Near-infrared spectroscopy in the diagnosis of testicular torsion – valuable modality or waste of valuable time? A systematic review

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Near infra-red spectroscopy in testicular torsion

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INTRODUCTION

Testicular torsion (TT) is a urological emergency that affects 1 in 4000 males younger than 25 years. Delays in the management of TT may result in testicular ischemia, testicular necrosis, orchidectomy and infertility ¹.

Various diagnostic modalities including the TWIST (Testicular Workup for Ischemia and Suspected Torsion) score, high-resolution ultrasonography (HRUS), color doppler sonography (CDS), dynamic contrast-enhanced magnetic resonance imaging (MRI) and scrotal scintigraphy have proven to aid in the assessment and

diagnosis of TT ²⁻⁴.

Near Infrared Spectroscopy (NIRS) is a relatively novel modality that has also shown promise in the diagnosis of TT. It uses infrared light to estimate tissue saturation of oxygen (StO₂) in superficial body tissues (up to several centimeters deep), such as the testis [figure 1]. NIRS devices have the advantages of being small, readily accessible at the bedside and easy to interpret without requiring specialty training ⁵.

Few studies have objectively reported on the diagnostic value of NIRS in TT. There is, however, a need to explore the literature regarding the clinical application and feasibility of NIRS in this regard. To better define the validity, role and statistical significance of the use of NIRS in TT, a comprehensive literature review was performed on the current body of literature.

METHODS

Search strategy

A search strategy was conducted in January 2019 using the following electronic databases: Cochrane Database of Systematic Reviews, EMBASE, Google Scholar, PubMed, Scopus and Web of Science. The following terms were searched: “testicular torsion” OR “testis” OR “torsion” OR “acute scrotum” AND (“near-infrared spectroscopy” OR “NIRS”). Citations of all papers retrieved were also analyzed for

additional relevant resources. The search was restricted to publications in the medical literature. No language restrictions were applied.

Study selection

Studies included in the review met the following criteria: (i) NIRS measurements where conducted on either human or animal subjects, (ii) full texts of the studies where available and (iii) the studies where clinical publications. All published studies relating to the topic where eligible for inclusion.

Review study definition of a positive NIRS test

In this systematic review, a positive NIRS test was defined as a reduction in the mean %StO₂ between the control testes and the torsed testis, as measured using a NIRS device.

Data extraction and methodical evaluation

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were applied to guide the electronic search ⁶. Eligible articles where screened by each reviewer. The selected studies were ranked using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool ⁷ [table 1]. Each reviewer then compiled a descriptive narrative of each study. The points of interest in each study where tabulated. These included the study origin, study population, NIRS oximetry device and probe used, study inclusion criteria, total

sample size, number of subjects with TT, mean duration of symptoms, mean age, tissue oxygen saturation in the torted and control testes as well as the difference between the two ($\Delta\%StO_2$), P values and author conclusions or comments [tables 2]. Conflicting entries, disagreements, and differences were resolved by consensus among all the reviewers.

RESULTS

Search

The electronic database search yielded 114 titles with the following breakdown: Google Scholar (28), EMBASE (27), PubMed (27), Scopus (23), Web of Science (8), and Cochrane Database of Systematic Reviews (1). Of these, 56 titles (44 duplicates and 12 titles that were not relevant to the topic) were removed. A further 41 articles that were also not relevant to the topic were removed after abstract review. The remaining 17 articles were fully reviewed. Nine articles were finally selected for inclusion in the systematic review after excluding a further 8 irrelevant articles⁸⁻¹⁶ [figure 2].

Design of the included studies

All nine studies included were prospective cohort studies⁸⁻¹⁶.

Definition of a positive NIRS test amongst the included studies

The definitions or description of a positive NIRS test to confirm the diagnosis of TT

amongst selected articles were essentially the same with some slight variation in the choice of words. It was summarily defined as a reduction in the mean %StO₂ between the control testes and the torsed testis,

Study aims of the included studies

The studies included in the review had slightly different aims, but all the studies attempted to prove that NIRS could detect TT by indicating the presence of testicular hypoxia when compared to the normal testes. Some studies also tried to establish whether NIRS could be used as an adjunct for the differential diagnosis of the causal pathologies of acute scrotum ^{13,15}.

Study population of the included studies

Five of the studies had human participants ¹²⁻¹⁶. The four animal studies used sheep ⁸, and rabbits ⁹ and rats ^{10,11}.

Age range of study subjects

None of the studies enrolled subjects over the age of 30 years. The age range of subjects in the 5 human studies were 14 months ¹⁴, 14-74 months ¹⁵, 1month to < 18 years ¹⁶. 16-29 years ¹³ and <30 years ¹².

Overall and study sample size

The total number of subjects across all studies was 253 (88 animals and 165

humans). Of the 253 participants, TT was confirmed in 122 (67 animals and 55 humans). The largest study had 121 participants¹⁶ whilst the smallest included manuscript had 1 subject¹⁴. The mean sample size of all included studies was 28.1 (SD 40.8)

Region of study origin

Amongst the 4 animal-based studies, 2 were conducted in the USA^{8,9} and one in Turkey¹⁰, whilst one study did not report the study site¹¹. Amongst the 5 human-based studies, 2 were conducted in the USA^{12,16}, whilst 1 study was conducted in USA and Turkey¹³. The remaining 2 studies did not specify the study site^{14,15}.

NIRS oximetry device and probe used

Three studies utilized an InSpectra device (various models)^{8,12,16}, 2 used an INVOS 5100C OxyAlert device^{10,13}, another 2 used a PortaMon Artinis Medical Systems continuous wave (CW) spatially resolved (SR) NIRS device^{14,15} and 1 study each used the OxiplexTS optical tissue spectrometer device⁹ and the Pathonix OxiTor M2 device¹¹.

Reference diagnostic standard utilized in the included studies

Amongst the 4 animal studies, 2 studies each used surgical induced TT with confirmatory CDS^{8,10} and surgical induced TT alone^{9,11} as the reference standard comparator. Amongst the 5 human studies, surgical exploration alone^{12,14}, doppler

ultrasound and/ or surgical exploration ^{13,16} and a combination of clinical assessment, laboratory tests, CDS and surgical exploration ¹⁵ were reported by various authors as the reference standard comparator.

Diagnostic value of NIRS in TT

The mean difference in testicular tissue oxygenation saturation between torsed and non-torsed testes ($\Delta\%StO_2$) in the 4 animal studies were 45% ⁸, 42% $\pm$ 5% ⁹, 26% ¹⁰ and 5%-18% ¹¹. The $\Delta\%StO_2$ was much lower in the human studies with 4 studies reporting values ranging from 2.0% to 6.8% ^{12,14–16} and one study reporting a $\Delta\%StO_2$ of 23.0% ¹³. In 5 studies, that alluded to the difference in testicular tissue oxygenation saturation between contralateral testes in subjects without TT, the differences were 8% ⁸, 3-10% ⁹, 1% ¹⁰, 3.5% ¹², and up to 9% ¹³.

None of the included studies reported on or provided sufficient data to extrapolate the sensitivity, specificity, negative predictive value or positive predictive value of the NIRS device in the assessment of TT. One study reported the area under the receiver operating curve (AUC) ¹⁶. Overall, there was insufficient data to conduct a meta-analysis.

DISCUSSION

The clinical diagnosis and management of TT remains difficult due to the presence of non-specific clinical signs, the occurrence of intermittent episodes of torsion and

the time sensitive manner in which surgical intervention is required to salvage the testis ¹⁷. CDS is the current standard recommended for the rapid radiological assessment of the testes ¹¹. It does however have various limitations ¹⁷, hence other diagnostic modalities need to be explored.

NIRS is currently being utilized in clinical practice as a non-invasive method to detect tissue oxygen saturation during vascular and cerebral surgical procedures as well as during the post-operative period. It has also been used for the detection of deep venous thrombosis, determining the adequacy of resuscitation during trauma induced shock ^{8,10}, measuring cerebral blood flow ¹⁸ and measuring muscle oxygenation in compartment syndrome ¹⁹. NIRS has shown promise in the assessment of TT ⁵. Of the nine included studies, the largest of the 2 human-based studies concluded that NIRS had no role ¹² or a very limited role ¹⁶ in the diagnosis of TT. Authors of the remaining 7 studies supported the use of NIRS in the assessment of TT ^{8–11,13–15}.

Due to the paucity of available studies in humans, animal model studies were also included in this review. The 2 earliest studies that were conducted in sheep and rabbits ^{8,9}, reported large mean differences in $\Delta\%StO_2$ (45% and 46% respectively). The other 2 animal model studies (both conducted in rat) reported a much smaller mean $\Delta\%StO_2$ differences of 26% and 5-18% respectively ^{10,11}. Unexpectedly, the mean baseline difference in tissue oxygen saturation between contralateral normal

testes prior to surgical induction of TT was not symmetrical in the animal model studies that alluded to this data. Differences of 8% (59% vs 67%)⁸, 3-10%⁹ and 1%¹⁰ were noted in three studies, with one study not reporting this figure¹¹. Although none of these studies suggested threshold levels of $\Delta\%StO_2$ for the diagnosis of TT, these findings caution against interpreting any change in tissue oxygen saturation as diagnostic of TT. Besides the study by Aydogdu et al. that enrolled 70 rats¹⁰, the other 3 animal model studies were also limited by very small sample sizes of 4-8 subjects^{8,9,11}.

The value of NIRS in the diagnosis of TT in humans is less convincing. Besides the most recent study by Schlomer et al. that enrolled a moderate sample size of 121 subjects (36 subjects with TT)¹⁶, the remaining studies had very had small sample sizes that ranged from 1-22 subjects¹²⁻¹⁵. Compared to the above animal model studies, the $\Delta\%StO_2$ was much smaller in the human studies with 4 of the 5 studies reporting mean $\Delta\%StO_2$ values below 6.9%^{12,14-16} and only one study reporting a relatively higher $\Delta\%StO_2$ of 23.0%¹³. Since the degree of surgically induced torsion was extreme in the animal studies (ranging between 360-1080 degrees)⁸⁻¹¹, this may have accounted for the large differences in $\Delta\%StO_2$ between human and animal studies.

The 2 smallest human-based studies were both conducted by Shadgan et al. In the first of the 2 article that had just a single subject, the authors report the use of a

wireless continuous wave near infrared spectroscopy device with a spatially resolved configuration (SR-NIRS) to accurately diagnose TT in a 14 month old patient in whom CDS findings were equivocal ¹⁴. In the second study, using the same SR NIRS device in 5 pediatric patients that presented with an acute scrotum, they compared readings of the affected testes to readings from the skin surface of the quadriceps muscle as the control. They reported an increase in tissue oxygen saturation of the affected testes in 2 cases of epididymitis, a decrease in 2 cases of TT (6.6% and 6.7% respectively) and no change in 1 case of torsion of the appendix testes.

Schoenfeld et al. ¹² reported a non-significant ($p = 0.174$) 3.0% difference in the mean $\Delta\%StO_2$ in 5 subjects with confirmed TT ($p = 0.174$) ¹², and a 3.5% mean difference in tissue oxygen saturation ($p=0.0007$) between contralateral healthy testes in 17 healthy controls. The authors concluded that NIRS was unable to demonstrate equal tissue oxygen saturations in contralateral testes of healthy controls and was also unable to demonstrate a significant reduction in $\%StO_2$ between torsed and non-torsed testes in patients with TT.

In the study by Burgu et al. ¹³, who reported the largest mean $\Delta\%StO_2$ amongst the human studies (23%), the authors state that the mean tissue oxygen saturation values were similar in the painful ($61.4\% \pm 3.71\%$) and the unaffected testes ($62.4\% \pm 3.78\%$) amongst 5/16 subjects that had presented with an acute scrotum that was

not due to TT (normal doppler US). However, it is also evident from their results that the tissue oxygen saturation of the painful testis was up to 9% lower than the contralateral normal testis in some of the 5 cases who did not have TT. This emphasizes the fact that a difference in tissue oxygen saturation between contralateral testes is not diagnostic of TT and must be interpreted with caution. The authors noted that when the $\Delta\%StO_2$ threshold was set at $\geq 11.5\%$, NIRS was able to identify all 11 cases of TT.

Schlomer et al.¹⁶, who conducted the largest of the human-based studies, reported a median $\Delta\%StO_2$ of only 2.0% (range -19 to +56, IQR -4.2 to +9.8) with an AUC of 0.66 (95% CI 0.55 to 0.78), suggesting poor reliability of NIRS as a diagnostic tool in TT. Although a detailed analysis of all subjects was not available, it was evident from the reported range/ IQR that in some cases of TT the normal testis had a lower $\%StO_2$ than the tortured testes. Sub-analysis of the data reported better diagnostic accuracy of the NIRS device in older children (Tanner stage 3-5) without scrotal edema or with a pain duration of ≤ 12 hours (AUC of 0.91 (95% CI 0.86-1.0) and 0.80 (95% CI 0.62-0.99) respectively). The authors concluded that the overall utility of NIRS in the assessment of TT in children is limited.

Due to various limitations, a meta-analysis of the data could not be conducted. A major limitation is that most of the studies only reported and compared mean $\%StO_2$ levels. In fact, only 1 study reported the AUC, and none reported on or provided

sufficient data to extrapolate sensitivity, specificity, negative predictive value or positive predictive value of NIRS. Several other noteworthy limitations include the small sample sizes of studies, differences in NIRS device models utilized between studies, inter-study heterogeneity with regards to study populations and the large variation in $\Delta\%StO_2$ between animal and human studies.

The relationship between time and the testicular salvage rate is well described. The delay being a common 'enemy', with testis loss rates being reported at 39-50 percent of cases^{20,21}. Although the proposed medicolegal acceptable time limit of 8 hours has been suggested by some experts, testis salvage rates of 18 percent have been reported in cases where intervention was only performed after a 24 hour period^{22,23}. In view of the time-dependent nature of this condition, only a diagnostic modality which has near perfect ability can be suggested as an adjunct to clinical suspicion.

In summary, the large variation in $\Delta\%StO_2$ between animal and human studies in cases of TT coupled with the lack of consistency in tissue oxygen saturation readings between contralateral normal testes clearly question the validity of NIRS in TT. Based on currently published data, the potential role for NIRS in the management of acute torsion remains an experimental modality. Well-designed clinical trials with large patient samples are required to determine whether NIRS may have some future role as a diagnostic modality in TT.

CONCLUSION

The current body of evidence does not support the use of NIRS in the work-up of testicular torsion. Well-designed clinical trials with large patient samples are required to determine whether NIRS may have some future role as a diagnostic modality in testicular torsion.

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