

Nasal Nalbuphine Analgesia in Prehospital Trauma Management by First-Responder Personnel on Ski Slopes in Switzerland

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Abstract

Background Pain is one of the major symptoms complained about by patients in the prehospital setting, especially in trauma. Due to the mountainous topography, there may be a time delay between injury and arrival of professional rescuers, in particular on ski slopes. Administration of a safe opioid by first responders (FR) may improve overall treatment. We therefore assessed the use of nasally administered Nalbuphine as analgesic treatment in trauma patients by FR at various skis resort in Switzerland.

Methods This observational study examined a cohort of 267 patients given Nalbuphine by FR in various ski resorts in Switzerland. All FR were instructed how to administer Nalbuphine before treating patients. A treatment algorithm was developed and distributed to assure that Nalbuphine was only administered following a strict protocol. Data regarding pain scores and pain reduction after administration of Nalbuphine were collected on-site. Refills were handed out with each completed questionnaire.

Results Nalbuphine decreased the level of pain statistically significant and clinically relevant by a median of 3 units on the NRS for pain. The multivariate regression model showed that pain reduction was more pronounced in patients with higher initial pain level. Nalbuphine was less effective in patients aged 20-60 years compared to the adolescent population. No major side effects were observed.

Conclusion Nasal Nalbuphine by FR was a noninvasive pain management strategy that provided safe and effective analgesia in prehospital, acutely injured patients. This may be an alternative method especially in circumstances of severe pain and prolonged time between arrival of the FR and arrival of EMS / HEMS personnel on scene.

Introduction

Pain is one of the major prehospital symptoms requiring prompt management, in particular in trauma patients. Nevertheless, many colleagues report that analgesia in the field is insufficient due to multiple reasons (1) (2) (3) (4) (5) (6), one reason being overly long response times of the emergency medical service (EMS). In Switzerland, EMS units are staffed with highly trained paramedics, but due to its mountainous and alpine terrain the time until arrival at the scene can be prolonged. Therefore, Switzerland has also a long history of helicopter emergency services (HEMS), staffed with a pilot, a paramedic and an emergency physician. Usually, a given HEMS can reach every point in Switzerland within 15 min (7) subject to weather conditions.

Winter sports such as downhill skiing or snowboarding attracts > 2.5 million skiers annually in Switzerland, with about 76,000 injured skiers requiring treatment (8). First responders (FR) in an accident on a ski slope are usually ski lift employees providing first aid, but no analgesia. However, analgesia on ski slopes may be achievable with Nalbuphine due to its safety features (mixed agonist / antagonist), ceiling effect regarding respiratory depression, equianalgesic potency to Morphine (9), simple handling, lack of abuse potential, safe in pregnant and lactating women (10) (11) (12), and possible employment by first responders (FR). (13) (10) (14) (15).

There are several approved routes of Nalbuphine administration including intravenously (IV), intramuscularly (IM), subcutaneously (SC) (10), and nasal due to its high lipophilicity and low molecular weight (14) (16) (17) (18) (19) (20) (21). Because of its simplicity and non-invasive nature, we chose the nasal route to administer Nalbuphine by ski slope first responders. Our hypothesis was that nasal Nalbuphine would have no effect on pain in victims of ski slope accidents.

Methods

This observational cohort study examined data collected from patients given Nalbuphine analgesia by FR in the prehospital phase. Reporting of the study conforms to the STROBE statement for the report of observational cohort studies.

Study design

All FR received a mandatory theoretical and practical instruction about nasal Nalbuphine using the Mucosal Atomization Device (Teleflex, Wayne, PA, USA). Specifically, they were instructed about the mechanisms of action, indications and contraindications as well as the potential side effects. Nalbuphine treatment according to an algorithm was required to assure patient safety (Fig. 1). Nalbuphine was restricted to cases when it was highly likely that the waiting time until arrival of an EMS or HEMS team was > 15 min.

Medication, administration, indications and contraindications

Nalbuphine (Nalbuphin OrPha®, OrPha Swiss, Kuesnacht, Switzerland) in a dose of 10 mg/ml in vials containing 2 ml (20 mg) was used. The dosage was according to body weight with a minimal dose of 5 mg for patients of 20–44 kg up to a maximum dose of 20 mg for adults > 75 kg with severe pain (Fig. 1). The total dosage was divided in half to administer a maximum 1 ml in each nostril. Main indication for Nalbuphine was severe pain being defined as a score of ≥ 5 on a numeric rating scale (NRS) with 0 defined as absence of pain and 10 being the maximal imaginable pain. If there was evidence of altered consciousness, alcohol consumption or noticeable abnormal vital signs, administration of Nalbuphine by FR was deemed contraindicated. Head trauma regardless of changes in mental status was an absolute contraindication for Nalbuphine to assure that no nasal drug was applied as long as a skull fracture was not excluded. Further Nalbuphine contraindications were known allergy to the drug or its additives, patient refusal, or body weight < 20 kg.

Data collection and statistical analysis

The study was performed in six different ski resorts in the canton of Graubünden, Switzerland (Arosa, Jakobshorn Davos, Lenzerheide, Marguns Engadin, Parsenn and Weisse Arena Laax). Observation period was from November 2017 until April 2020. Data collection was performed directly by FR using an online questionnaire with predefined endpoints. Apart from age and gender, no further personal data was

recorded to ensure de-identification of patients. Also, no personal data of the FR on scene was collected so no conclusion about the rescuer could be drawn during later analysis.

Statistical analysis

Patient's characteristics were summarized and presented by tables. Continuous variables were summarized by mean \pm standard deviation if normally distributed or by median and the interquartile range if skewed. Normality was tested using the Shapiro-Wilk test. Categorical variables were summarized with counts and percentages for each level of the variable. Wilcoxon-Mann-Whitney-*U* Test was used to assess differences in pre- vs. post Nalbuphine NRS. To further elaborate factors that are potentially associated with the effectiveness of Nalbuphine, a multiple linear regression model was built including the variables sex, age in categories and initial pain level in a complete-case-analysis. To adjust for difference in absolute pain reduction for depending on the initial reported pain level, the same regression model was built on a calculated relative pain reduction variable (i.e. percentage of NRS from initial NRS). Dose of Nalbuphine applied was excluded from the model due to multicollinearity of this variable, and the initial pain level. Location of injury was not included in the model due to the low number of patients per injury location, and the substantial proportion of missing data in this variable.

Results

Patient characteristics

During the observation period, a total of 267 patients (male gender, 61.1%; age, 33.3 ± 18.2 years) were treated with nasal Nalbuphine by FR (Table 1). Injuries were located on the upper extremity (44.2%), with more than the half of these involving the shoulder (23.6% of all injuries). Lower extremities were injured in 35.2%, with a majority of knee and lower leg injuries (12% and 14.6% of total injuries, respectively). The remaining 20.6% were injuries of the trunk including back, thorax and abdominal injuries. From 28 patients, (10.5%) there was no data available about the site of injury (Table 1).

Table 1
Baseline Characteristics and pain.

Variable	Total n = 267
Age in years	
Mean, \pm SD	33.3 \pm 18.2
< 20, <i>n</i> (%)	84 (31.5)
20–60, <i>n</i> (%)	163 (61.1)
\geq 60, <i>n</i> (%)	20 (7.5)
Male sex, <i>n</i> (%)	157 (58.8)
Pain (NRS)	
Initial, <i>median</i> (IQR)	8 (7 to 9)
After nalbuphine	5 (4 to 7)
Missing, <i>n</i> (%)	19 (7.1)
Pain reduction (NRS)	
Median (IQR)	-3 (-4 to -1)
Clinically relevant pain reduction, <i>n</i> (%)	145 (58.5)
Missing, <i>n</i> (%)	19 (7.1)
Dose of Nalbuphine	
5 mg, <i>n</i> (%)	24 (9.0)
10 mg, <i>n</i> (%)	128 (47.9)
15 mg, <i>n</i> (%)	35 (13.1)
20 mg, <i>n</i> (%)	80 (30.0)
Location of Trauma	
Shoulder, <i>n</i> (%)	63 (23.6)
Upper arm, <i>n</i> (%)	22 (8.2)
Elbow, <i>n</i> (%)	1 (0.4)
Forearm or hand, <i>n</i> (%)	32 (12.0)
Hip or femur, <i>n</i> (%)	22 (8.2)
Knee, <i>n</i> (%)	32 (12.0)
No missing data if not stated explicitly. SD = Standard Deviation. IQR = Inter Quartile Range.	

Variable	Total n = 267
Lower leg, <i>n (%)</i>	39 (14.6)
Foot, <i>n (%)</i>	1 (0.4)
Neck, <i>n (%)</i>	0 (0.0)
Back, <i>n (%)</i>	8 (3.0)
Thorax or clavícula, <i>n (%)</i>	18 (6.7)
Abdomen, <i>n (%)</i>	1 (0.4)
Missing, <i>n (%)</i>	28 (10.5)
Adverse Events	
None, <i>n (%)</i>	252 (94.4)
Nausea or vomiting, <i>n (%)</i>	3 (1.1)
Retching, <i>n (%)</i>	5 (1.9)
Nasal discomfort, <i>n (%)</i>	3 (1.1)
Major adverse events, <i>n (%)</i>	0 (0)
Technical device problem, <i>n (%)</i>	4 (1.5)
No missing data if not stated explicitly. SD = Standard Deviation. IQR = Inter Quartile Range.	

Nalbuphine decreased the level of pain statistically significant and clinically relevant by a median of 3 NRS units (Table 1, Fig. 2). The multivariate regression model showed that pain reduction was more pronounced in patients with higher initial pain level. This effect decreased, but remained statistically significant in the second multivariate model using a relative scale for pain reduction (Table 2). Nalbuphine was less effective in patients aged 20–60 years compared to the adolescent population where Nalbuphine was more effective. The same tendency was observed for the elderly population (i.e. ≥ 60 years of age). However, there were only 20 patients in this age group and the difference was not statistically significant. The level of pain reduction was similar for both genders (Table 2, Fig. 2). In 41 (15.3%) patients, a dissatisfaction of the treatment was documented.

Table 2
Multivariate Linear Regression Models on Pain Reduction after Nasal Nalbuphine.

Variable	Absolute NRS reduction model			Relative NRS reduction model		
	Estimate	95% C.I.	p-value	Estimate	95% C.I.	p-value
Age 20–60 years	-0.606	-1.110 to -0.103	0.018	-0.869	-14.894 to -2.478	0.006
Age > 60 years	-0.591	-1.540 to 0.358	0.221	-7.767	-19.474 to 3.941	0.193
Female sex	0.075	-0.394 to 0.543	0.754	1.158	- 4.212 to 7.347	0.594
Initial pain (NRS)	0.512	0.308 to 0.715	< 0.001	2.534	0.028 to 5.041	0.048

Complete-case analysis: Included observations n = 244, 19 missing observations. Estimate = Difference in NRS reduction after application of nasal Nalbuphine according to either level of the factor variable or initial pain level (absolute difference or relative difference in percentage respectively). 95% C.I. = 95% confidence interval of the estimate. Male sex and Age < 20 years served as the reference groups in both models.

Side effects were reported in 5.6% (n = 11) of patients. Three patients (1.1%) complained of nausea and eight patients (3.0%) reported an uncomfortable feeling in the nose during and after Nalbuphine administration, or disliked the bitter taste. No major adverse event was observed.

Discussion

In our study, the majority of the patients reported a mean reduction of 3 points on the NRS without any major adverse events after Nalbuphine administration.

The reported pain relief in our study is consistent with the literature, where a decrease of more than 2 points on the NRS was deemed a good pain relief after (22). A study with out-of-hospital use of nasal Fentanyl showed also an average reduction of 3 points on the NRS, concluding that nasal Fentanyl is effective for analgesia in the pre-hospital phase (23). Only few studies evaluated analgesia with Nalbuphine in the prehospital setting, however with conflicting results. When given by paramedics out-of-hospital, IV or IM Nalbuphine reduced pain by 5 points on the NRS (24), while the same strategy resulted in excessive Morphine requirements after hospital admission in a case series. That study even reported less decline in pain scores after further administration of analgesics in the emergency department in prehospital Nalbuphine patients (25), which is in accordance with a case review that described increased opioid requirements after Nalbuphine (15). In fact, this is expected because the mixed agonist / antagonist effects of Nalbuphine, with agonistic effects on the κ -receptors and antagonistic effects on the μ -receptor (9). Therefore, if analgesia is continued with pure μ -receptor agonists, an increased dose is needed to overcome the antagonistic effect exerted by Nalbuphine. Our study could not follow up patients after hand-over to EMS / HEMS personnel. Another possible disadvantage of mixed opioid

agonist / antagonists is a limited analgesic effect or ceiling effect (9). This could explain that no patient was completely free of pain after Nalbuphine with a minimal NRS of one after treatment.

We did not find any significant differences between genders regarding pain intensity before or after Nalbuphine, regardless of the administered dose. There is some evidence that Nalbuphine has a pain facilitating effect in males, at least if it is administered in small doses of 5 mg (26), an effect we did not observe. There was a predominance of males in our study (58.8% vs 41.2%) which is consistent with the average distribution of injured people on Swiss ski slopes (56.6% male vs 43.4% female) (27). We observed only a few minor side effects. Although unlikely, the risk of respiratory depression exists also following Nalbuphine (9) (13) (14), but this was not reported in our study. Interestingly, in our study only 15% reported a bad satisfaction with Nalbuphine even though the number of patients who reported a good analgesic effect was high (60.0%). This phenomenon was already described in labouring women treated with Nalbuphine; only 54–57% of the parturient women experienced good pain relief but 78% were willing to have the same treatment in a subsequent birth (12). This could possibly be explained by a reported feeling of relaxation, more than pain relief (12). There is also evidence that satisfaction with opioid treatment seems to be influenced, at least in part, by a rapid onset (13). Nasally administered drugs are normally well absorbed and show a rapid onset of action due to the rich blood supply and large surface of the mucosa, bypassing of a first-pass-effect and, maybe at least in part bypassing the blood-brain-barrier (18).

Our study has some limitations. We mainly observed traumatic shoulder and knee injuries, which is expected with the predominance of our study sites being in Swiss ski resorts (27). There could be a bias in data collection because it was performed directly by FR. If a patient felt sympathies for his rescuer, it is possible that the answers have been whitewashed, in particular regarding qualitative outcomes such as overall satisfaction. Although the qualitative pain reduction from each patient was reported, there were missing NRS values after Nalbuphine 10.5% (n = 28) of the patients, which is to be expected in an observational study in the pre-hospital setting. There was also a predominance of the male gender; this could have had an influence on the described pain reduction. We observed only a few minor side effects with Nalbuphine. However, we did not follow up the patients, and we cannot prove that Nalbuphine administration is always safe.

Conclusion

In conclusion, nasal Nalbuphine by FR was a noninvasive pain management strategy that provided safe and effective analgesia in prehospital, acutely injured patients. This may be an alternative method especially in circumstances of severe pain and prolonged time between arrival of the FR and arrival of EMS / HEMS personnel on scene.

List Of Abbreviations

CI confidence interval

CNS central nervous system

Da Dalton

EMS emergency medical service, ambulance service

FRS first-rescue service

HEMS helicopter emergency medical service

i.m. intra muscular

i.v. intra venous

NRS numeric rating scale

s.c. subcutaneous

SD standard deviation

VAS visual analogue scale

Declarations

Ethics approval and consent to participate

The local ethical committee evaluated the study with a waiver for written informed consent (KEK 2019-01444).

Consent for publication: Not applicable.

Availability of data and supporting materials section: Not applicable.

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Competing interests: The authors declare that they have no competing interests.

Authors' contributions: R.A., D.S. and U.P. developed the original idea for the manuscript and helped write it. Y.B., L.T., L.M., V.W. helped to write the manuscript, gathered additional data, and made important recommendations. All authors read and agreed to the final version of the manuscript.

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Figures

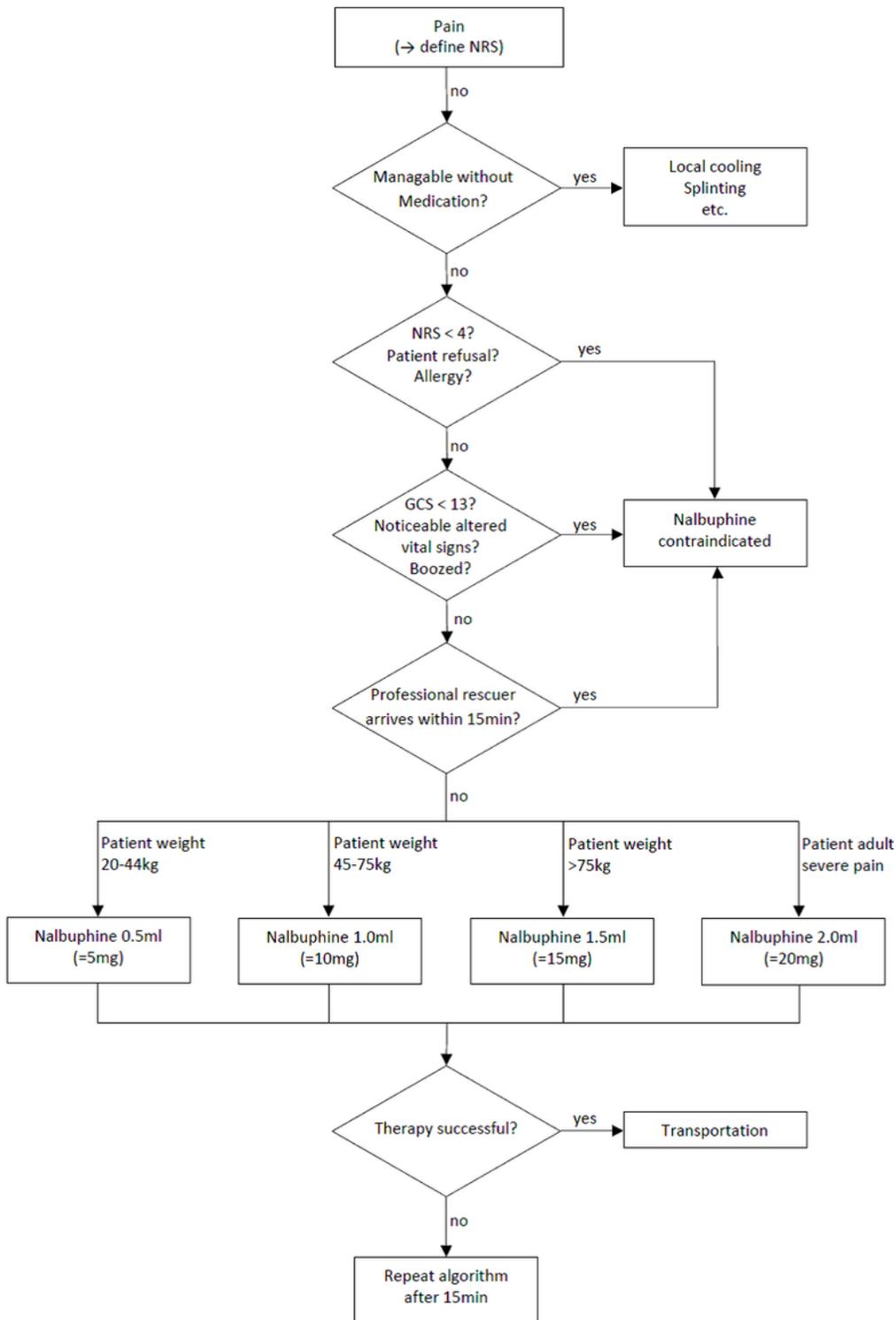


Figure 1

Treatment algorithm that had to be followed by the lay rescuers to assure drug administration only if indicated. NRS = numeric rating scale. GCS = Glasgow coma scale.

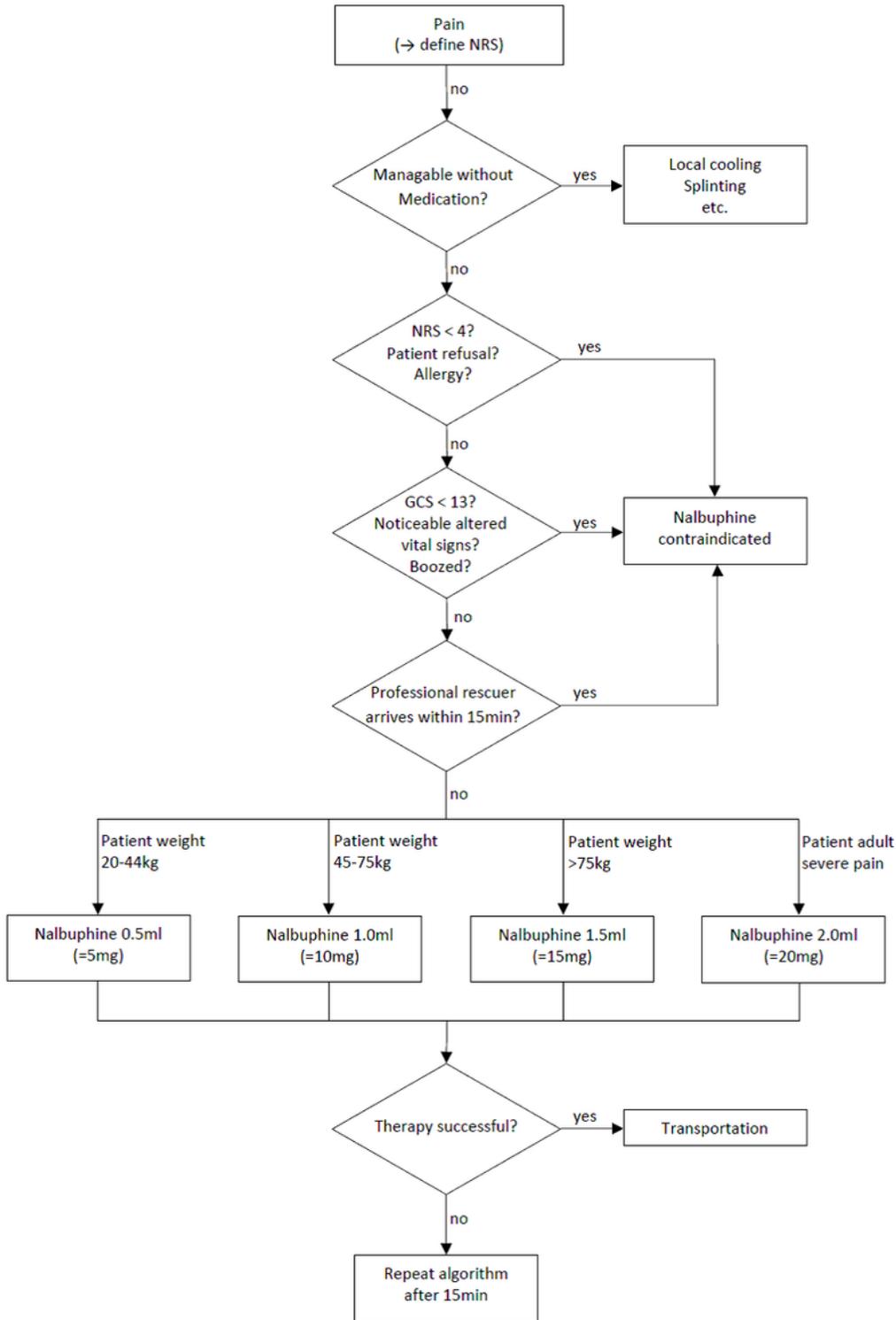


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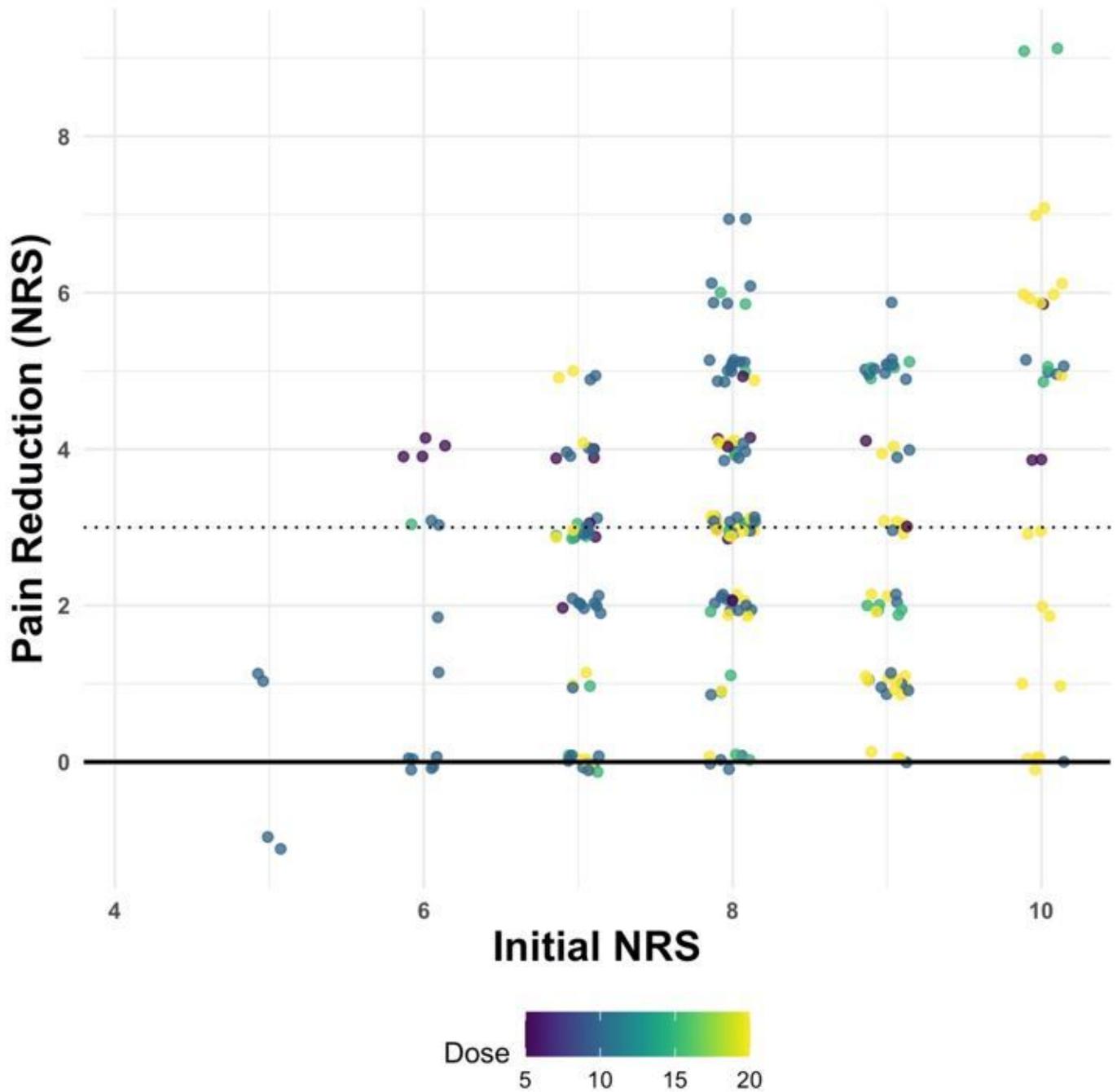


Figure 2

Distribution of Pain Reduction Depending on Initial Pain Level and Dose Applied. Jitter plot: to increase readability of the plot, the points were jittered around the true value. Dotted line indicating the median pain reduction of 3 NRS units. 145 patients had a pain reduction of at least 3 units on the numeric rating scale.

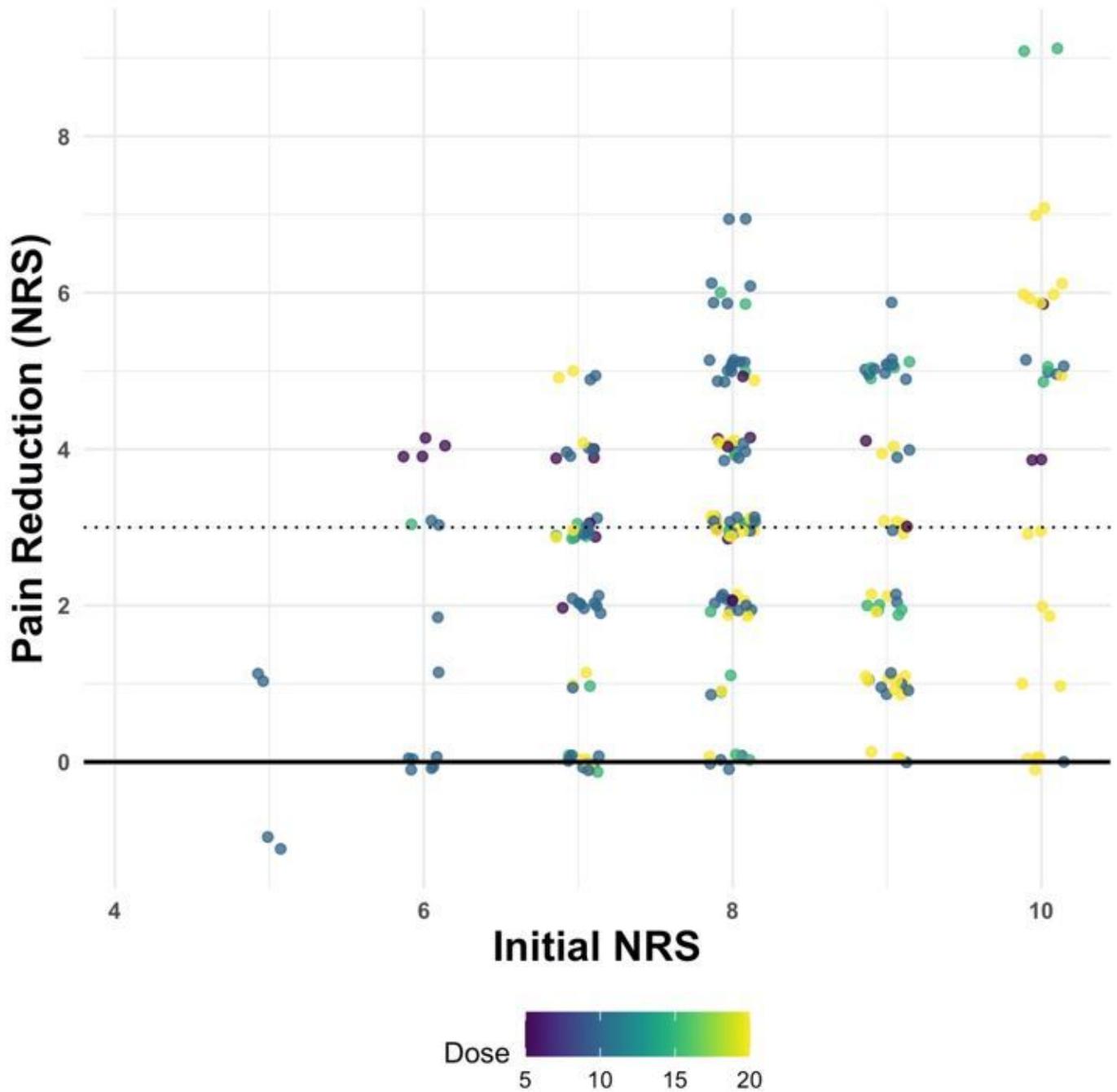


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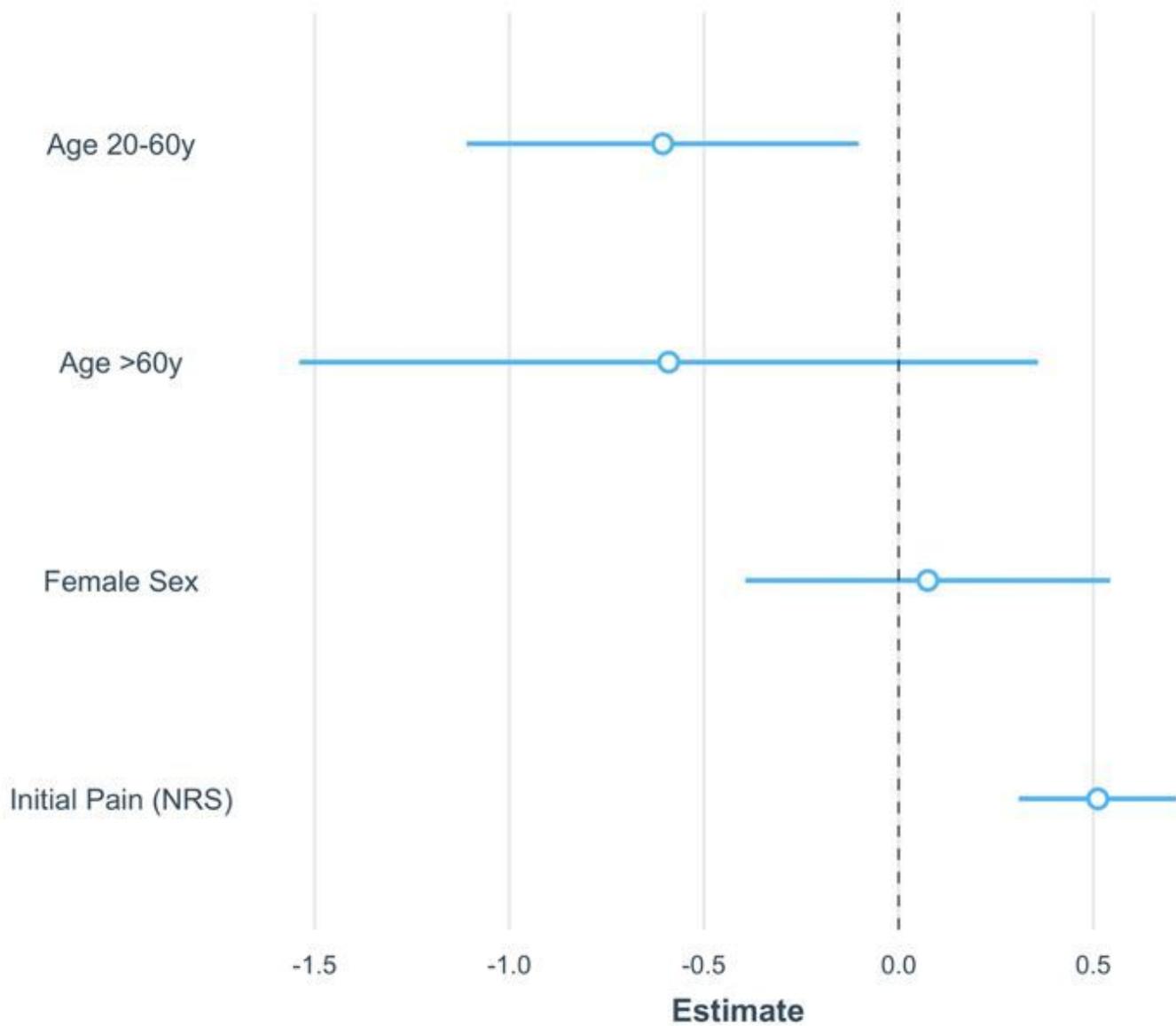


Figure 3

Multivariate Linear Regression Models on Pain Reduction after Nasal Nalbuphine application. Complete-Case Analysis: Included observations n=244, 19 missing observations. Male sex and Age <20 years served as the reference groups. Reading example: For every point the initial NRS was higher, pain reduction was approximately 0.5 units bigger, holding the other variables constant.

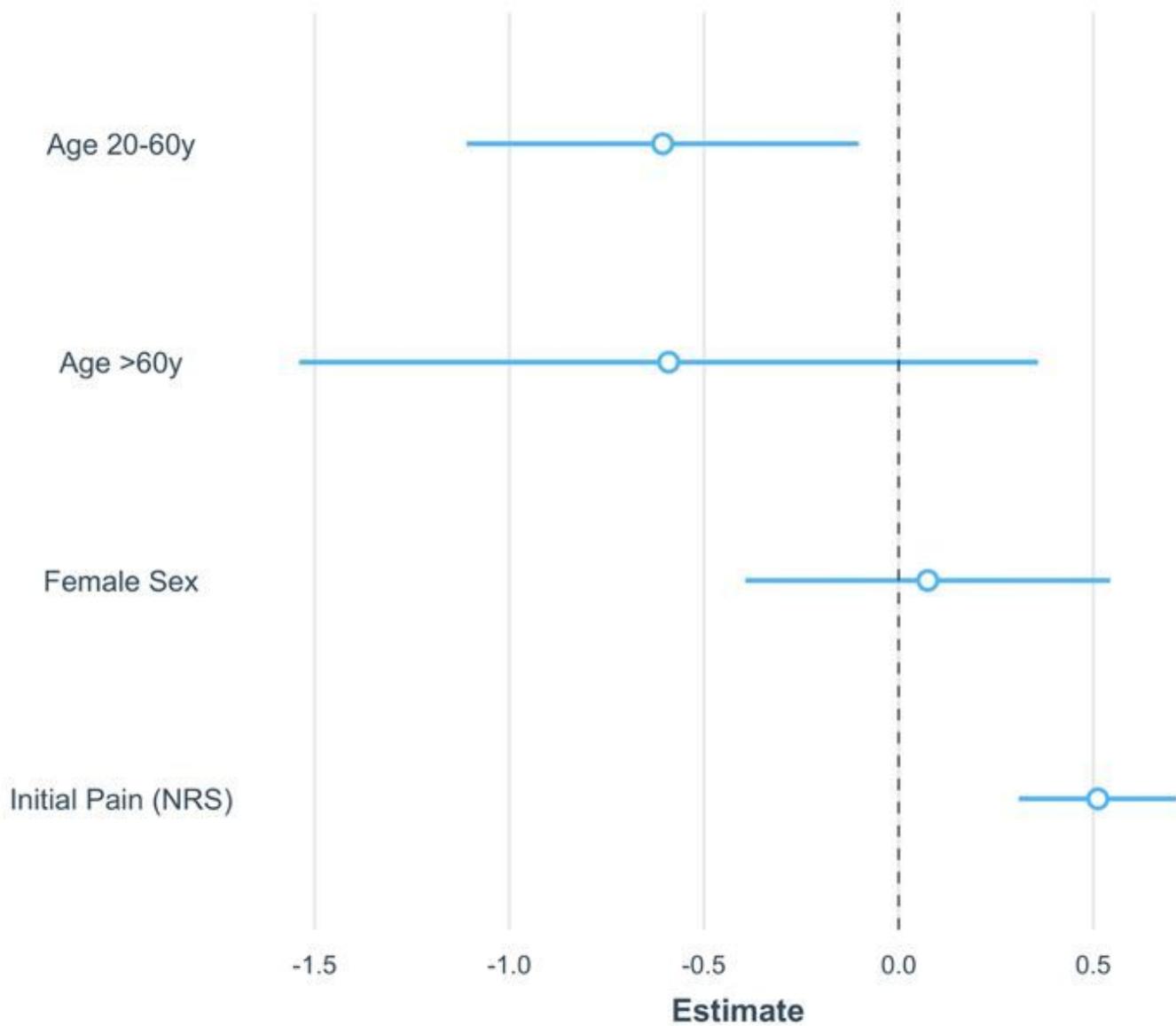


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