^{57}\)Co as a Ca-tracer in patients with mild traumatic brain injury.

Material/Methods: 8 patients with mild TBI (GCS 15) were clinically examined and studied with EEG, neuropsychological testing (NPT) and SPECT within 2 days post-TBI. After iv-administration of 37 MBq (1 mCi) \(^{57}\)Co (effective radiation dose 0.34 mSv·MBq\(^{-1}\); 1.24 rem·mCi\(^{-1}\); physical half-life 270 days, biological half-life 37.6 h), single-headed SPECT (12 h pi) was performed, consecutively followed by standard 925 MBq (25 mCi) Tc-99m HMPAO SPECT.

Results: In 6 of the 8 patients, baseline NPT and SPECT showed focal abnormalities in the affected frontal and temporal brain regions, which were in good topographical accordance. CT and EEG did not detect (structural) lesions in any of these cases.

Conclusions: Single-headed \(^{57}\)Co-SPECT is able to show the site and extent of brain damage in patients with mild TBI, even in the absence of structural lesions. It may confirm and localize NPT findings. The predictive value of \(^{57}\)Co-SPECT should be assessed in larger patient series.

key words: cobalt • SPECT • traumatic brain injury • functional imaging


Word count: 2509

Tables: 2

Figures: 2

References: 32

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BACKGROUND

Minor TBI is usually classified according to symptoms and cause, while the contribution of brain imaging techniques is limited. Some studies [1,2], though not all [3], show that positron emission tomography (PET) and single-photon emission computed tomography (SPECT) may confirm apparent cortical dysfunction as assessed with neuropsychological testing (NPT). Structural imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) usually do not show lesions in mild TBI [4, detailed literature in 5].

Generally, in evaluating the TBI patient, scores on the Glasgow Coma Scale (GCS) [6], and duration of Loss of Consciousness (LOC) and estimates of severity of injury based on Post Traumatic Amnesia (PTA) [7] are useful measures of neuronal injury, and hence outcome.

Mild TBI is usually diagnosed on the basis of loss of consciousness for less than 20–30 minutes, PTA not exceeding 24 hours, a GCS score of 13–15, and no hospitalisation or a brief stay not exceeding 48 hours [8,9]. However, an average mild TBI patient is described as having a brief or no LOC, a GCS of 15 in the emergency room, and PTA of less than one hour [10], or even less than 5 minutes. Hence neither the duration of PTA nor the GCS are useful measures of neuronal injury in mild TBI.

The acute condition in mild TBI is consistently described as a triad of neuropsychological dysfunctions: attention deficits, impaired verbal retrieval, and emotional distress [8]. A majority of patients recover in the following days without further complaints [11]. A subgroup of patients, however, continue to experience disabling symptoms beyond this period, interfering with return to work or resumption of social activities [12]. The failure to predict outcome in this mildly injured group of patients may be related to the lack of a consistent (positive) definition of mild TBI, the varying relative contribution of individual psychological coping strategies after sustaining TBI, and the complex nature of minor TBI.

The application of nuclear neuro-imaging modalities, including positron emission tomography (PET) or single-photon emission computed tomography (SPECT), may increase the accuracy of predicting outcome in this category of patients. Considering the logistical problems posed by nuclear imaging of TBI patients (in the acute phase), SPECT may be more useful in clinical routine than PET, due to the physical half-life of the tracer and camera availability [13–15]. Early and delayed SPECT brain perfusion imaging (flow SPECT) is a rapidly evolving diagnostic technique in TBI [16,17]. However, an intrinsic problem with radiopharmaceuticals for flow-SPECT is the requirement of intact neuronal cell metabolism for tracer fixation, preventing back diffusion and subsequent washout [18,19]. The very nature of minor TBI, however, involving subtle neural cell damage, may decrease or even increase such perfusion tracer fixation, resulting in artefacts.

A different approach involves the use of cobalt (Co) radionuclides as a Ca-analogue to monitor the Ca-mediated damage in minor TBI. We previously studied five patients with moderate TBI using cobalt-55 ($^{55}$Co), PET (Co-PET), non-enhanced CT, MRI, EEG and NPT [20], showing that Co-PET is potentially useful for diagnostic localization of both structural and functional abnormalities in moderate traumatic brain injury. The following pilot study, intended for proof of concept, describes a small series of 8 mild TBI patients studied with cobalt-57 ($^{57}$Co) SPECT, non-enhanced CT, EEG and NPT.

Material and Methods

This study was conducted in patients with mild TBI who were consecutively admitted for overnight observation to the Department of Neurology at the St Luke Hospital in Brugge, Belgium, within 1–2 hours after a road traffic accident, a fall, or a sports injury. The study was approved by the ethics committee of the St Luke Hospital. All patients gave their written informed consent prior to inclusion in the study. The inclusion criteria included age 18 years or older and the mental capability to adhere to the protocol. The exclusion criteria were potential pregnancy, a history of previous cranial trauma, epilepsy or other neurological disorders, as well as mental retardation, psychiatric diseases or chronic drug or alcohol abuse.

Eight patients, seven men and one woman, aged 18 to 60 years (mean 40 years) were enrolled. Baseline information collected at the time of admission (taken from either the patients or their relatives) included past medical history, premorbid intellectual functioning, and cause of the injury. All patients had a neurological examination. The influence of alcohol was assessed by clinical judgement and alcohol dosage in blood.

All patients had brain CT and EEG on the day of admission, Cobalt- and flow-SPECT within 24 hours, and NPT within 2 days post-TBI. Plain CT was performed with a GE ProSpeed SX camera. Contiguous 10 mm-thick slices were made parallel to the orbito-meatal line. The total CT time did not exceed 10 minutes (Figure 1). Awake 21-channel EEGs were performed according to the International Ten-Twenty system for 30 minutes. Hyperventilation for two minutes was used as a challenge. An experienced neurophysiologist read all EEGs, and special attention was given to focal abnormalities.

$^{57}$Co-SPECT of the brain was performed 24 hours after the intravenous administration of 37 MBq (1 mCi)
$^{57}$CoCl$_2$ (Nycomed-Amersham, UK), and flow-SPECT of the brain was performed 15 minutes after intravenous administration of 925 MBq (25 mCi) of Tc-99m HMPAO (Nycomed-Amersham, UK), using a single-headed rotating gamma camera (Toshiba GCA-90B) equipped with a low-energy high-resolution parallel hole collimator. Although a single-headed camera was used in this pilot study for logistical and technical reasons involving the double-tracer ($^{57}$Co/$^{99m}$Tc) assessment, this was deemed sufficient for the purposes of a proof of concept study. Also, it was the purpose of this study, among other things, to show the proof of concept with Nuclear Medicine tools which belong to the minimum standard at any location. As an example, please see Figure 2.

The patient was lying supine with eyes open in a quiet, dimly lit room. Data were acquired in a 64×64 matrix size with 60 projections (step-angle 6°) at 20 seconds (flow-SPECT) or 40 seconds ($^{57}$Co-SPECT) per projection. The radius of rotation did not exceed 22 cm and was as close to the head as possible. No attenuation or scatter correction was applied. The projection data were reconstructed using filtered back projection with a Butterworth filter (order 8; cut-off frequency 0.24 cyc.cm$^{-1}$). The final data were oriented in axial, coronal and transversal planes, and were displayed on 2 pixels (5.3 mm pixel size) on a 10 graded colour scale adjusted for 100% maximum uptake in the cerebellum. The $^{57}$Co-SPECT was consecutively followed by the flow-SPECT, and the total SPECT acquisition time did not exceed 60 minutes. Image analysis ($^{57}$Co- and cerebral blood flow-SPECT) was performed blind to clinical or radiological information. On flow-SPECT, any region in the cerebral cortex and basal ganglia of less than 70% of the maximum cerebellar uptake or 50% in the medid temporal lobe was considered abnormal. On $^{57}$Co-SPECT, the contribution of Co-accumulation in the skull, cerebrospinal fluid, meningeal veins and (transversal and sagittal) sinuses surrounding the brain was discarded, after outlining the circumference of the brain using the flow-SPECT as a ‘brain mask’. This flow-mediated brain outline was used to assess the site and size of any Co-accumulation. Activity on $^{57}$Co-SPECT in the midline area (ascending vessels) or in the choroid plexus was rejected as non-lesion.

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Neuropsychological testing (NPT) was performed within 2 days post TBI. Raw NPT results were collected and age-, gender-, educational level-, or occupational level-corrected scores were calculated where appropriate. In order to make inter-individual comparisons, the disparate test scores were converted to a scale with identical units derived from a normal probability curve based on standard deviation units (SD) [22]. Assessment of the site of lesion with neuropsychological testing was based on the rationale that a number of test score deviations can form a pattern consistent with neuro-anatomically probable behavior patterns [23]. In order to refer to a neuro-anatomical localization, at least three different measures forming a pattern had to be significantly abnormal, meaning that they had to differ more than two standard deviations from the mean in an appropriate control group. Scores between 2 to 3 SD below the mean were considered abnormal, and scores 3 or more SD below the mean were considered abnormal at a high level of confidence [22].

**RESULTS**

Clinical and biographical data, flow- and $^{57}$Co-SPECT data and NPT results are summarized in Table 1.

Neurological examination was normal in all patients, and the GCS score was 15 in all patients. Information obtained from patients and witnesses revealed no evidence of a PTA-period exceeding five minutes. No patient or witness of the accident reported LOC. Non-enhanced CT and EEG did not show structural lesions in any of these cases. Overall, all subjects made adequate efforts to perform their NPT examination as correctly and quickly (where appropriate) as possible.

We found Co deposition in 5 out of 7 patients. In 4 of these 5 patients, at least partly corresponding neuropsychological deficits were found. We found no $^{57}$Co deposition in 2 patients, in whom no neuropsychological deficits could be demonstrated, either. These results are summarized in Table 2.
Calcium is an important mediator in the pathophysiology of mild TBI [19,24], and visualization of Ca flux has been suggested to be an indicator of the amount and severity of brain injury [25–27]. Unquestionably, the best tracer for Ca would be Ca. However, due to their radiation characteristics, no Ca isotopes are suitable for in vivo imaging [21]. There is a wide variety of in vitro evidence that Co deposition actually reflects Ca accumu-
lation, and hence may point to regional brain damage [28]. The exact mechanism of Co deposition still needs to be elucidated. The extra-vascular contribution to Co deposition in vivo is relatively slow, essentially unidirectional (without back diffusion or washout) and consists of gath-
ing through voltage-dependent or receptor-operated Ca channels, accumulation of protein (albumin) bound Co via the disrupted blood-brain barrier (BBB), and infiltr-
ation of Co-labelled leukocytes [28]. The intra-vascular contribution to Co deposition may also be considerable (hemorrhage; luxury perfusion) [28]. Both types of con-
tribution are time-dependent, and different uptake mechanisms may intermingle in the course of time.

As expected from clinical investigation, CT did not detect any abnormalities in our patients. CT has proven its clinical value, especially in the detection of subdural or epidural hematoma, subarachnoid hemorrhage and cerebral swelling due to edema. Not all TBI patients should undergo CT, however, because of radia-
tion exposure and financial costs [29]. Key indications for CT are impaired consciousness, skull fracture, and the presence of certain focal neurological signs.

Flow-SPECT has clinical value in TBI, especially as a negative predictor, i.e. a normal acute flow-SPECT is correlated with a clinical outcome without neurological or neuropsychological sequelae [15,16,30,31]. This is fully consistent with the presumed cellular retention mechanism of both perfusion tracers. In our study, 57Co-SPECT revealed lesions in TBI which only par-
tially correlate with findings on flow-SPECT (see Table 2). This emphasizes both the high sensitivity of Co accumu-
lation in focal brain damage and the advantage of hot spot-detection (Co) over cold spot-detection (flow). The detection of small high-content ‘hot’ Co lesions is less susceptible than the detection of ‘cold’ flow lesions to differences in the observer’s detection threshold, such as a non-linear scale display, non-uniform pixel-intensity profile, and the shape and width of the lesion.

The actual nature of the impact during TBI partly determines site and size of the brain damage and, hence, the expected NPT deficits (the choice of the NPT battery was based on previous reported test results in mild TBI [23]). To begin with, damage to the brain can appear as the result of the actual blow, called coup, or as the result of contusion in an area opposite to the blow, called contrecoup [32]. Most of these lesions are the result of the force of impact in static injuries, in which a rela-
tively still victim receives a blow to the head. The impor-
tance of contrecoup lesions, even in less injured subjects, cannot be underestimated, since it has been shown that at least half of the victims experience focal injuries at the contrecoup site [8,10]. Coup and contrecoup lesions account for specific and localizable behavioral changes accompanying closed-head TBI [25]. Considering the nature of the accident, the data from imaging and NPT pointed at defects in the frontal region in our subjects A-E; it can be expected that these were coup localizations. In cases B-E these sites showed evident Co accu-
mulation. In subjects B and C possible contrecoup Co-uptake (right parieto-occipital region) accompanied coup Co-activity (Figure 2). Interestingly, flow SPECT never indicated a lesion at the contrecoup site. NPT demonstrated abnormalities in the contrecoup region in subject C, but not B. In subject A there was no evidence for Co-activity in the predicted coup localization, but there was clear Co-uptake at the contrecoup site.

Secondly, clearly distinguishable focal deficits are much less likely to be seen when there is momentum during the impact, as occurs in moving vehicle accidents. In such cases damage tends to be widespread, without clear evidence of lateralization, regardless of the site of impact. No such TBI pattern was found in the patients in this study.

Thirdly, shear effects, in the form of microscopic lesions resulting in damage to axons (diffuse axonal injury) probably cannot be demonstrated by the Co-technique.

**CONCLUSIONS**

The results of this study suggest a role for 57Co as a trac-
er for mild traumatic brain injury. We found a good association between 57Co deposit and neuropsychologi-

cal functioning deficits in a time frame shortly after the injury. 57Co appeared to be especially valuable in show-
ing contrecoup lesions, which is of considerable clinical impo-
rtance. The clinical significance impact of 57Co-
SPECT thus may lie in estimating the organic aspect of the impact of brain injury in patients. This is a matter of some importance, since both organic and environmental factors can be responsible for the neuropsychiatric sequelae after mild TBI. The relative impact of these separate factors is difficult to determine. Patients with persistent symptoms have long been regarded as malingerers, with vague complaints and minor NPT disturbances, resulting in considerable strain for both these patients and their caregivers.

**Acknowledgements**

We would like to thank Dr Karel Schelstraete for reviewing the manuscript, Ms Sonja Van Haesebrouck for secretarial assistance, Mr. Frans Adams, and Mr. Kris Vastesaeger for helping with the data-acquisition, Dr Luc Beelaert, Dr Jaques Goethals, Dr Philip Maere for patient inclusion and Mr Johan van Coile for helping in data-analysis.

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