AWARD NUMBER: W81XWH-14-C-0048

TITLE: Pupillometry and Saccades as Objective mTBI Biomarkers

PRINCIPAL INVESTIGATOR: LTC Jose E. Capo-Aponte

CONTRACTING ORGANIZATION: Geneva Foundation
Tacoma, WA 98402

REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
1. REPORT DATE
October 2016

2. REPORT TYPE
Annual

3. DATES COVERED
30 Sep 2015 - 29 Sep 2016

4. TITLE AND SUBTITLE
Pupillometry and Saccades as Objective mTBI Biomarker

5a. CONTRACT NUMBER
W81XWH-14-C-0048

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)
LTC Jose E. Capo-Aponte

E-Mail: Jose.E.CapoAponte.mil@mail.mil

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Geneva Foundation
Tacoma, WA 98402

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR’S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
mild traumatic brain injury (mTBI), infrared pupillometers, King-Devick (KD) test, near point of convergence (NPC) rule, objective biomarkers

14. ABSTRACT
The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mild traumatic brain injury (mTBI) using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred mTBI and 100 age-matched non-TBI (controls) military personnel are to be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed to determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. Preliminary results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI.

15. SUBJECT TERMS
Nothing listed

16. SECURITY CLASSIFICATION OF:

a. REPORT
Unclassified

b. ABSTRACT
Unclassified

c. THIS PAGE
Unclassified

17. LIMITATION OF ABSTRACT
Unclassified

18. NUMBER OF PAGES
29

19a. NAME OF RESPONSIBLE PERSON
Jose E. Capo-Aponte

19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION:
The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4% (DVBIC 2015). The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters (Marion 2011). The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred acute mTBI (≤72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed to determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. There are five hypotheses being tested. First, those who have suffered acute mTBI/concussion will have abnormal PLR findings in comparison to controls. Second, those who have suffered acute mTBI/concussion will have abnormal KD test score in comparison to controls. Third, those who have suffered acute mTBI/concussion will have receded NPC compared to controls. Fourth, those who have suffered acute mTBI/concussion will have higher Convergence Insufficiency Symptoms Survey (CISS) scores in comparison to controls. Fifth, the PLR values measured by the PLR-200 pupillometer (research grade) are not different to those measured by the NPi-100 pupillometer (clinic grade).

BODY:
Major Task 1: Administrative Requirements
Subtask 1: Hire Optometrist and Ophthalmic Assistance: COMPLETED
Subtask 2: Purchase equipment and supplies: COMPLETED
Subtask 3: WAMC IRB approval: COMPLETED
Subtask 4: USAMRMC HRPO approval: COMPLETED

Major Task 2: Data Collection on Military Personnel at WAMC
Subtask 1: Procedures and data collection training/standardization: COMPLETED
Subtask 2: Complete data collection in 100 subjects with mTBI: COMPLETED
Subtask 3: Complete data collection in 100 age-matched control subjects (non-TBI): COMPLETED

Major Task 3: Data Analysis and Report Writing
Subtask 1: Complete progress report: COMPLETED
WAMC IRB and USAMRMC HRPO approved the study protocol continuing review on 14 March 2016. Quarterly reports \((n = 3)\) were submitted during Year 2 to Contract Specialist, U.S. Army Medical Research Acquisition Activity and Science Officer, Congressionally Directed Medical Research Programs, USAMRMC, following the timeline indicated in the contract.

Subtask 2: Complete data analysis: PRELIMINARY ANALYSIS COMPLETED

All subjects were corrected to 20/20 and had similar spherical equivalent refractive error (mTBI \(-0.49 \pm 2.07\) D; non-TBI \(+0.12 \pm 0.98\) D; \(p = 0.25\)). All subjects, in both groups, had normal pupil response and no afferent pupil defect with the manual penlight examination. Pupillary light reflexes (Figure 1) and oculomotor functions can be affected by age; therefore, an accurate data analysis requires to age-match the experimental (mTBI) and the control subjects. Preliminary analysis was completed to evaluate initial results. The initial results compared monocular (right eye (OD; left eye (OS)) PLR of 100 Service members with mTBI during the acute stage (≤72 hrs) post injury and 100 age-matched controls who had neither experienced an mTBI nor been exposed to a blast event. The initial analysis showed that following results:

**Figure 1. Schematic diagram of the pupillary reaction curve illustrating PLR recorded parameters:** 1) maximum diameter; 2) minimum diameter; 3) percent of constriction; 4) constriction latency; 5) average constriction velocity; 6) maximum constriction velocity; 7) average dilation velocity; 8) 75% recovery time.

1) Maximum pupil diameter showed no significant difference between the acute mTBI and control group (OD \(P = 0.201\); OS eye \(P = 0.171\)), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.
2) Minimal pupil diameter showed no significant difference between the acute mTBI and control group (OD $P = 0.431$; OS $P = 0.30$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

3) Percent of pupil constriction showed no significant difference between the acute mTBI and control group (OD $P = 0.188$; OS $P = 0.719$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.
4) Constriction Latency (Con Lat) for the preliminary findings did not show a statistical difference (OD $P = 0.259$; OS $P = 0.108$), see figure below. This is inconsistent with the only pupillometry study in the literature in subacute patients (Capo-Aponte 2013); however time post-injury is different in both studies (acute vs. subacute). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

5) Maximum constriction velocity (MCV) for the preliminary findings did not have between groups statistical difference (OD $P = 0.423$; OS $P = 0.509$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.
6) Average Constriction velocity is significantly reduced in mTBI subjects mTBI (OD $P < 0.0001$; OS $P = 0.0001$), see figure below. This is in agreement with a previous study (Capo-Aponte 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

7) Average dilation velocity (ADV) is significantly reduced in mTBI subjects mTBI (OD $P < 0.0001$; OS $P < 0.0001$), see figure below. This is in agreement with a previous study (Capo-Aponte 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.
8) The total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction is significantly longer in mTBI group (OD $P < 0.0001$; OS $P < 0.0001$), see figure below. This is in agreement with a previous study (Capo-Aponte 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

9) mTBI group had a significantly reduced NPC compared to the control group ($P < 0.0001$), see figure below.
10) The KD test is used to evaluate saccadic eye movement. The KD test is based on measurement of the speed of rapid number naming and involves reading aloud a series of single-digit numbers from left to right on three test cards. KD test showed significantly longer performance time for mTBI group compared to the control group \((P < 0.0001)\). The expected mean time (sec) for the KD test are: pass <45; borderline 45-60; fail >60.

11) The CISS documents the frequency of visual symptoms. Each symptom question had five possible answers with an associated value, where 4 = always, 3 = frequently, 2 = sometimes, 1 = rarely, and 0 = never. Thus, the cumulative symptoms score can vary from 0 to 60. An average normal adult should score <21 points. There was a significantly higher score on CISS score for the mTBI group \((P < 0.001)\), see figure below.
Subtask 3: Complete final report: NO INITIATED (A 6-month No Cost Extension was approved to complete data analysis and manuscript writing.)

KEY RESEARCH ACCOMPLISHMENTS:
- Received Yr-2 continuing review approval by WAMC IRB
- Received Yr-2 continuing review approval by USAMRMC HRPO
- Collected Data in 100 mTBI subjects
- Collected Data in 100 age-matched control subjects

REPORTABLE OUTCOMES:
- Presented lecture at WAMC Annual Research Symposium on 4 May 2016. First Place prize for faculty lectures. (Appendix A).
- Presented poster at the American Optometric Association (AOA) Meeting on 2 July 2016 Selected on Top 5 research presentation at the meeting (Appendix B).
- Presented lecture at the American Optometric Association (AOA) Meeting on 3 July 2016 (Appendix C).
- Presented poster at the Military Health System Research Symposium (MHSRS) on 16 August 2016. Second Place prize for all posters in the category (Appendix D)

CONCLUSION:
Preliminary results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI.

REFERENCES:

APPENDICES:
- Appendix A: Lecture at WAMC Annual Research Symposium (4 May 2016)
- Appendix B: Poster at American Optometric Association (2 July 2016)
- Appendix C: Lecture at American Optometric Association Meeting (3 July 2016)
- Appendix D: Poster at Military Health System Research Symposium (16 Aug 2016)
- Appendix E: Article published in the Journal of the Neurological Sciences: Assessment of the King-Devick (KD) test for screening acute mTBI/concussion in warfighters (Sep 2016)
Pupillometry and Saccades as Objective mTBI Biomarker

RIF13R623
W81XWH-14-C-0048

PI: LTC Jose Capo-Aponte, OD, PhD
Org: Womack Army Medical Center/Geneva Foundation
Award Amount: $491,815

Study/Product Aim(s)
- The DOD reported 333,169 cases of traumatic brain injury (TBI) confirmed since 2000, with 82.4% diagnosed with mild TBI (mTBI)
- mTBI diagnosis is challenging for the military due to lack of objective assessment tools
- The aim of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively.

Approach
100 acute mTBI (≤72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center. The study will determine within each group the effectiveness of these COTS tests, individually and/or in combination, to correctly identify patients with mTBI.

Timeline and Cost

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<td>Task 3: Data Analysis and Report Writing</td>
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| Estimated Budget ($K)                         | $255.9 | $235.9 | NTE   |

Goals/Milestones
- **FY15 Goals** – Study initiation / Initiate Data collection
  - Hire study staff and purchase equipment/supplies
  - Initial protocol approval by WAMC IRB and MRMC HRPO
  - Enroll 100 mTBI subjects
  - Enroll 100 age-matched non-TBI subjects

- **FY16 Goals** – Cont. Data collection / Data Analysis / Reports
  - Continuing review approval by WAMC IRB and MRMC HRPO
  - Cont. enrollment mTBI
  - Cont. enrollment age-matched non-TBI subjects
  - Data Analysis and Report Writing (in Progress)

Comments/Challenges/Issues/Concerns
- Staff hiring issues delayed study completion; however a 6-month No Cost extension was approved

Budget Expenditure to Date
- Projected Expenditure: $393,452
- Actual Expenditure: $287,919

**Accomplishment:** Preliminary results showed 3 of 8 PLR parameters are statistically different between groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. KD test and NPC are also significantly effected in mTBI group.

**Updated:** (24 Oct 2016)
Validation of Visual Objective Biomarkers for Acute non-Blast Mild Traumatic Brain Injury (mTBI)

LTC Jose E. Capó-Aponte, OD, PhD, FAAO

Department of Optometry
Womack Army Medical Center, Fort Bragg, NC

Introduction

• The DOD reported that over 340,000 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
• The diagnosis of mTBI has been a challenge for the military primarily because:
  - Lack of objective assessment tools
  - Diagnosis is based on self-reported symptoms by injured Warfighters
  - Overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder
• Prompt and accurate diagnosis and management of mTBI generally increases prognosis for recovery and safe return to duty (RTD).
• Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma.

Methods: Design

• Case-Control Correlational
• 200 AD military personnel
  - 100 acute mTBI: 87 males & 13 females
    - Documented mTBI/concussion during the acute phase (≤ 72 hrs)
    - ≤ 30 min Loss of Consciousness
    - ≤ 24 hrs Post-Traumatic Amnesia
    - ≤ 24 hrs Alteration of Mental State
    - Glasgow Coma Scale score (13 – 15)
    - Normal structural brain imaging
  - 80 age-matched Non-TBI: 79 males & 21 females
• Age ranged from 19 to 44 years; Mean age 26.31±5.81 years

Methods: Pupillometry

NeuroOptics PLR-200
Hand-held, easy to use, quick, deployable, objective, non-invasive, requires no specialized training and causes no added discomfort or risk to the patient.

- Monocular Infrared pupillometry under mesoscopic (dim) conditions (~3 cd/m²).
- Subject fixated with the non-tested eye on a distance target (10 ft).
- Stimulus: 180 µW light for 185 msec.
- 8 pupillary light reflex (PLRs) were recorded twice in the right eye and then twice in the left, alternating between eyes with an interval of about 10 seconds between recording.

Gaps

• Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to diagnose Warfighters with mTBI/concussion.
• Valid objective markers are important in the field to assist deployed clinicians to make an accurate determination of fit for duty (FFD)/RTD or evacuation.
• DoD WG- Ideal tool must be: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, and low cost.

Objectives

• This study investigates oculomotor functions as potential biomarkers for acute mTBI: pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements
• Approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision
• It is not surprise that the patient with TBI may manifest visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The authors have no financial interest on any of the products included in this study.

Funded by US Army Medical Research and Materiel Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP), Award # W81XWH-14-C-0049.
1) Max. Pupil Diameter
2) Min. Pupil Diameter
3) % of Constriction
4) Constriction Latency
5) Avg. Constriction Velocity
6) Max. Constriction Velocity
7) Avg. Dilation Velocity
8) 75% Recovery of Dilation

Methods: Pupillometry

Methods: Near Point Convergence

- Near Point Rule was used to examine NPC
- 20/30 Snellen single letter stimulus.
- Repeated 2X

Methods: King-Devick Test

Eye movement/version test: Subject is asked to read numbers aloud while being timed. Speed and accuracy is emphasized.

Methods: CISS

Convergence Insufficiency Symptoms Survey

- Score based on scale:
  - always (4)
  - frequently (3)
  - sometimes (2)
  - rarely (1)
  - never (0)
- Passing score ≤20

Results: Maximum Diameter

Results: Minimum Diameter
Results: % of Constriction

OD: \( P = 0.188 \)
\( C: 33.08 \pm 3.94 \)
\( M: 32.30 \pm 4.68 \)

OS: \( P = 0.719 \)
\( C: 33.30 \pm 4.12 \)
\( M: 33.09 \pm 4.79 \)

Results: Constriction Latency

OD: \( P = 0.259 \)
\( C: 219.4 \pm 21.67 \)
\( M: 215.9 \pm 22.17 \)

OS: \( P = 0.108 \)
\( C: 219.4 \pm 21.67 \)
\( M: 215.9 \pm 22.17 \)

Results: Avg Constriction Velocity

OD: \( \*P < 0.0001 \)
\( C: 4.01 \pm 0.56 \)
\( M: 3.63 \pm 0.77 \)

OS: \( \*P < 0.0001 \)
\( C: 4.09 \pm 0.55 \)
\( M: 3.68 \pm 0.79 \)

Results: Max Constriction Velocity

OD: \( P = 0.423 \)
\( C: 5.26 \pm 0.73 \)
\( M: 5.18 \pm 0.82 \)

OS: \( P = 0.509 \)
\( C: 5.37 \pm 0.70 \)
\( M: 5.29 \pm 0.81 \)

Results: Avg Dilation Velocity

OD: \( \*P < 0.0001 \)
\( C: 0.91 \pm 0.22 \)
\( M: 0.62 \pm 0.27 \)

OS: \( \*P < 0.0001 \)
\( C: 0.97 \pm 0.22 \)
\( M: 0.62 \pm 0.27 \)

Results: 75% Dilation Recovery Time

OD: \( \*P < 0.0001 \)
\( C: 2.65 \pm 0.63 \)
\( M: 3.97 \pm 1.09 \)

OS: \( \*P < 0.0001 \)
\( C: 2.54 \pm 0.66 \)
\( M: 4.03 \pm 1.11 \)
Results: Near Point of Convergence

*P < 0.0001
C: 8.18 ± 2.15
M: 13.24 ± 8.07

Results: King-Devick Test

(Subjective and uses baseline pre-injury time)

*P < 0.0001
C: 44.24 ± 7.74
M: 59.20 ± 19.06

Results: CISS

(Subjective)

*P < 0.0001
C: 8.82 ± 7.42
M: 24.76 ± 12.06

Results: Near Point of Convergence

*P = 0.0301
C: 11.50 ± 10
M: 13.24 ± 8.07

Results: King-Devick Test

*P = 0.0001
C: 49.24 ± 7.35
M: 58.26 ± 9.46

Conclusion

– Oculomotor functions tests are effective tools to identify mTBI
• Pupillometry: PLR (i.e., ACV, ADV, T75%) – Objective test
• NPC rule: Convergence eye movement – Objective test
• KD Test: Saccadic eye movement – Objective test
• CISS: visual symptoms has good correlation with affected visual functions
– Easily performed by subjects, including mTBI
– Easily administered by technicians (can delegate to medics)
– Faster (3 min) than conventional oculomotor examination (15 min)
  • Pupillometry = 30 sec; NPC = 15 sec; KD Test = 60 sec; CISS = 60 sec
– Provide tool to determine RTD (Military Ops) or Return-to-Play (Sport)
– Future Direction:
  • Develop concussion risk matrix/algorithm based on parameters sensitivity and specificity to assist in RTD/RTP decision

Acknowledgements

– Womack Army Medical Center (WAMC)
  • Thomas A. Beltran

– Defense and Veterans Brain Injury Center / WAMC Department of Brain Injury Medicine
  • Dr. Wesley R. Cole

– The Geneva Foundation / WAMC
  • Joseph Y. Dumayas
  • Dr. Ashley Ballard

– US Army Aeromedical Laboratory
  • LTC David V. Walsh
References


Introduction

The Department of Defense reported that over 340,000 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.5% of all cases. Unfortunately, Warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. Currently, there is a lack of mTBI objective biomarkers, and this study aims to identify and validate objective visual biomarkers for mTBI.

Methods

200 military personnel (100 acute mTBI ≤ 72 hrs) and 100 age-matched Controls; 19 to 44 yrs with mean age 26.31±5.81 yrs) were evaluated with three tests and a subjective questionnaire. Pupillary Light Reflex (PLR) functions were measured with a handheld monocular infrared pupillometer (NeurOptics PLR-200) (Fig 1). Near Point of Convergence (NPC) was measured with a NPC rule (Fig 2). Saccadic eye movement function was assessed with the King-Devick (KD) Test (Fig 3). The Convergence Insufficiency Symptoms Survey (CISS) was used to assess visual symptoms (Fig 4).

Results

Of the 8 PLR outcome measures, only average the constriction velocity, average dilation velocity and 75% recovery time were significantly affected in mTBI group (Figs 5, 6 and 7). In addition, mTBI group had significantly higher scores for NPC (receded NPC; P < 0.0001), KD Test (took longer; P < 0.0001), and CISS (more symptoms; P < 0.0001) than Controls as shown in Figs 8, 9, and 10.

Conclusion

Results strongly suggest the PLR (i.e., ACV, ADV, T75%) and NPC tests can serve as objective biomarkers for mTBI. The CISS and KD tests also appear to be useful for identifying mTBI, despite of being subjective. These tests that can be quickly interpreted by frontline providers, which is vitally important due to the increased risk of sending an injured Warfighter back to the fight and exposing him or her to greater damage to an already injured brain.
Validation Study of Visual Objectives Biomarkers for Acute Mild Traumatic Brain Injury
American Optometric Association Meeting 3 July 2016
LTC Jose E. Capó-Aponte, OD, PhD, FAAO

Introduction

• The DOD reported that over 340,000 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
• The diagnosis of mTBI has been a challenge for the military primarily because: lack of objective assessment tools; overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD); interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters.
• Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery and safe return to duty (RTD).
• Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma.
• Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.

Methods: Design

• Case-Control Correlational
• 200 AD military personnel
  – Age ranged from 19 to 44 years: Mean age 26.31±5.81 years
    • 100 acute mTBI: 87 males & 13 females
      – Medically documented mTBI/concussion during the acute phase (≤ 72 hrs)
        – ≤ 30 min Loss of Consciousness
        – ≤ 24 hrs Post-Traumatic Amnesia
        – ≤ 24 hrs Alteration of Mental State
        – Glasgow Coma Scale score (13 – 15)
        – Normal structural brain imaging
    • 100 age-matched Non-TBI: 79 males & 21 females

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The authors have no financial interest on any of the products included in this study.

Funded by US Army Medical Research and Material Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). Award # W81XWH-14-C-0048.
Methods: Pupillometry

1) Max. Pupil Diameter
2) Min. Pupil Diameter
3) % of Constriction
4) Constriction Latency
5) Avg. Constriction Velocity
6) Max. Constriction Velocity
7) Avg. Dilation Velocity
8) 75% Recovery of Dilation

Methods: Near Point Convergence

• Near Point Rule was used to examine NPC
• 20/30 Snellen single letter stimulus.
• Repeated 2X

Methods: King-Devick Test

Eye movement/version test: Subject is asked to read numbers aloud while being timed. Speed and accuracy is emphasized.

Methods: CISS

Convergence Insufficiency Symptoms Survey

• Score based on scale:
  - always (4)
  - frequently (3)
  - sometimes (2)
  - rarely (1)
  - never (0)
• Passing score ≤20

Results: Maximum Diameter

Results: Minimum Diameter
Results: % of Constriction

OD: $P = 0.188$
C: 33.08 ± 3.94
M: 32.30 ± 4.68

OS: $P = 0.719$
C: 33.30 ± 4.12
M: 33.09 ± 4.79

Results: Constriction Latency

OD: $P = 0.259$
C: 219.4 ± 21.67
M: 215.9 ± 22.17

OS: $P = 0.108$
C: 219.4 ± 21.67
M: 215.9 ± 22.17

Results: Avg Constriction Velocity

OS: $*P < 0.0001$
C: 4.09 ± 0.55
M: 3.68 ± 0.79

OD: $*P < 0.0001$
C: 4.01 ± 0.56
M: 3.63 ± 0.77

Results: Max Constriction Velocity

OD: $P = 0.423$
C: 5.26 ± 0.73
M: 5.18 ± 0.82

OS: $P = 0.509$
C: 5.37 ± 0.70
M: 5.29 ± 0.81

Results: Avg Dilation Velocity

OS: $*P < 0.0001$
C: 0.97 ± 0.22
M: 0.62 ± 0.27

OD: $*P < 0.0001$
C: 0.91 ± 0.22
M: 0.62 ± 0.27

Results: 75% Dilation Recovery Time

OS: $*P < 0.0001$
C: 2.54 ± 0.66
M: 4.03 ± 1.11

OD: $*P < 0.0001$
C: 2.65 ± 0.63
M: 3.97 ± 1.09
**Results: Near Point of Convergence**

*P* < 0.0001

- **C:** 8.18 ± 2.15
- **M:** 13.24 ± 8.07

**Results:** Near Point of Convergence

**Results: King-Devick Test**

*P* < 0.0001

- **C:** 44.24 ± 7.74
- **M:** 59.20 ± 19.06

**Results:** King-Devick Test (Subjective)

**Results: CISS**

*P* < 0.0001

- **C:** 8.82 ± 7.42
- **M:** 24.76 ± 12.06

**Results:** CISS (Subjective)

**Discussion**

- All methods prove effective tool to differentiate mTBI Vs. Controls.
- Objective component: PLR (i.e., ACV, ADV, T75%)
- Objective and Subjective component: NPC
- Subjective component: KD test
- Good correlation with CISS
- Easily performed by subjects, including mTBI
- Easily administered by technicians
- Faster (3 min) than conventional oculomotor examination (15 min)
- Provide tool to expedite mTBI diagnosis and management
- Delegate to technician/medics
- Future Direction
  - Develop decision matrix to assist medical personnel make RTD decision

**Acknowledgement**

- Womack Army Medical Center (WAMC)
  - Thomas A. Beltran
- Defense and Veterans Brain Injury Center / WAMC
  - Dr. Wesley R. Cole
- The Geneva Foundation / WAMC
  - Joseph Y. Dumayas
  - Dr. Ashley Ballard
- US Army Aeromedical Laboratory
  - LTC David V. Walsh

**WAMC**

Department of Optometry

Questions?
References

APPENDIX D
Validation of Visual Objective Biomarkers for Acute Concussion

Jose Capo-Aponte, OD, PhD1, Wesley R. Cole, PhD2, Thomas A. Beltran, BS3, David V. Walsh, OD, PhD4, Joseph Y. Dumayas, MS2,5

1Department of Optometry, WAMC, Fort Bragg, NC; 2Department of Clinical Investigations, WAMC, Fort Bragg, NC; 4U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL; 5Geneva Foundation1Intrepid Spirit, Womack Army Medical Center (WAMC), Defense and Veterans Brain Injury Center, GDIT, Fort Bragg, NC;

Introduction
According to the DoD, 82.5% of the 340,000 diagnosed traumatic brain injuries (TBI) since 2000 have been concussion/ mild TBI (mTBI). Accurate and quick diagnosis of mTBI can assist with return to duty (RTD) decisions. However, there is a lack of objective mTBI biomarkers. As approx. 30 areas of the brain and 7 of 12 cranial nerves deal with vision, it is reasonable to expect visual problems post mTBI. This study aims to identify and validate objective visual biomarkers for mTBI.

Methods
200 military personnel (100 acute mTBI ≤ 72 hrs) and 100 age-matched Controls; 19 to 44 yrs with mean age 26.31±5.81 yrs) were evaluated with three tests and a self-report questionnaire. Pupillary Light Reflex (PLR) functions were measured with a hand-held monocular infrared pupillometer (NeurOptics PLR-200; Fig 1). Near Point of Convergence (NPC) was measured with a NPC rule (Fig 2). Saccadic eye movement function was assessed with the King-Devick (KD) Test (Fig 3). Visual symptoms were assessed with the Convergence Insufficiency Symptoms Survey (CISS (Fig 4).

Results
Three of the eight PLR outcome measures were significantly impacted by group status: Average Constriction Velocity (ACV), Average Dilation Velocity (ADV), and 75% Recovery Time (T75%) (Figs 5, 6 and 7). In addition, mTBI group had significantly higher scores for NPC (i.e. receded NPC; p < 0.0001), took longer on the KD Test (p < 0.0001), and rated more symptoms on the CISS (p < 0.0001) than Controls (Figs 8, 9, and 10). Effect sizes (Cohen’s d) were generally very large.

Conclusion
Results strongly suggest the PLR (i.e., ACV, ADV, T75%) and NPC tests could serve as objective biomarkers for acute mTBI. The CISS and KD tests also appear to be useful for identifying mTBI related problems, despite being more subjective. All of these assessments are deployable, can be quickly administered by non-eye care providers, and are easily interpreted by frontline providers. These factors are important due to the risks associated with prematurely returning an injured Warfighter to duty. Future studies should establish diagnostic algorithms.


Fig 2. Left: Near Point Convergence (NPC) rule. Right, demonstration of NPC assessment using a 20/30 Snellen single letter stimulus.

Fig 3. King-Devick (KD) Test. Right: Top left, Demo Card; Top right Test 1; Lower left, Test 2; Lower right, Test 3. Cumulative times were recorded.

Fig 4. Convergence Insufficiency Symptoms Survey (CISS). Each question was scored based on severity: always (4), frequently (3), sometimes (2), rarely (1), and never (0). A passing score is ≤ 21.

Fig 5. Average Constriction Velocity. The mTBI group showed slower right-sided average constriction velocity than the Control group.

Fig 6. Average Dilation Velocity. The mTBI group showed slower average dilation velocity than the Control group.

Fig 7. 75% Recovery (re-dilation) Time. The mTBI group showed longer time to reach 75% re-dilation than the Control group.

Fig 8. Near Point Convergence. mTBI group had more receded NPC than Controls.

Fig 9. King-Devick Test. mTBI group took longer to complete than Controls.

Fig 10. CISS. mTBI group showed more symptoms (higher scores) than Controls.

Disclaimer: The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Funding: US Army Medical Research and Materiel Command, FY13 Department of Defense Army Rapid Innovation Fund Research Programs of the Office of the Congressionally Directed Medical Research Programs, Award # W81XWH-14-1-C-0048.
Assessment of the King-Devick® (KD) test for screening acute mTBI/concussion in warfighters

David V. Walsh, OD, PhD a,*, José E. Capó-Aponte, OD, PhD b, Thomas Beltran, BS c, Wesley R. Cole, PhD d, Ashley Ballard, OD b, Joseph Y. Dumayas, MS b

a Vision Protection and Performance Division, U.S. Army Aeromedical Research Laboratory, 6901 Farrel Rd, Fort Rucker, AL 36362, United States
b Department of Optrometry, Womack Army Medical Center, 2817 Reilly Rd; Stop A, Fort Bragg, NC 28310, United States
c Department of Clinical Investigation, Womack Army Medical Center, 2817 Reilly Rd; Stop A, Fort Bragg, NC 28310, United States
d Department of Brain Injury Medicine/Defense and Veterans Brain Injury Center, Womack Army Medical Center, 2817 Reilly Rd; Stop A, Fort Bragg, NC 28310, United States

A R T I C L E   I N F O

Article history:
Received 30 May 2016
Received in revised form 8 September 2016
Accepted 8 September 2016
Available online 11 September 2016

Keywords:
King-Devick (KD) test
Saccades
Mild traumatic brain injury (mTBI)
Military

A B S T R A C T

Objectives: The Department of Defense reported that 344,030 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.3% of all cases. Unfortunately, warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. This study aims to identify and validate an eye-movement visual test for screening acute mTBI.

Methods: Two-hundred active duty military personnel were recruited to perform the King-Devick® (KD) test. Subjects were equally divided into two groups: those with diagnosed acute mTBI (≤72 h) and age-matched controls. The KD test was administered twice for test-retest reliability, and the outcome measure was total cumulative time to complete each test.

Results: The mTBI group had approximately 36% mean slower performance time with significant differences between the groups (p < 0.001) in both tests. There were significant differences between the two KD test administrations in each group, however, a strong correlation was observed between each test administration.

Conclusions: Significant differences in KD test performance were seen between the acute mTBI and control groups. The results suggest the KD test can be utilized for screening acute mTBI. A validated and rapidly administered mTBI screening test with results that are easily interpreted by providers is essential in making return-to-duty decisions in the injured warfighter.

Published by Elsevier B.V.

1. Introduction

The Department of Defense reported that 344,030 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.3% of all cases [1]. Warfighters who experienced mild head impacts producing subtler injuries are harder to diagnose versus those warfighters who have suffered moderate to severe head injuries. Some of the confounders in identifying post-concussive problems include the overlap of symptoms in co-morbid disorders such as post-traumatic stress disorder (PTSD) [8,20], and the difficulty in diagnosing self-reported symptoms to the health provider [19].

A recently convened military mTBI diagnostics workshop emphasized the lack of biomarkers or diagnostic tests for mTBI [15,19]. Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to diagnose warfighters with mTBI/concussion [15]. In combat or training scenarios, warfighters having cognitive and neurosensory difficulties triggered by an mTBI event can put lives and safety in danger when operating in environments that depend on optimal situational awareness and perception of the surrounding environment. Having a rapid and accurate diagnostic tool in the management and treatment of mTBI generally improves an individual’s prognosis for neurological recovery [10,17,18] and safe return-to-duty (RTD) [9,11,25]. Valid diagnostic tests are particularly important in theater to assist deployed clinicians in making accurate determination of RTD or evacuation from theater. Returning a warfighter with a possible head injury back to duty prior to recovery puts the warfighter at a greater risk of disability if they suffer further brain trauma [22].

Seven of the twelve cranial nerves, along with approximately 30% of the brain [23,24], are involved in visual processing; therefore, it should be no surprise that oculomotor/saccadic eye movements are commonly affected in individuals with mTBI/concussion [2–4,7]. Saccades are rapid movements of the eyes as they shift fixation from one point to another. The King-Devick® (KD) test is a rapid, easy-to-administer eye movement test developed in 1976, and used to assess dyslexia and other learning disabilities [5]. In recent studies, the KD test has been examined as a potential screening tool for assessment of concussions in sports such as boxing, football, hockey, soccer, and rugby [5,6,12,13]. All of

http://dx.doi.org/10.1016/j.jns.2016.09.014
0022-510X/Published by Elsevier B.V.
these studies have demonstrated promising results in assessing pre-and post-concussive differences which suggests the KD test could potentially be used to identify warfighters who have suffered mTBI/concussion. Finally, test–retest reliability for the KD test has been examined in previous studies and shown to be high, with intraclass correlations of 0.97 (95% confidence interval [CI] 0.90, 1.0) between measurements in the absence of concussion [5,6].

The purpose of this study was to assess an “off-the-shelf” eye movement test, the King-Devick®, in those who have experienced an acute mTBI/concussion. The results of this study may validate the use of an easy-to-administer and interpret eye movement test as a post-mTBI screening tool which can be added to a range of concussion assessment tools in assisting health-care providers with RTD decisions in warfighters.

2. Methods

2.1. Subjects

Two-hundred active duty military personnel were recruited for the study. The subjects were divided into two groups: those with diagnosed acute mTBI (≤72 h; n = 100) and age-matched controls (n = 100). The diagnosis of mTBI was made by primary care providers at a military Concussion Care Clinic based on a Glasgow Coma Scale score from 13 to 15, normal structural brain imaging, if available, and meeting at least one of the following criteria: any alteration of mental state; loss of consciousness though not exceeding 30 min; posttraumatic amnesia of no more than 24 h. Inclusion criteria for the control group were any active-duty service member with no history of mTBI/concussion. The study was approved by the Womack Army Medical Center Institutional Review Board and the US Army Medical Research and Materiel Command (USAMRMC), Human Research Protection Office. Each subject was provided written informed consent before participating in the study.

2.2. Equipment & procedures

The KD test used to evaluate saccadic eye-movement performance is shown in Fig. 1. The KD test is based on the measurement of the speed of rapid number naming and involves reading aloud a series of single-digit numbers from left to right on three progressively more difficult test cards. Standardized instructions provided with the instrument were used. The KD test was administered in a well-lit room at a normal reading distance (i.e., 40 cm) with the subject's best near-visual correction, if needed (e.g., glasses, contact lenses). To begin, a demonstration card was shown to the subject with explicit instructions on how to perform the test. The subject was instructed to read the numbers as fast as possible without making errors. If error(s) were made, and the subject returned to correct the error(s), then the error(s) were not counted. The subjects were instructed not to use their hands or fingers on the card to assist during the testing. Speed and accuracy were emphasized throughout the test and the cumulative times were recorded by the tester. The cumulative time was measured with a stopwatch, and the test was administered twice with an approximately 5-minute gap between each test administration.

2.3. Statistical analyses

Means and standard deviations were calculated for each group with cumulative time to complete each KD test being the outcome measure. A Shapiro-Wilk test for normality was performed on all data, and indicated the presence of non-normal distributions. Thus, in each group, a Wilcoxon Matched-Pairs Signed-Rank Test was used to confirm test-re-test reliability by comparing the KD test results from time 1 to time 2. A Mann-Whitney U was performed to compare control vs. mTBI group.

![Fig. 1. King-Devick cards. The first card (top left) is the demonstration card, and subsequent cards are tests I, II, and III.](image-url)
performance. Since non-parametric statistical analyses were performed on the groups’ data, medians (Mdns) and Interquartile Ranges (IQRs) were also reported. Statistical significance was set at \( p < 0.05 \), and statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 20.0 software and GraphPad Prism 6 (GraphPad Software, San Diego, CA).

3. Results

3.1. Demographics & mechanisms of injury

Demographics information of both groups is shown in Table 1. The mean age of both groups was 26.31 ± 5.83. In both groups, subjects were predominantly male (87% mTBI vs. 79% controls), Caucasian, and most were junior enlisted (E1–E4) Army soldiers. The mechanisms of injury (MOI) of the acute mTBI group are shown in Table 2. Out of the 100 mTBI subjects, a little more than two-thirds were injured due to parachute jump. Each of the remaining MOI reported (blunt force, combatives, fall, motor vehicle accident, sports/recreational activities, other) accounted for <10% of the injuries in this sample population. None of the subjects suffered from a blast-induced mTBI.

3.2. King-Devick test

Table 3. In test 1, the mean cumulative test times for the mTBI and control groups were 62.01 ± 19.91 s (95% CI [58.06, 65.96]) and 45.65 ± 8.31 s (95% CI [44.00, 47.30]), respectively. In test 2, the mean cumulative test time for the mTBI and control groups were 58.57 ± 19.71 s (95% CI [54.64, 62.47]) and 43.40 ± 8.10 s (95% CI [41.80, 45.01]), respectively. The Wilcoxon Matched-Pairs Signed-Rank Test revealed a significance difference between the two test administrations (time 1 versus time 2) in both groups (controls: \( z = -5.90, p < 0.001 \); mTBI: \( z = -5.32, p < 0.001 \)). Due to the significant differences between the two tests administered to both study groups, a correlation analysis was performed. Spearman’s \( \rho \)’s were 0.918 (\( p < 0.001 \)) and 0.949 (\( p < 0.001 \)) for repeated tests for the control and mTBI groups, respectively (Fig. 2).

For test time 1, a Mann-Whitney \( U \) test revealed significant differences between the mTBI (Mdns = 58.29, IQR = 49.41–72.97 s) and control (Mdns = 44.93, IQR = 39.21–50.49 s) groups, \( U = 2168, p \leq 0.001 \) (Fig. 3). Finally, the mTBI mean cumulative reading times were approximately 36% slower in both administration times 1 and 2.

4. Discussion

The primary aim of the present study was to investigate the potential use of the KD test, an eye-movement screening test, as a diagnostic tool for war fighters who may have suffered an mTBI/concussion event. Results from the study demonstrated significant differences in KD test performance between the acute mTBI and age-matched control groups. The KD test showed a little more than one-third slower reading time in the mTBI group. For both groups, there was a statistically significant difference between the two test administration times, though the test-retest correlations were strong, indicating solid test-retest reliability in both the mTBI and control groups.

Numerous previous studies have validated the KD test on athletes, though with study subjects receiving baseline assessments and serving as their own controls [5,6,12,13]. Prior KD test studies utilizing separate control groups have shown significant differences between the controls and experimental groups; however, their experimental groups consisted of patients with Parkinson’s disease [14] and multiple sclerosis [16], not acute mTBI as seen in the present study. But a recent KD test study on subjects recruited from an emergency department did include acute (<72 h) mTBI patients and controls [21]. Their study did not find significant differences in KD test performance between the mTBI and control groups. This finding was contrary to previous sports-related concussions studies, and Silverberg et al. primary argument concerning the different results was their patients’ mean assessment time was 31 h post-injury, whereas, the data collected in the other sports-related injury studies referenced here was within 60 min post-injury. Silverberg et al. theorized “sensitivity of the K-D may dissipate rapidly over the hours to days following an mTBI.” In the present study, the subjects’ mean assessment time was 2.02 days post-injury; therefore, the average post-injury was more comparable to the Silverberg et al. study. The differences in results between the studies could be due to the approximately 3.4 times greater sample size in the present study (200 vs. 59).

A limitation of the present study was no baseline KD testing was performed on the two groups of subjects. The KD test decision matrix in screening head injuries is based upon differences in baseline and post-injury KD times of the injured individuals. However, the study’s significant result between the groups does strongly suggest that

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics.</th>
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<tbody>
<tr>
<td></td>
<td>mTBI (n = 100)</td>
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<tr>
<td>Age (years ± SD)</td>
<td>26.31 ± 5.83</td>
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<tr>
<td>Sex (%)</td>
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SD = standard deviation.

Table 2

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<td>Fall</td>
<td>7</td>
</tr>
<tr>
<td>Parachute jump</td>
<td>69</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>6</td>
</tr>
<tr>
<td>Sports/recreational activities</td>
<td>5</td>
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<tr>
<td>Other</td>
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</table>

Percent (%)

Table 3

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Descriptive statistics.</th>
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</thead>
<tbody>
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<td>mTBI</td>
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<tr>
<td>Test 1 Mean ± SD</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Test 1 62.01 ± 19.91</td>
<td>(58.29, 49.41–72.97)</td>
</tr>
<tr>
<td>Test 2 58.57 ± 19.71</td>
<td>(53.49, 45.70–70.94)</td>
</tr>
</tbody>
</table>

s = seconds; SD = standard deviation; IQR = Interquartile Range.
baseline testing should be performed on warfighters prior to exposure to combat or training environments.

Finally, there are two drawbacks to the KD card test. First, a confounding variable with test results is the reading speed is controlled by the subject. This confounder may produce false positive or false negative results in soldiers. To reduce this issue, the KD test should not be used as a stand-alone screening test for mTBI events. Other screening tests, preferably objective, should be used in combination with the KD test when determining RTD. Second, the KD card test is that it does not provide information on what the eyes or visual system are doing while performing the test. To address this limitation, KD test technology has advanced with automated testing, and an automated KD test with eye tracking integrated is currently undergoing test-retest validity at US Army Aeromedical Research Laboratory in a separate study. However, a disadvantage of such an automated test is that it has a larger physical “footprint” (compared to KD test card), and thus may have difficulties being used as a screening device in deployment settings. The ideal screening device would be developed into smaller device such as a smartphone or tablet. With ever-advancing technology at the fingertips of front-line providers, having a quick mTBI assessment tool can not only help make rapid screening decisions, but also give eye-movement/attention information to higher echelons of care that may be helpful for any potential rehabilitation treatments on the brain-injured warfighter.

5. Conclusion

Traumatic brain injury, and especially mTBI, is an ongoing concern among the military medical community and operational commanders. Premature RTD places warfighters at greater risk of short- and long-term disability if they suffer additional concussive brain trauma. Results of the present study indicate the KD test shows promise as an additional screening tool for mTBI. However, due to intrasubject performance variability that can impact subjective test results, we recommend the KD test be utilized as a supplementary screening tool in those who have suffered an mTBI event. In addition, having pre-injury KD data will allow a more precise determination; therefore, we recommend the KD test be included as a baseline test for all warfighters prior to exposure to risk of mTBI/concussion. Having a validated, rapid, easy-to-assess mTBI brain screening test can assist frontline providers in making the RTD decision to send the warfighter back to the “fight”, or to a higher echelon of care for more comprehensive tests.

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation. I, or any of the co-authors, have no conflict of interest to report.

Acknowledgement

This research was funded by the Military Operational Medicine Research Program of the U.S. Army Medical Research and Materiel Command (USAMRMC), and FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP) under contract No.
W81XWH-14-C-0048. This research was conducted with support from the Geneva Foundation as well as the Defense and Veterans Brain Injury Center (DVIBC) and staffing support from General Dynamics Information Technology.

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