

NIO™ HUMAN CADAVER STUDIES

REPORT OF CLINICAL STUDY ON HUMAN CADAVERS

Central Morgue of Lima, Peru, Georgia Health Sciences University, New York Institute of Technology College of Osteopathic Medicine

1. BACKGROUND

This paper compiles the results of the human cadaver studies performed with the NIO™ device during 2012 and 2013 as part of the device's 510(k) FDA submission.

The purpose of this document is to disseminate the main conclusions drawn following each study.

This paper describes the results of the following studies:

- NIO™ A.V Protocol.10 - 2012 Sep. 28 Lima Cadaver Lab, at the Central Morgue of Lima (Lima, Peru)
- NIO™ A.V Protocol.11 - 2012 Oct. 05 Georgia Cadaver Lab, at Georgia Health Sciences University (Augusta, Georgia)
- NIO™ A.V Protocol.13 - 2013 Mar. 15 Lima Cadaver Lab, at the Central Morgue of Lima (Lima, Peru)
- An additional study conducted by Avram Flamm, OMSII, and Bennett Futterman, MD at the New York Institute of Technology College of Osteopathic Medicine (Old Westbury, New York)

2. OBJECTIVES

2.1. The main objective of the Lima studies was to validate the functionality and performance of the device and to evaluate the success rate.

2.1.1. Validate the reliability of the trigger mechanism.

2.1.2. Insertion sites considered for validation included the proximal tibia and humeral head. The insertion depth of the needle after activation of the NIO™ is pre-determined by a mechanical stopper.

2.1.3. Visually validate that the needle maintains its structural integrity and that there are no structural deformations observed following the insertion process.

2.1.4. Validate that the needle mechanical stopper (needle stabilizer) is preventing over-penetration or unintentional withdrawal of the needle from the bone.

2.1.5. Validate bone integrity following NIO™ activation using X-ray images to diagnose bone fractures.

2.1.6. Assess the success rate of the NIO™ in terms of successful operation and fluid administration.

2.2. The main objective of the Georgia study was to conduct a usability test for the NIO™. In addition to the usability study, all objectives discussed in section 2.1 were tested.

2.3. A secondary parameter aimed at assessing the success rate of the NIO™ when activated at an incorrect insertion site on the proximal tibia. Attempts were made to inject the NIO™ device at a "wrong" location on the proximal tibia in order to mimic user errors and to evaluate the device's tolerance to common operator mistakes.

2.3.1. Anatomically, the tibial cortical bone (compact bone) is thinnest near the kneecap joint (epiphysis), growing thicker towards the middle part of the bone.

2.3.2. For adults, the insertion site on the proximal tibia is located by palpating the tibial tuberosity and moving approximately two fingers medial and one finger proximal.

2.3.3. Two of the most common mistakes in determining the insertion location of the proximal tibia are:

2.3.3.1. Injecting the needle two fingers medial to tibial tuberosity - marked as "0cm."

2.3.3.2. In Pediatric treatment, the most common mistake is injecting the needle two fingers medial from the tibial tuberosity and one finger distal instead of proximal - marked as "Ped. Loc."

2.4. The main objective of the New York study was to determine if there is a difference in frequency of successful first attempts for vascular access between the tibia and humerus on a cadaver model.

2.5. The main objective of this summary is to evaluate the success rate of the NIO™ based on successful operation and fluid administration. Other objectives described above are analyzed and discussed in each relevant validation test.

3. TEST ACCEPTANCE CRITERIA

3.1. The insertion depth of the needle is pre-adjusted $\pm 10\%$ mm at each insertion site:

3.1.1. At proximal tibia and humeral head 25 ± 3 mm.

3.2. No structural deformations are visually seen on the needle.

3.3. The needle stabilizer prevents less than 3mm of over-penetration.

3.4. X-ray images of the limbs show no skeletal deformations or fractures due to the insertion.

3.5. Successful operation of the device entails:

3.5.1. The trigger mechanism operated properly and the needle stabilizer was easily released.

3.5.2. The device successfully inserted the needle into the bone.

3.5.3. It was possible to separate the trocar from cannula using manual vertical force while twisting.

3.5.4. Fluids were flushed into the intended area with no noticeable extravagation of fluids, thus, administration of fluids was successful.

3.6. For the secondary study on proximal tibia and for the study performed in NY, the success rate was assessed by successful operation of the device as described in section 3.5.

3.7. The usability study is described in detail in "NIO™-A.V.Protocol.08 Usability Study Protocol." The reviewer evaluated each user and the performance of each device according to a list of criteria. At the end of the procedure, the user was asked to evaluate the ease of use of the device on a scale of 1-10, 10 being "easy" and 1 being "hard". The acceptance criteria of the study was defined as 80+ points for each procedure.

3.8. The study in NY compared first attempt success rates for vascular access after activating the NIO™ device in the proximal tibia and humeral head.

4. NIO™ USERS

4.1. Initial tests conducted in Lima were performed by trained Research and Development personnel.

4.2. The study conducted in Georgia was performed by 12 different users with Para/Medical education, the majority of whom were residency students.

4.3. The study conducted at the New York Institute of Technology College of Osteopathic Medicine was performed by Avram Flamm, OMSII, and Bennett Futterman, MD.

5. STUDY SUBJECTS

5.1. The overall studies were conducted on 55 adult human cadavers, both male and female.

5.2. The studies conducted in Lima, Peru were performed at the Central Morgue of Lima on seventeen fresh human adult cadavers. Subjects' age ranged from 20-80 years old, both female and male; specifically, there were two subjects in their 80s, three subjects in their 70s, two subjects in their 60s, one subject in his 50s, two subjects in their 40s, three subjects in their 30s, and four subjects in their 20s.

5.3. The study conducted in Georgia was performed at Georgia Health Sciences University on twelve embalmed and preserved human adult cadavers. Subjects' age ranged from 50-90 years old, both female and male; specifically, there was one subject in

his 90s, three subjects in their 80s, six subjects in their 70s, one subject in his 60s, and one subject in his 50s.

5.4. In the studies, for each subject, 8 insertion locations were reviewed according to the exclusion criteria: proximal tibia and humeral head, for right and left sides of the body.

5.5. The study conducted at the New York Institute of Technology College of Osteopathic Medicine was performed on 26 embalmed and preserved human adult cadavers. The IO needle was inserted bilaterally at the humeral and tibial sites, with a total of 6 insertions per cadaver.

6. EXCLUSION CRITERIA

6.1. Subjects with systemic skeletal diseases (Osteoporosis, etc.)

6.2. Subjects with malformations at the insertion site.

6.3. Subjects with surgical scars at the insertion area.

6.4. Subjects age 12 or younger.

7. RESULTS

7.1. The following summary relates to the three cadaver studies excluding the study in NY (The NY study will be addressed in a separate section):

7.2. For each study, success rates were measured in two different ways:

· 7.2.1. All acceptance criteria mentioned in section 3.

· 7.2.2. Successful operation of the device and successful fluid administration.

7.2.3. Since the main goal of the IO procedure is to allow successful fluid administration without putting the patient's life at risk, it should be noted that the criteria mentioned in section 7.2.2 is the commonly accepted intraosseous criteria.

7.3. This summary will address only the success rate according to successful operation of the device and successful fluid administration. Each validation test report relates to a different single criteria mentioned in section 3.

7.4. The overall study was conducted on twenty-nine adult human cadavers, age 20-80 years old, both male and female.

7.5. 263 NIO™ devices were used for the cadaver study; 222 at various medically approved insertions sites, and 41 devices at different tibial locations, distal to the correct insertion site.

7.5.1. 58 devices were used on the proximal tibia insertion site, 58 on the humeral head, 53 on the distal tibia, and 53 on the distal radius.

7.5.2. 41 NIO™ devices were used on incorrect proximal tibia insertion sites: two fingers medial to tibial tuberosity (marked as "0cm") and down to 4cm distal to the "0cm" location.

7.6. Proximal tibia insertion site:

7.6.1. Of 58 attempts, 53 were successful, resulting in a 91.4% success rate.

7.6.2. In all failed attempts, the user determined that the device was not inserted into the correct insertion site.

7.6.3. In all successful attempts, the needle penetrated to the required penetration depth and fluid administration was successful.

7.7. Humeral head insertion site:

7.7.1. Of 58 attempts, 54 were successful, resulting in a 93.1% success rate.

7.7.2. All 4 failures encountered in the Georgia study were due to user error. In all failed attempts, the user determined that the device was not inserted into the correct insertion site.

7.7.3. In one attempt, the needle failed to meet the required penetration depth. The measured penetration depth was 21.9mm, where the minimal allowed range is 22mm.

7.7.4. In all successful attempts, fluid was properly administered. Additionally, in the failed attempt at which the needle penetrated to 21.9mm, fluid administration was successful.

7.8. The usability study in Georgia demonstrated:

7.8.1. The average insertion time for the proximal tibia was 13.6 seconds, while the average insertion time for the humeral head was 23 seconds. Thus, the average overall insertion time was 18.3 seconds.

7.8.2. The average user rated the NIO™'s ease of use as 8.5. The average rating for the proximal tibia was 9.1, while the average rating for the humeral head location was 7.9.

7.9. "Wrong" location on proximal tibia:

7.9.1. Out of 41 attempts to activate the device at different "wrong" locations, 35 cases were successful, resulting in an 85.4% success rate.

INSERTION SITE	STUDY LOCATION AND DATE	TOTAL INSERTIONS	SUCCESSFUL NEEDLE PENETRATIONS	SUCCESSFUL SALINE INJECTIONS	SUCCESS RATE	NOTES
PROXIMAL TIBIA	Sep. 28, 2012; Lima	12	12	12	100%	N/A
	Oct. 5, 2012; Georgia	29	24	24	82.76%	All 5 failures were due to user error. Users attempted to insert the NIO™ into soft tissue or at an incorrect location.
	Mar. 15-17, 2013; Lima	17	17	17	100%	N/A
	Total	58	53	53	91.38%	N/A
HUMERAL HEAD	Sep. 28, 2012; Lima	12	12	12	100%	N/A
	Oct. 5, 2012; Georgia	27	23	23	85.19%	All 5 failures were due to user error. Users attempted to insert the NIO™ into soft tissue.
	Mar. 15-17, 2013; Lima	19	18	19	100%	In one case, the needle penetrated to 21.9mm.
	Total	58	53	54	93.10%	N/A
WRONG LOCATIONS	Oct. 5, 2012; Georgia	26	N/A	22	84.62%	N/A
	Mar. 15-17, 2013; Lima	15	N/A	13	86.67%	N/A
	Total	41	N/A	35	85.37%	N/A

Table 1 summarizes the results of each study based on successful fluid administration at different insertion sites. The table is organized based on the location of the study.

7.9.2. The study was performed on a total of 12 cadavers, age 20-93 years old, both female and male. Specifically, there was one subject in his 90s, two subjects in their 80s, four subjects in their 70s, two subjects in their 60s, one subject in his 40s, one subject in his 30s, and one subject in his 20s.

7.9.3. Initially, all cadavers used for this study were injected with the NIO™ at the correct proximal tibia location. All of these initial attempts were successful.

7.9.4. Out of six failures, two were in the same cadaver, a 35 year old male; three in another cadaver, a 73 year old male; and one in a 75 year old male cadaver.

7.9.5. It is important to emphasize that the NIO™ should be used at the correct insertion site, according to the IFU. However, the study demonstrates that even when inserted distal to the acceptable location (due to user error), the NIO™ maintains a high rate of success.

7.10. Bone fractures:

7.10.1. The study conducted in Lima, Peru included X-ray images taken both pre and post-insertion. All attempts, including those at a "wrong" location on the proximal tibia (i.e more than one attempt on the same limb and in some cases even up to 5 attempts on the same limb), were X-rayed.

7.10.2. The X-ray images were analyzed by an orthopedic surgeon. The full results are summarized and discussed in the bone fractures study result "NIO™-A.V.Report.09 Occurrence of Fractures In Bones".

7.11. NY study at the New York Institute of Technology College of Osteopathic Medicine:

7.11.1. Utilizing a cadaver model, the NIO™ was used on the tibia and humerus, and first attempt success rates for vascular access were compared.

7.11.2. The NIO™ was used on 26 cadavers with a total of 127 attempts.

NIO™ SUCCESS RATE (%)

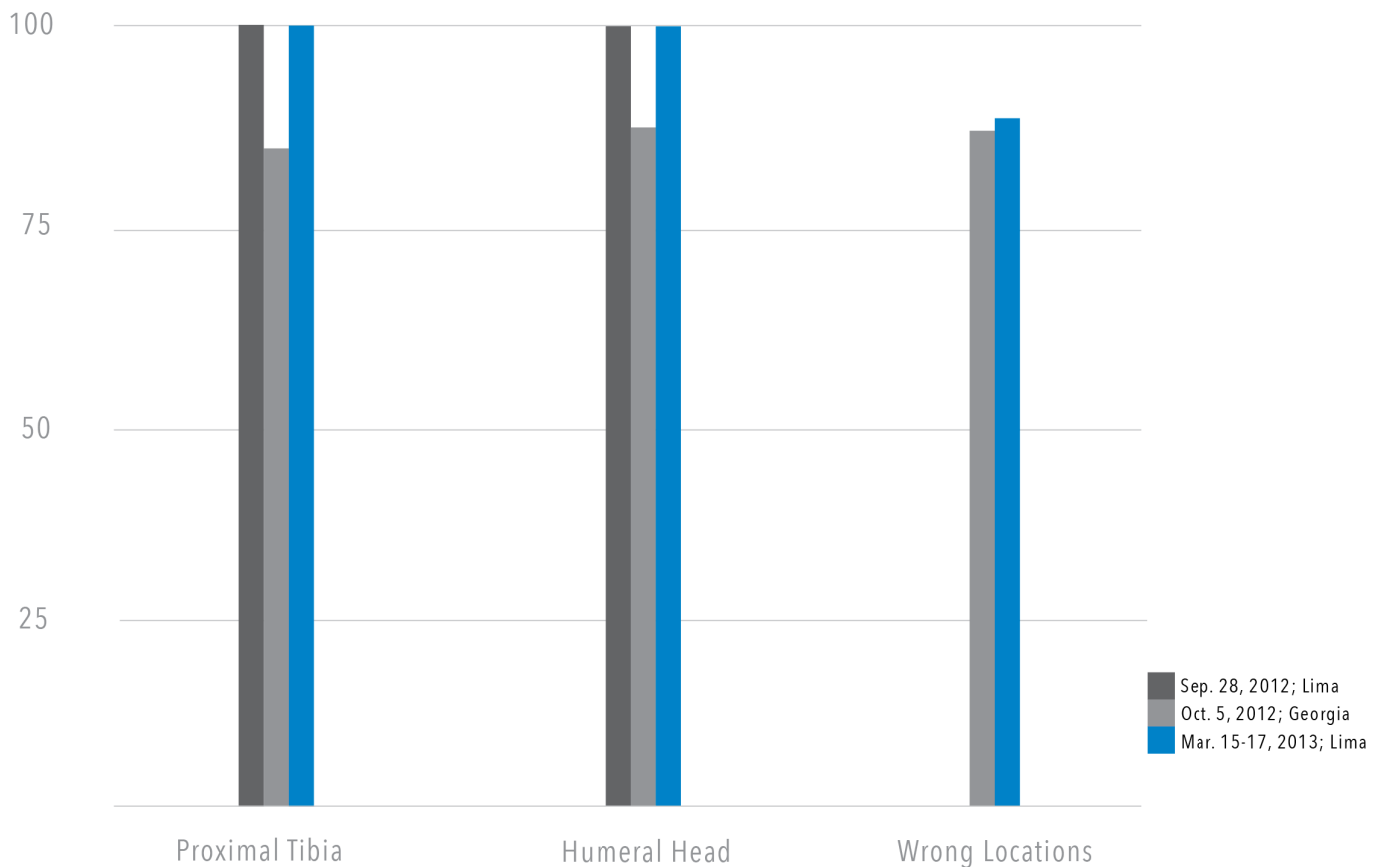


Figure 1 summarizes the results of each study based on successful fluid administration at different insertion sites. It was observed that when inserted at the wrong location, the NIO™ maintained an 85% success rate. The table is organized based on the location of the study.

7.11.3. 12 of the cadavers were male and 14 were female.

7.11.4. The average age of the cadavers was 79 years at death.

7.11.5. The first attempt success rate for inserting the NIO™ at the tibia was 98%, while the humerus was 91%.

8. DISCUSSION

8.1. Nearly 390 NIO™ devices were used for these studies. 263 devices were used for the internal cadaver studies in Lima, Peru and Georgia, and 127 for the study in New York.

8.2. All post-insertion X-rays showed no evidence of bone fractures due to the insertion. In some cases, after the needle was injected into the proximal and distal tibia, additional insertions were made at a “wrong location” on the same limb. Even in these cases, there was no evidence of bone fracture on the limb due to injection.

8.3. The trigger mechanism operated as required.

8.4. The results of the usability study showed that the average procedure time for the NIO™ was 18.3 seconds.

8.5. The average user graded the ease of use of the NIO™ as 8.5.

8.6. In all cases there were no structural deformations of the needle such as bending or breaking.

8.7. The results of the study demonstrate the efficiency of the NIO™ device when applied at the proximal tibia or humeral head insertion sites. Specifically, 91.4% at the proximal tibia and 93.1% at the humeral head.

8.8. The NIO™ demonstrated accuracy and effectiveness when used as indicated (at the correct injection site), as well as when used at a location distal to the correct injection site. The NIO™ demonstrated a 91.4% success rate at the correct injection site (58 cases) and an 85.4% success rate when injected distal to the correct injection site (35 cases).

8.9. Despite the fact that the humeral head is difficult to locate, 54 out of 58 insertions were successful - a 93.1% success rate.

9. CONCLUSION

The results of the human cadaver study validate the accuracy and efficiency of the NIO™ device when used at the proximal tibia or humeral head insertion sites. Following 58 attempts at both injection sites, the NIO™ has proven to have a 91.4% success rate at the proximal tibia and 93.1% success rate at the humerus. The study in NY showed a higher success rate of 98% at the proximal tibia and 91% at the humeral head. The usability study showed that the average procedure time was 18.3 seconds and the average user graded the ease of use of the NIO™ at 8.5, 10 being very easy.

NIO™ SUCCESS RATE (%)

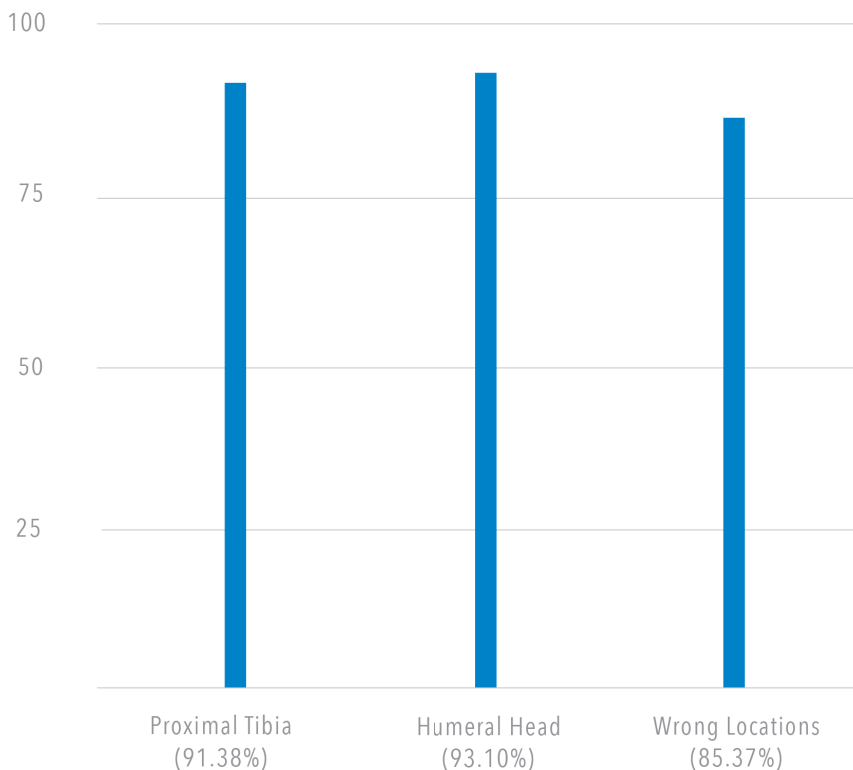
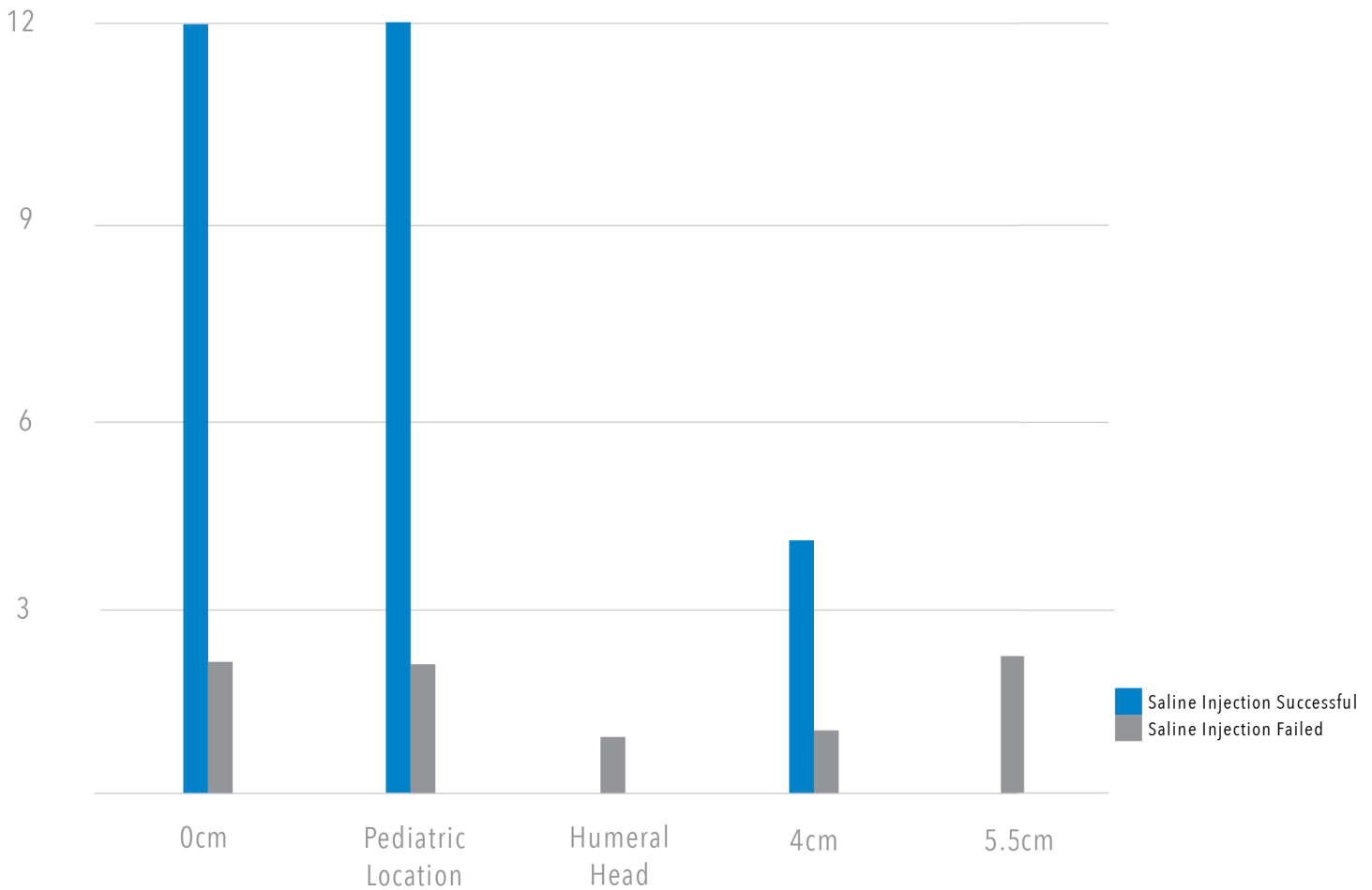


Figure 2 and Table 2 summarize the NIO™'s overall success rate based on insertion site.

INSERTION SITE	SUCCESS RATE	SAMPLE SIZE
PROXIMAL TIBIA	91.38%	58
HUMERAL HEAD	93.10%	58
WRONG LOCATIONS	85.37%	41

SUCCESS BASED ON SALINE INJECTION - "WRONG" LOCATIONS



When used as indicated, the accuracy and effectiveness of the NIO™ has been demonstrated. Additionally, the NIO™ has proven to be both accurate and effective when used distal to the correct injection site. The NIO™ demonstrated a 91.4% success rate at the correct injection site (58 cases) and an 85.4% success rate distal to the correct injection site (35 cases).

The results support a conclusion that the NIO™ is tolerant to common operator errors related to the correct location of insertion sites. If a user (mistakenly) penetrated at the "pediatric location" or locations distal to the tibia, or as far as 5cm distal to locations accepted by medical guidelines, a success rate of at least 85% can be expected.

10. ANNEXES

- NIO™ A.V Protocol.10 - 2012 Sep. 28 Lima Cadaver Lab
- NIO™ A.V Protocol.11 - 2012 Oct. 05 GA USA Cadaver Lab - NIO™ A.V Protocol.13 - 2013 Mar. 15 Lima Cadaver Lab
- Abstract and a short result summary for the study conducted by Avram Flamm, OMSII, Bennett Futterman, MD at the New York Institute of Technology College of Osteopathic Medicine

INSERTION SITE	TOTAL INSERTIONS	SUCCESSFUL INJECTIONS	FAILED INJECTIONS	SUCCESS RATE
0 cm	16	14	2	87.50%
Ped. Location	16	14	2	87.50%
3 cm	1	0	1	0.00%
4 cm	5	4	1	80.00%
5.5 cm	2	2	0	100.00%
8.6 cm	1	1	0	100.00%
Total Insertions	41	35	6	85.37%

Table 3 summarizes all attempts made at different distal locations relative to the correct penetration site on the proximal tibia. The markings "0 cm" and "Ped. Location" are defined in Section 2.3. Other insertion locations are marked according to their distal distance from the correct insertion site.