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Ocena skuteczności analgezji wyprzedzającej (pre-emptive analgesia) w leczeniu bólu pooperacyjnego po zabiegach otolaryngologicznych u dzieci

Rozprawa doktorska oparta o cykl powiązanych tematycznie publikacji

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Spis treści

STRESZCZENIE

1. Wstęp

Zgodnie z definicją International Association for the Study of Pain (IASP), ból jest nieprzyjemnym zmysłowym i emocjonalnym doświadczeniem związanym z rzeczywistym lub potencjalnym uszkodzeniem tkanki, powstającym pod wpływem bodźców uszkadzających tkanki (nocyceptywnych). Ból ostry wywołany przez zabieg operacyjny, związany z bezpośrednim uszkodzeniem tkanek, jest główną przyczyną dyskomfortu pacjenta w okresie pooperacyjnym. Ból jest zawsze subiektywny i może prowadzić do powikłań oraz zaburzeń metabolicznych, endokrynologicznych i immunologicznych, jeśli nie jest leczony lub nie jest odpowiednio leczony. Do indukcji bólu dochodzi w receptorach (nocyreceptorach), następnie sygnał przekazywany jest drogami nocyceptywnymi do ośrodkowego układu nerwowego uruchamiając szereg zmian w układzie somatosensorycznym. Podczas zabiegu operacyjnego, pod wpływem omawianego bodźca, z tkanek wydzielane są enzymy proteolityczne, które indukują wydzielanie kinin i prostaglandyn, zwiększając odpowiedź na kolejne bodźce, w efekcie nasilając dolegliwości bólowe. Poprzez uwrażliwienie szlaków bólowych, może dochodzić do zjawiska „pamięci bólu", a nieleczony ból może prowadzić do rozwoju bólu przewlekłego.

Analgezja wyprzedzająca to postępowanie ochronne, które rozpoczyna się przed wystąpieniem bodźca bólowego, a zatem przed zabiegiem chirurgicznym i trwa przez cały zabieg, aby ograniczyć fizjologiczne konsekwencje transmisji nocyceptywnej. Ze względu na ten ochronny efekt może być skuteczniejsze niż analgezja peri- i pooperacyjna. Zgodnie z klasycznym rozumieniem tej metody terapeutycznej wszelkie badania oceniające jej skuteczność, powinny być skonstruowane w ten sposób, że pacjenci w porównywanych grupach badawczych powinni otrzymywać dokładnie ten sam lek, a jedyną między nimi różnicą ma być czas ich podania: przed nacięciem skóry lub po zabiegu operacyjnym.

W anglojęzycznym piśmiennictwie istnieją opracowania badań dotyczące wpływu analgezji wyprzedzającej na ból pooperacyjny, jednakże dotyczą one głównie pacjentów dorosłych. Nieliczne badania przeprowadzone w grupie pacjentów pediatrycznych, nie pozwalają na jednoznaczną, pozytywną ocenę skuteczności analgezji wyprzedzającej w leczeniu bólu pooperacyjnego.

2. Cele i założenia pracy

Głównym celem projektu badawczego była ocena skuteczności zastosowania analgezji wyprzedzającej, w odniesieniu do natężenia bólu pooperacyjnego po zabiegach otolaryngologicznych u dzieci, przy użyciu powszechnie dostępnych skal werbalnych i behawioralnych. Dodatkowo zastosowano urządzenie monitorujące ból, którego działanie opiera się na pomiarze zmian transdukcji skóry pacjenta – Skin Conductance Algesimeter – PainMonitor™. Cel projektu zrealizowano dokonując przeglądu piśmiennictwa dotyczącego najczęściej stosowanych narzędzi do oceny bólu pooperacyjnego oraz przeprowadzając dwa randomizowane badania. Każde z badań stanowiło podstawę artykułu współtworzącego cykl publikacji.

3. Materiał i metody

Przed rozpoczęciem badań klinicznych randomizowanych przeszukano bazę PubMed pod kątem słów kluczowych "postoperative", "pain assessment" i "pain scale", wyszukując artykuły opublikowane w latach 1950-2019. W sumie znaleziono 8 769 artykułów. Po przefiltrowaniu pod kątem wieku od niemowlęcego do 18 lat pozostały 1 944 artykuły. Artykuły w języku innym niż angielski nie były brane pod uwagę. Po przeanalizowaniu tytułów i streszczeń wykluczono kolejne 1666 prac, które - pomimo zastosowania przedziału wiekowego - odnosiły się także do pacjentów dorosłych i do skal stosowanych w okresie innym niż pooperacyjny, pozostawiając 278 artykułów kwalifikujących się do przeglądu. Ich analiza pozwoliła na identyfikację 10 różnych powszechnie stosowanych w praktyce klinicznej skal dedykowanych do oceny bólu pooperacyjnego u dzieci. Wśród nich znalazły się wizualna skala analogowa (VAS), skala Wong-Baker Faces Pain Rating Scale (WB) oraz skala Face, Legs, Activity, Cry, and Consolability (FLACC). Z uwagi na największą ilość cytowań oraz randomizowanych badań kontrolnych, w których zastosowano powyższe skale, wykorzystano je w przeprowadzonych badaniach.

Badania kliniczne objęły ocenę wpływu analgezji wyprzedzającej z użyciem paracetamolu podanego doustnie przed zabiegiem operacyjnym. Do badania klinicznego włączono 51 pacjentów z Kliniki Otolaryngologii Uniwersyteckiego Szpitala Klinicznego we Wrocławiu, poddanych zabiegom adenotomii, tonsillotomii oraz tonsillektomii. Kryteria włączenia do badania stanowiły wiek od 3 do 17 lat oraz pisemna świadoma zgoda rodziców (lub opiekunów prawnych). Kryteriami wyłączenia z badania były: niepełnosprawność intelektualna, poważne

choroby współistniejące, uczulenie na paracetamol, deksametazon lub nalbufinę oraz ból przed zabiegiem operacyjnym.

W celu losowego przydzielenia pacjenta do grupy badanej lub kontrolnej zastosowano randomizację blokową (permuted block randomization). Pacjent, rodzic, anestezjolog i chirurg nie wiedzieli, do jakiej grupy został przydzielony pacjent. Jedynie pielęgniarka podająca dziecku premedykację nie została poddana próbie ślepej. Po otrzymaniu przez dziecko premedykacji, formularz przydziału do grupy był chowany do koperty. Dokładną dawkę leków przeciwbólowych w okresie pooperacyjnym przepisywano co 6 godzin, w zależności od masy ciała dziecka.

W grupie badanej oprócz midazolamu (0,5 mg/kg) jako premedykacji podawano paracetamol (15 mg/kg) (n=26), natomiast w grupie kontrolnej placebo (n=25). Roztwór premedykacyjny z paracetamolem był koloru czerwonego i miał smak truskawkowy. Celem upewnienia się, że grupa kontrolna otrzymała płyn o tej samej masie i kolorze, do midazolamu dodano zagęszczony sok truskawkowy. Około 30-45 minut po podaniu premedykacji dziecko przewożono na salę operacyjną. Wszystkim dzieciom podawano wziewnie sewofluran, dożylnie propofol (2-4 mg/kg) i fentanyl (2 mcg/kg). Podczas zabiegu operacyjnego wszyscy pacjenci otrzymali pojedynczą dawkę dożylną deksametazonu (0,2 mg/kg) i nalbufiny (0,2 mg/kg) jako standardową analgezję okołooperacyjną. Po zabiegu chorzy byli przenoszeni do sali pooperacyjnej, a następnie na oddział otolaryngologiczny, co trwało około 45 min.

Ból pooperacyjny oceniano za pomocą wizualnej skali analogowej (VAS), skali Wong-Baker Faces Pain Rating Scale (WB), skali Face, Legs, Activity, Cry, and Consolability (FLACC) oraz urządzenia monitorującego przewodnictwo skórne w pierwszej, drugiej, czwartej i szóstej godzinie po zabiegu operacyjnym.

Skala FLAAC jest narzędziem oceny, które służy do ilościowej oceny bólu w skali od 0 do 10 przy użyciu pięciu kategorii takich jak: wyraz twarzy, ułożenie nóg, aktywność, płacz i możliwość uspokojenia dziecka. Obserwacja trwała 2-5 minut. Każdy parametr był oceniany w skali od 0 do 2; wynik całkowity interpretowany był następująco: 0 = komfort pacjenta, 1-3 = łagodny dyskomfort, 4-6 = umiarkowany ból, 7-10 = silny dyskomfort/ból.

Drugim narzędziem oceny stosowanym w okresie pooperacyjnym była skala Wong-Baker Faces Pain Rating Scale (WB). Składa się ona z serii wyrazów twarzy, od radosnej o wartości 0, która oznacza brak bólu, do płaczliwej o wartości 10, która sugeruje najgorszy możliwy ból. Pacjent wybierał ten wyraz twarzy, który najlepiej odzwierciedlał jego aktualny poziom bólu. Z kolei skala VAS to linia o długości 10 cm, na której końcach znajdują się oznaczenia "1"

i "10". Symbol "1" oznacza brak bólu lub dyskomfortu, a "10" - bardzo silny ból. Pacjent oznaczał pionową linią skalę, aby wyrazić natężenie swojego bólu.
Dodatkowo zastosowano urządzenie monitorujące ból, którego działanie opiera się na pomiarze zmian transdukcji skóry pacjenta – Skin Conductance Algesimeter – PainMonitor™. Służy on do pomiaru natężenia bólu u dzieci i dorosłych, pacjentów nieprzytomnych, zarówno tych znajdujących się pod wpływem znieczulenia ogólnego, jak i tych, u których komunikacja werbalna jest ograniczona lub wręcz niemożliwa. Metoda oparta jest na rejestracji w czasie rzeczywistym zmian przewodnictwa skórnego, spowodowanego działaniem acetylocholiny uwalnianej w reakcji bólowej na receptory muskarynowe z następczym uwalnianiem potu, który zwiększa przewodnictwo skóry. Podczas oceny obecny był zespół badawczy oraz rodzice lub opiekunowie. W analizie bólu uwzględniono jedynie ból gardła.

4. Wyniki i wnioski

W pierwszej pracy z cyklu dokonano przeglądu piśmiennictwa, wybierając skale najczęściej stosowane i zwalidowane w okresie pooperacyjnym u dzieci. W celu ustalenia prostych kryteriów wyboru skali zastosowano kryterium wieku pacjenta. W przypadku pacjentów w wieku 3-5 lat należy stosować skale, m.in. CHEOPS i FLACC, które są skalami behawioralnymi i nie wymagają samooceny ze strony pacjenta. U dzieci starszych, które są w stanie opisać natężenie i intensywność swojego bólu, zaleca się stosowanie głównie skal obrazkowych - takich jak zróżnicowana etnicznie skala Oucher, skala Wong-Baker FACES Pain Rating Scale lub najczęściej stosowanej skala VAS. Niezależnie od tego, jakie narzędzie zostanie zastosowane do pomiaru bólu, powinno ono uwzględniać wiek, język, pochodzenie etniczne i zdolności poznawcze dziecka.
W drugiej pracy z cyklu zbadano korelację pomiędzy pomiarem przewodnictwa skórnego a subiektywnymi skalami oceny natężenia bólu u dzieci po zabiegach otolaryngologicznych. Zebrano dane dotyczące 33 dzieci (17 dziewczynek i 16 chłopców). Jedenaścioro dzieci (33,3%) poddano adenoidektomii, 15 (45,5%) adenotonsillotomii, a 7 (21,2%) tonsillektomii. Średni wiek dzieci wynosił 6,1 roku (SD = 3,0; zakres: 3-17 lat). Nie stwierdzono istotnych statystycznie różnic między obiema grupami badawczymi: proporcje płci ($p=0.869$) i wieku ($p=0.186$) były podobne. Nie stwierdzono istotnej statystycznie korelacji pomiędzy poziomem bólu zgłaszanego przez pacjenta a liczbą fluktuacji przewodnictwa skóry na sekundę zarówno w całej grupie badanej, jak i w podgrupach zróżnicowanych ze względu na płeć ($p>0.05$). Natomiast stwierdzono istotną statystycznie korelację między wszystkimi subiektywnymi

skalami bólu w całej grupie badanej ($p<0.05$). Perspektywa stworzenia obiektywnego narzędzia do pomiaru bólu, a następnie jego wdrożenie, ułatwiłoby właściwe leczenie bólu. Dlatego też podjęto próbę zbadania istnienia korelacji pomiędzy oceną dolegliwości bólowych mierzonych z użyciem najczęściej stosowanych skal dedykowanych do oceny bólu pooperacyjnego u dzieci, a tą uzyskiwaną z pomiaru zmian transdukcji skóry w wyniku działania bodźca nocyceptywnego. Dotychczas większość badań klinicznych z zastosowaniem pomiaru przewodnictwa skórnego opierała się na pomiarze bólu ostrego, występującego w momencie pomiaru, czyli pojedynczego jego incydentu. Jednakże ocena bólu u dzieci, które nie doświadczają pojedynczego incydentu bólowego, na przykład w okresie pooperacyjnym, jest trudniejsza. Obecne badanie jest pierwszym, w którym porównano trzy subiektywne skale oceny bólu z pomiarem przewodnictwa skóry w okresie pooperacyjnym u pacjentów pediatrycznych. W badanej grupie 33 dzieci liczba wahań przewodnictwa skóry na sekundę wzrosła między pierwszą a drugą godziną (0,08 vs. 0,11 Hz; $p = 0,008$), a jednocześnie subiektywne oceny bólu wskazywały na spadek jego odczuwania. Być może należy to tłumaczyć tzw. przyzwyczajeniem się dzieci do dyskomfortu jaki ze sobą niósł przedłużający się ból i uruchomienia przezeń sposobów radzenia sobie z nim. Uzyskane wyniki potwierdzają przydatność powszechnie stosowanych skal ocen bólu zarówno tych behawioralnych jak i opartych na relacji własnej pacjenta. Okazały się one wiarygodne, łatwe w użyciu, a przede wszystkim zrozumiałe dla młodych pacjentów. Wydaje się, że pomiary przewodnictwa skóry nie stanowią dodatkowego wiarygodnego narzędzia do oceny bólu u pacjentów po zabiegach otolaryngologicznych. Trzeba jednocześnie podkreślić, że ograniczeniem niniejszego badania jest fakt, że przeprowadzono je w jednym ośrodku i objęto nim niewielką liczbę pacjentów. Na pewno rozszerzenie badania o inne ośrodki i objęcie nimi większej ilości dzieci jest niezbędne dla bardziej wiarygodnej oceny tego sposobu monitorowania bólu u dzieci.

W trzeciej pracy z cyklu zbadano wpływ analgezji wyprzedzającej na ból pooperacyjny u dzieci po zabiegach otolaryngologicznych. Z uwagi na wyniki poprzednich badań klinicznych oraz na brak istotnie statystycznej korelacji pomiędzy narzędziem monitorującym zmiany przewodnictwa skórnego a skalami samooceny natężenia bólu, nie wykorzystywano tego narzędzia w badaniach. W badaniu klinicznym wykazano istotną statystycznie korelację pomiędzy podawaniem analgezji wyprzedzającej a placebo w zmniejszaniu bólu u dzieci po zabiegach otolaryngologicznych, przy zastosowaniu skali Wong-Baker Faces Pain Rating Scale i skali VAS, z wyjątkiem 2. godziny po zabiegu. Ponadto ponownie stwierdzono istotną statystycznie korelację między punktacją bólu mierzoną skalami WB, VAS i FLACC w pierwszej, drugiej, czwartej i szóstej godzinie po operacji. Najwyższy wskaźnik zgodności

między skalami oceny poziomu bólu wystąpił między skalą Wong-Baker Faces Pain Rating Scale i skalą VAS. W drugiej godzinie po operacji dane nie wykazały istotnej statystycznie różnicy pomiędzy ocenami natężenia bólu w obu badanych grupach chociaż była ona zaznaczona na korzyść grupy dzieci, u których w premedykacji zastosowano paracetamol (niższa ocena bólu np. przy użyciu skali VAS). W badaniu klinicznym wykazano istotną statystycznie korelację między podawaniem analgezji z wyprzedzeniem (paracetamol) a placebo w zmniejszaniu bólu u dzieci po zabiegach otolaryngologicznych. U większości dzieci zarówno w grupie badanej, jak i w grupie kontrolnej nie wystąpił silny ból pooperacyjny. Jednak pozytywny efekt analgezji wyprzedzającej był statystycznie istotny w zmniejszeniu bólu do absolutnego minimum.

Uzyskane wyniki badań pozwoliły na obiektywną ocenę skuteczności zastosowania analgezji wyprzedzającej. Odpowiedziały na pytanie, czy metoda ta wpływa na zmniejszenie dolegliwości bólowych w okresie pooperacyjnym w grupie pacjentów pediatrycznych, a tym samym poprawia jakość prowadzonej analgezji. Dzięki pozytywnej jej weryfikacji, możliwa jest modyfikacja schematów terapeutycznych bólu pooperacyjnego, której nadrzędnym celem jest poprawa zarówno komfortu dziecka w tym okresie, jak i zmniejszenie ryzyka wystąpienia Zespołu Bólu Przetrwałego, inaczej przewlekłego. Dodatkowo skutecznie leczony ból przyczynia się do skrócenia czasu hospitalizacji. Biorąc te wyniki pod uwagę, w przyszłości zdaniem autora, zaleca się stosowanie analgezji wyprzedzającej u pacjentów przed zabiegami otolaryngologicznymi.

ABSTRACT

1. Introduction

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage stemming from tissue-damaging (nociceptive) stimuli. Acute pain caused by direct tissue damage during surgery is the primary cause of patient discomfort in the postoperative period. Pain is always subjective and can lead to complications and metabolic, endocrine and immunologic disorders if left untreated or inadequately treated. Pain is induced in receptors (nociceptors), then the signal is transmitted through nociceptive pathways to the central nervous system, triggering a number of changes in the somatosensory system. During surgery, under the influence of the stimulus, proteolytic enzymes are secreted from the tissues, which induce the secretion of kinins and prostaglandins, in turn increasing the response to further stimuli and thus exacerbating the pain. Through sensitization of pain pathways, the phenomenon of "pain memory" may occur, while untreated pain may lead to the onset of chronic pain.
Pre-emptive analgesia is a protective treatment that begins before the onset of the pain stimulus (i.e., before the surgical procedure) and continues throughout the procedure to limit the physiological consequences of nociceptive transmission. Because of this protective effect, it may be more effective than peri- and postoperative analgesia. According to the classical understanding of this therapeutic method, all studies evaluating its efficacy should be designed in such a way that patients in all study groups receive exactly the same medication; the only difference between them should be the time of administration: before skin incision or after surgery.
In the English-language literature, there are studies on the effect of pre-emptive analgesia on postoperative pain; however, they mainly concern adult patients. The few studies performed in pediatric patients do not provide a positive evaluation of the efficacy of pre-emptive analgesia in the treatment of postoperative pain.

2. Aims and Objectives

The main objective of this study was to evaluate the effectiveness of pre-emptive analgesia on the level of postoperative pain after otolaryngological procedures in children, using commonly available verbal and behavioral scales. Additionally, a pain monitoring device that measures skin conductance changes, the PainMonitor™ skin conductance algesimeter, was used. The

purpose of this project was accomplished by reviewing the literature on the most common tools to assess postoperative pain and by carrying out two randomized controlled trials. Each study was the foundation for an article in a series of publications.

3. Material and Methods

Prior to randomized controlled clinical trials, the PubMed database was queried with the keywords “postoperative,” “pain assessment,” and “pain scale,” searching for articles published between 1950 and 2019. In total, 8,769 articles were found. After filtering for a patients’ age between infancy and 18 years, 1,944 articles remained. Articles in any language other than English were not considered. An evaluation of the titles and abstracts excluded a further 1,666 studies which – despite the age range filter – also referred to adult patients and to scales used outside of the postoperative period, leaving 278 articles eligible for review. A total of 10 distinct common pain scales were identified. All scales were used in the postoperative period in children. These included the Visual Analog Scale (VAS), the Wong–Baker Faces Pain Rating Scale (WB), and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale. Because these scales had the most citations and randomized control trials using them, they were chosen for the studies.

The clinical trial evaluated the effect of pre-emptive analgesia with paracetamol administered orally before surgery and included 51 patients from the Department of Otolaryngology of the University Clinical Hospital in Wrocław, undergoing adenoidectomy, tonsillotomy, and tonsillectomy. The inclusion criteria were healthy children between the ages of 3 and 17 years who qualified for surgical treatment in the Department of Otolaryngology and the written informed consent of their parents (or legal guardians). The exclusion criteria were intellectual disability, major coexisting diseases, allergy to acetaminophen, dexamethasone, or nalbuphine, and pain prior to surgery. To randomly allocate a patient to a study or control group, permuted block randomization was used. The patient, parent, anesthetist, and surgeon were all blinded to the study; only the nurse delivering the premedication to the child was not blinded. Once the child received their premedication, the group allocation sheet was concealed in an envelope. The exact dose of postoperative analgesics was prescribed every 6 h, based on the child’s weight.

The study group (n=26) received paracetamol (15 mg/kg) in addition to midazolam (0.5 mg/kg) as premedication, while the control group (n=25) received a placebo. The premedication solution with paracetamol was red and strawberry flavored. To ensure that the

control group received a liquid of the same weight and color, strawberry juice was added to the premedication with midazolam. Approximately 30 to 45 min after the premedication was administered, the children were transported to the operating room. Anesthesia was induced with propofol at a dosage of 2–4 mg/kg iv, sevoflurane as an inhalation agent, and fentanyl at a dosage of 2 mcg/kg iv. Sevoflurane was used to maintain the anesthesia. At the end of the surgical procedures, all patients received intravenous dexamethasone (0.2 mg/kg) and nalbuphine (0.2 mg/kg) as standard perioperative analgesia. Postoperatively, the patients were transferred to the postop room and then to the otolaryngology ward, which took approximately 45 min.

Postoperative pain was assessed 1, 2, 4, and 6 h after the surgery using the Wong–Baker Faces Pain Rating Scale, the VAS, the FLACC scale, and the skin conductance algesimeter. The FLAAC scale [14] is an assessment tool that is used to quantify pain on a score from 0 to 10 using 5 categories: facial expression, legs, activity, crying, and consolability. The observation lasted for 2 to 5 min. Each parameter was scored on a scale from 0 to 2; the total score was interpreted as follows: 0 = patient comfort, 1–3 = mild discomfort, 4–6 = moderate pain, and 7–10 = severe discomfort/pain. The second assessment tool used in the postoperative period was the WB. It consists of a series of facial expressions ranging from cheerful (with a value of 0, indicating no pain) to tearful (with a value of 10, suggesting the worst possible pain). The patients chose the facial expression that best reflected their current level of pain. The VAS scale, on the other hand, is a line 10 cm long and labelled “1” and “10” at the ends. A “1” indicates no pain or discomfort, while a “10” indicates very severe pain. The patients marked the scale with a vertical line to express the intensity of their pain. Additionally, a pain monitoring device that measures changes in the patient’s skin transduction, the PainMonitor™, was used. It is designed to measure pain intensity in both children and adults, unconscious patients under general anesthesia or with whom verbal communication is limited or even impossible. The method is based on real-time recording of changes in skin conductance due to the action of acetylcholine (released in the pain response) on muscarinic receptors, with a subsequent release of sweat, which increases skin conductance. The study team and parents or guardians were present during the assessment. Only throat pain was included in the pain analysis.

4. Results and Conclusions

The first article in the series reviewed the literature, selecting the most commonly used scales which had been validated in the postoperative period in children. Criteria were used for patient age: for patients aged 3 to 5 years, scales such as CHEOPS and FLACC, which are behavioral scales and do not require self-assessment by the patient, should be used; in older children who are able to describe the intensity and severity of their pain, it is recommended to mainly use visual scales such as the ethnically diverse Oucher scale, the Wong–Baker FACES Pain Rating Scale, or the most commonly used VAS scale. Whichever tool is used to measure pain, it should take into account the child's age, language, ethnicity, and cognitive ability.
The second study in the series investigated the correlation between measurements of skin conductance and results of subjective pain intensity rating scales in children after otolaryngological procedures. Data were collected on 33 children (17 girls and 16 boys). Eleven children (33.3%) underwent adenoidectomy, 15 (45.5%) adenotonsillotomy, and 7 (21.2%) tonsillectomy. The mean age of the children was 6.1 years (SD: 3.0; range: 3–17 years). There were no statistically significant differences between the two study groups: the ratios of sex (p=0.869) and age (p=0.186) were similar. There was no statistically significant correlation between the level of pain reported by the patient and the number of skin conductance fluctuations per second, either in the whole study group or in subgroups differentiated by gender (p>0.05). In contrast, a statistically significant correlation was found between all subjective pain scales in the entire study group (p<0.05).
The prospect of developing and implementing an objective pain measurement tool would facilitate proper pain management. Therefore, an attempt was made to investigate the existence of any correlations between pain scores from the most common scales dedicated to postoperative pain assessment in children and measurements of changes in skin conductance due to nociceptive stimuli. To date, most clinical studies using skin conductance measurement have relied on the measurement of acute pain occurring at the time of measurement, that is, a single incident of pain. However, pain assessment is more difficult in children who do not experience a single incident of pain, such as in the postoperative period.
The current study is the first to compare three subjective pain rating scales with skin conductance measurements in the postoperative period in pediatric patients. In the study group of 33 children, the number of skin conductance fluctuations per second increased between the first and second hour (0.08 vs. 0.11 Hz; p=0.008), while at the same time the subjective pain ratings indicated a decrease in pain sensation. This may be explained by the

children becoming accustomed to the discomfort of prolonged pain and activating their subconscious coping mechanisms. Our results confirm the usefulness of the commonly used pain assessment scales, whether behavioral or self-reported. They proved to be reliable, easy to use, and – most importantly – understandable for young patients. It seems that skin conductance measurements are not an additional reliable tool for pain assessment in patients after otolaryngological procedures. It should also be emphasized that a limitation of the current study is that it was conducted at a single center and included a small sample of patients. Expanding the study to other centers and including more children is certainly necessary for a more reliable evaluation of this method of pain assessment in children.

The third article in the series investigated the effect of pre-emptive analgesia on postoperative pain in pediatric otolaryngology. Considering the results of previous clinical trials and the lack of a statistically significant correlation between the skin conductance algesimeter measurements and self-reported pain intensity scores, this tool was not used in this study. In a clinical trial, a statistically significant correlation was found between administration of pre-emptive analgesia versus placebo scale (except for 2 h after surgery) in reducing pain in children after otolaryngological procedures, using the WB and the VAS. In addition, there was again a statistically significant correlation between pain scores measured by the WB, VAS, and FLACC scales 1, 2, 4, and 6 h after surgery. The highest rate of agreement between pain rating scales was between the WB and the VAS scales. In the second hour after surgery, the results did not demonstrate a statistically significant difference between the pain scores in the two study groups, although the difference was in favor of the group of children premedicated with paracetamol (lower pain scores, e.g., using the VAS scale). The clinical trial also demonstrated a statistically significant correlation between pre-emptive analgesia (paracetamol) and placebo in reducing pain in children after otolaryngological procedures. Most children in both the study and control groups did not experience severe postoperative pain. However, the positive effect of pre-emptive analgesia was statistically significant in reducing pain to an absolute minimum.

The results of the study allowed for an objective evaluation of the effectiveness of pre-emptive analgesia. They demonstrated whether this method reduces postoperative pain in pediatric patients and improves the quality of analgesia. With the positive results, it is possible to modify the therapeutic protocols for postoperative pain, whose overriding aims are to improve the comfort of children and to reduce the risk of chronic pain syndrome. In addition, effectively treated pain contributes to shorter hospitalization stays, which means a reduction in costs

dedicated to patient care in the hospital. Considering these results, the author recommends the use of pre-emptive analgesia in patients before otolaryngological procedures in the future.

Pain assessment and management in children in the postoperative period: A review of the most commonly used postoperative pain assessment tools, new diagnostic methods and the latest guidelines for postoperative pain therapy in children

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Abstract

Pain is one of the most common complaints expressed by hospital patients and is the main reason they seek medical help. Pain is always subjective, so its severity should be assessed individually for each patient. The main issue with pain management in children is the difficulty involved in evaluating it. Numerous studies have developed tools that would allow for an accurate assessment of the intensity of pain in children in the postoperative period. Adequate postoperative pain assessment in pediatric patients may significantly improve their comfort and quality of life. Postoperative pain prolongs recovery and hospitalization; therefore, the severity of the pain should be part of a routine assessment. Whichever tool is applied to measure pain, it should take into account the child's age, language, ethnicity, and cognitive ability. There is no one universal method for pain assessment which is appropriate for every pediatric patient. This article provides a review of the available subjective methods of postoperative pain assessment, including new objective diagnostic methods and the latest guidelines for postoperative pain therapy in a group of pediatric patients.

Key words: pain, postoperative pain, pain treatment, pediatric

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Introduction

The main issue with pain management in children – especially young children – is the difficulty involved in evaluating it. When a patient's level of pain cannot be accurately assessed, effective analgesia cannot be prescribed. When children are not sufficiently treated for pain, stress hormones are released into their systems, resulting in increased catabolism, immunosuppression and hemodynamic instability.

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, and is caused by pain stimuli (also known as nociceptive stimuli). Pain is induced in the appropriate receptors, the nociceptors, and then transmitted through nociceptive pathways to the central nervous system, by signals that trigger a cascade of changes in the somatosensory system. These changes increase the response to further stimuli, thus increasing the pain.[1]

Pain is one of the most common complaints experienced by hospital patients[2] and is the main reason they seek medical help. Pain is always subjective, so its severity should be assessed individually for each patient. Pain consists of everything the patient describes as pain, regardless of the objective symptoms associated with it. A lack of verbal communication does not equate to a lack of pain sensation, so appropriate analgesic treatment may still be required. In 1992, the American Academy of Pediatrics and the American Pain Society issued a statement aimed at providing comprehensive treatment for pain and suffering in all children and adolescents, suggesting that attention should be focused on interdisciplinary treatment, including pharmacological, cognitive behavioral, psychological, and physical treatment.[3] Compared to adult patients, it is more difficult to assess and treat pain in children, a fact which often results in insufficient analgesics being administered. The available literature documents the harmful physiological effects of pain on young patients[4,5] as well as the beneficial results of effective analgesia in children.[6] The commonly available methods of assessing pain intensity are based on the patient's own account or depend on a clinical evaluation performed by medical personnel. It is necessary to increase the use of the available pain assessment tools and scales that allow for the most objective assessment of pain severity and the most effective analgesia possible.

Description of current knowledge

Numerous studies have developed tools that would allow for an accurate assessment of the intensity of pain in children in the postoperative period. In this review, the PubMed database was queried with the keywords 'postoperative', 'pain assessment' and 'pain scale', searching for articles published between 1950 and 2019. In total, 8,769 articles were found. After filtering for age from infancy to 18 years, 1,944 articles were left. Articles in any language other than English were not considered. An evaluation of the titles and abstracts excluded a further 1,666 studies which – despite the age range filter – also referred to adult patients and to scales used in a period other than the postoperative one, leaving 278 articles eligible for review. A total of 10 distinct common pain scales were identified. All scales were used in the postoperative period in children. A summary of the scales is provided in Table 1.

Table 1. Most often used pain scales from the literature which meet the search criteria

Acronym	Age range	First reference (author)	Number of citations
CHEOPS	1–7 years	McGrath PJ et al.[8]	33
FLACC	2 months–7 years	Merkel S et al.[11]	26
CHIPPS	0–5 years	Büttner W et al.[14]	9
OPS and MOPS	8 months–13 years	Broadman LM et al.[22] Wilson GAM et al.[24]	23
Poker Chip Tool	from 3 years	Hester N et al.[27]	4
Oucher Scale	3–12 years	Beyer JE et al.[35]	10
Wong-Baker FACES® Pain Rating Scale	from 3 years	Whaley L et al.[30] Wong DL et al.[31]	34
FPS-R	from 4 years	Hicks CL et al.[39]	31
VAS	from 5 years	Hayes MH et al.[45]	92
NRS	from 8 years	Jensen MP et al.[49]	16

CHEOPS – Children's Hospital of Eastern Ontario Pain Scale; FLACC – Face, Legs, Activity, Cry and Consolability; CHIPPS – Children and Infants Postoperative Pain Scale; OPS/MOPS – Objective Pain Scale/Modified Objective Pain Scale; FPS-R – Faces Pain Scale – Revised; VAS – Visual Analogue Scale; NRS – Numeric Rating Scale.

Pain assessment tools: Evaluation of pain according to the patient's age

As a result of growth differences, the expression of pain is different in each age group.

Infants and toddlers

Self-assessment scales do not apply to the youngest group of patients due to their inability to communicate verbally. According to Pawar and Garten,[6] the symptoms of pain in this age group include body rigidity, facial overexpression (furrowed eyebrows and exaggerated eye closure), loud crying, sleep disorders, resistance, and shifting the painful part of the body away from touch. Toddlers may do any of the following: exhibit verbal aggression, cry because of the pain, show regressive behavior, repel the harmful stimuli, or defend the part of the body exposed to pain.

Behavioral parameters – even non-specific ones – can be used in conjunction with physiological parameters, such as heart rate, blood pressure or palm sweating. A number of behavioral scales have been developed which include these symptoms.[7] The most commonly used ones are the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS),[8–10] Face, Legs, Activity, Cry and Consolability (FLAAC)[9,11–13] and the Children and Infants' Postoperative Pain Scale (CHIPPS).[14–17]

Children's Hospital of Eastern Ontario Pain Scale

The CHEOPS is a behavioral scale used to assess postoperative pain in young children aged 1–7 years. According to this scale, pain assessment should be performed every 3 h, 15–20 min after intravenous analgesics and 30–45 min after oral or rectal analgesics. The child's behavior is assessed according to the criteria shown below (Table 2);

Table 2. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

Parameter	Criteria	Score	Definition
Cry	no cry	+1	Child is not crying.
	moaning	+2	Child is moaning or quietly vocalizing silent cry.
	crying	+2	Child is crying, but the cry is gentle or whimpering.
	scream	+3	Child is in a full-lunged cry; sobbing; may be scored with complaint or without complaint.
Facial	smiling	0	Score only if definite positive facial expression.
	composed	+1	Neutral facial expression.
	grimace	+2	Score only if definite negative facial expression.
Child verbal	positive	0	Child makes any positive statements or talks about other things without complaint.
	none	+1	Child not talking.
	other complaints	+1	Child complains, but not about pain, e.g., 'I want to see mommy' or 'I am thirsty'.
	pain complaints	+2	Child complains about pain
	both complaints	+2	Child complains about pain and about other things, e.g., 'It hurts' and 'I want my mommy'.
Torso	neutral	+1	Body (not limbs) is at rest; torso is inactive.
	shifting	+2	Body is in motion in a shifting or serpentine fashion.
	tense	+2	Body is arched or rigid.
	shivering	+2	Body is shuddering or shaking involuntarily.
	upright	+2	Child is in a vertical or upright position.
	restrained	+2	Body is restrained.
Touch	not touching	+1	Child is not touching or grabbing at wound.
	reach	+2	Child is reaching for but not touching wound.
	touch	+2	Child is gently touching wound or wound area.
	grab	+2	Child is gently touching wound or wound area.
	restrained	+2	Child is grabbing vigorously at wound area.
Legs	neutral	+1	Legs may be in any position but are relaxed; includes gentle swimming or separate-like movements.
	squirm/kicking	+2	Definitive uneasy or restless movements in the legs and/or striking out with foot or feet.
	drawn up/tensed	+2	Legs tensed and/or pulled up tightly to body and kept there.
	standing	+2	Standing, crouching or kneeling.
	restrained	+2	Child's legs are being held down.

Adapted from: McGrath PJ, Johnson G, Goodman JT, et al. CHEOPS: A behavioral scale for rating postoperative pain in children. *Adv Pain Res Ther.* 1985;9:395–402. Accessed February 8, 2019 with permission from Patrick McGrath.

Table 3. Face, Legs, Activity, Cry and Consolability (FLAAC) scale

Categories	Scoring		
	0	1	2
Face	no particular expression or smile	occasional grimace or frown, withdrawn, disinterested	frequent to constant frown, clenched jaw, quivering chin
Legs	normal position or relaxed	uneasy, restless, tense	kicking, or legs drawn up
Activity	lying quietly, normal position, moves easily	squirming, shifting back and forth, tense	arched, rigid or jerking
Cry	no cry (awake or asleep)	moans or whimpers, occasional complaint	crying steadily, screams or sobs, frequent complaints
Consolability	content, relaxed	reassured by occasional touching, hugging or being talked to, distractible	difficult to console or comfort

Merkel S, Voepel-Lewis T, Shayevitz S, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997;23(3): 293–297. Copyright© 2002, The Regents of the University of Michigan. All rights reserved.
Each of the 5 categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored 0–2, which results in a total score between 0 and 10.

the minimum score is 4 points and the maximum score is 13 points. A score ≥5 should be considered for the administration of an analgesic, whilst a score ≥8 should be interpreted as requiring the administration of an analgesic.

Face, Legs, Activity, Cry and Consolability

The FLAAC scale (Table 3) is a tool for assessing the intensity of postoperative pain in young children and infants or in children without contact, who are asleep, aged from 2 months to 7 years, with exposed body and limbs; the observation should last 2–5 min. Each parameter is evaluated on a scale from 0 to 2; the total score is interpreted as follows: 0 = relaxed and comfortable, 1–3 = mild discomfort, 4–6 = moderate pain, 7–10 = severe discomfort/pain. A score of more than 3 points suggests the need for analgesics.

Children and Infants' Postoperative Pain Scale

The CHIPPS (Table 4) is intended to assess the intensity of postoperative pain in infants and children under the age of 5 years. The pain evaluation should be carried out within 15 s. In the postoperative period, values from 0 to 3 points indicate that there is no pain, whilst a score ≥4 points indicates the need for analgesics.

COMFORT scale

It is also necessary to emphasize the COMFORT scale, which is less frequently used in surgical wards due to the complexity of measuring blood pressure and heart rate. This scale is used primarily for patients in a critical care setting. The COMFORT[18] scale is used to assess both behavioral and physiological elements in children. This scale has 8 indicators: alertness, calmness/agitation, respiratory response, physical movement, blood pressure, heart rate, muscle tone, and facial tension.

Each parameter is scored from 1 to 5. The overall score is between 8 and 40 points. A score between 17 and 26 indicates adequate sedation and pain control. Values above 26 indicate that the patient is experiencing pain. Initially,

Table 4. Children and Infants Postoperative Pain Scale (CHIPPS)

Item	Structure	Points
Crying	none moaning screaming	0 1 2
Facial expression	relaxed/smiling wry mouth grimace (mouth and eyes)	0 1 2
Posture of the trunk	neutral variable rear up	0 1 2
Posture of the legs	neutral, released kicking about tightened legs	0 1 2
Motor restlessness	none moderate restless	0 1 2

Büttner W, Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: A comprehensive report on 7 consecutive studies. *Paediatr Anaesth*. 2000;10(3):303–318.

the COMFORT scale was used to evaluate the level of sedation or distress and procedural pain.[19,20] Currently it is also used in the postoperative period.[21]

Preschoolers

Children aged 3 to 7 years are able to describe the severity of their pain on an individual basis and grow increasingly expressive with age in describing the severity, location and value of pain. They can understand pain as punishment, they complain and refuse to cooperate with parents, a nurse, or a doctor, they try to push away harmful stimuli, they demand emotional support, and – as with younger patients – they may suffer from sleep disorders.[6] At this age, both scales based on observation of the child and those that require the patient's self-assessment are used. The most commonly used scales are the Objective Pain Score (OPS)[22,23] and the modified version of it, the Modified Objective Pain Scale (MOPS),[24–26] the Poker Chip Tool (Pieces of Hurt Tool),[27–29] the Wong–Baker FACES® Pain

Rating Scale,[30–34] the Oucher Scale,[35–38] and the Faces Pain Scale – Revised (FPS-R).[39–42]

Objective Pain Scale and Modified Objective Pain Scale

The Objective Pain Scale (OPS) and the Modified Objective Pain Scale (MOPS) (Table 5) are used to evaluate both the physiological parameters of pain and the behavioral changes in children which accompany pain or discomfort after surgical procedures. Wilson and Doyle[24] modified the OPS by substituting posture assessment for blood pressure in order to assess pain in children ranging in age from 8 months to 13 years. The MOPS can be used by a patient's parents, and the criterion 'holds injury site' could be substituted for the type of surgery performed. The minimum score is 0 and the maximum is 10; the higher the score, the greater the pain experience for the child.

Table 5. Modified Objective Pain Scale (MOPS)

Criteria	Finding	Points
Crying	none consolable not consolable	0 1 2
Movement	none restless thrashing	0 1 2
Agitation	asleep/calm mild hysterical	0 1 2
Posture	normal flexed holds injury site	0 1 2
Verbal	asleep/no complaint complains/cannot localize complains/can localize	0 1 2

Wilson GAM, Doyle E. Validation of three pediatric pain scores for use by parents. *Anaesthesia.* 1996;51(11):1005–1007.

Poker Chip Tool

The Poker Chip Tool (Fig. 1) is based on using 4 red poker chips. In the beginning, the child is asked whether he/she has any pain right now. If the child replies 'no', 0 is recorded. If the child says 'yes', he/she is given 4 chips. The child selects the number of chips that reflects the intensity of his/her pain, where 0 chips indicate little pain and 4 chips indicate the worst pain. It is used to assess the severity of pain in children aged from 3 to 18 years.[43]

The Wong–Baker FACES® Pain Rating Scale

The Wong–Baker FACES® Pain Rating Scale (Fig. 2) represents a series of faces from a 0-value happy face (which represents a lack of pain) to a 10-value crying face (which suggests the worst possible pain). On this basis, the patient chooses the face that best describes his/her level of pain.

Oucher Scale

The Oucher Scale (Fig. 3–5) is a combination of 2 separate scales: a photographic facial scale and a numerical scale from 0 to 10. The photographic scale contains 6 images of the same child, whose expressions suggest different levels of pain. The advantage of this scale is that there are different ethnic versions, e.g., presenting examples for white, black and Hispanic children. A vertical numerical scale from 0 to 10 is adjacent to these photographs. A numerical scale can be used by children who can count up to at least 100 and who understand, e.g., that 77 is more than 43. Children who do not understand the digits should use only the photographic facial scale.

Faces Pain Scale – Revised

The revised Faces Pain Scale (FPS-R) (Fig. 6) has been adapted to the commonly used metrics from 0 to 10 on the basis of the Faces Pain Scale (FPS).[44] It presents faces in a horizontal row, where the one on the left side indicates no pain and the one on the right side indicates the greatest possible pain. The researcher should explain to the child, 'These faces show how much something can hurt. This face [pointing to the face on the far left] shows no pain. The faces show more and more pain [pointing to each one from left to right] up to this one [pointing to the face on the far right], which shows very much pain.

Fig. 1. The Poker Chip Tool (Pieces of Hurt Tool)

Fig. 2. Wong–Baker FACES® Pain Rating Scale

Fig. 3. Caucasian Oucher scale

Fig. 4. African-American Oucher scale

Fig. 5. Hispanic Oucher scale

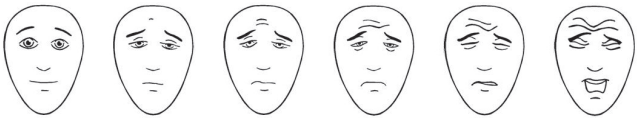

Fig. 6. Faces Pain Scale – Revised (FPS-R)

Point to the face that shows how much you hurt [right now].' Additionally, under each facial image are the numbers 0, 2, 4, 6, 8, and 10, ranging from the lowest to the highest intensity of pain, which can be seen on the back of the sheet and are not visible to the patient. The FPS-R is used to assess the intensity of the child's pain, which indicates how he or she feels; the researcher does not analyze the appearance of the patient's face or correlate it with the images.

School-age children

The verbalization of pain is common in this age group and is a great diagnostic facilitator. In addition, school-age children may experience nightmares associated with pain, increased muscular tension or body rigidity, e.g., clenching their fists and teeth or wrinkling their forehead. Adolescents may deny pain in the presence of their peers, experience appetite disorders or show regressive behavior in the presence of family members.[6]

The most commonly used scales at this age include the Visual Analogue Scale (VAS),[45–48] the Faces Pain Scale – Revised (FPS-R)[39] and the Numeric Rating Scale (NRS).[33,49–52] These are the gold standard for pain assessment.

Visual Analogue Scale

The VAS (Fig. 7) is a line that is typically 10 cm long, with markings '0' and '10' on opposite sides. Zero stands for no pain and 10 indicates very strong pain. The patient is asked to mark a line or to select a point on the scale to indicate the intensity of their pain. There are many versions of VAS in the literature, and the differences between them include units of measurement, e.g., centimeters or millimeters, length – 10 or 15 cm – and whether the scale is shown as a vertical or horizontal line.

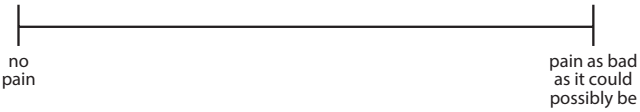

Fig. 7. Visual Analogue Scale (VAS)

Numeric Rating Scale

The Numeric Rating Scale (Fig. 8) is a segmented numerical version of the VAS scale in which patients chooses the integer from 0 to 10 which best reflects the severity of their pain. The assessment of pain intensity is as follows: no pain = 0, mild pain = 1–3, moderate pain = 4–6, and severe pain ≥7.

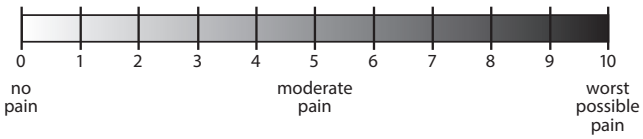

Fig. 8. Numeric Rating Scale (NRS)

New diagnostic methods – towards an objective assessment of pain

Skin conductance

Stimulation of the autonomic nervous system by nociceptive stimuli leads to skin conduction changes caused by the action of acetylcholine released in pain response to muscarinic receptors, with the subsequent release of sweat.[53] This reduces the electrical resistance of the skin and increases its conductivity. Fluctuations in skin amplitude and conductivity frequencies can then be used to assess pain.[54] This is a nociceptive phenomenon which is not affected by the changes in heart rate, blood pressure or body temperature that might occur in response to a child's anxiety, e.g., hunger, fear of separation from parents or a foreign environment. A skin conductance algesimeter is used to measure the severity of pain in children and adults, unconscious patients, patients under general anesthesia or with verbal communication limitations. This type of pain assessment is therefore considered to be the most objective,[55–57] despite the fact that the literature describes technical issues which may cause artifacts, such as electrode dislocation, wire stretching or excessive sweating by the patient.[58] Measuring skin conduction changes is an excellent pain detector, requiring further validation and clinical trials.

Analgesia Nociception Index

Analgesia Nociception Index (ANI)[59] is a non-invasive tool based on an analysis of fluctuations in heart rate, which combines electrocardiography and respiratory rate with high-frequency heart rate variability (HRV), in a frequency domain analysis. Heart rate variability is mediated primarily by changing the levels of parasympathetic and sympathetic outflow from the central nervous system to the sinoatrial node of the heart. The ANI monitor records the ECG signal continuously, enabling quantitative evaluation of respiratory variations in heart rate, which decreases during nociceptive stimulation. The ANI monitor was developed for patients over 2 years of age. Most of the ANI evaluation studies were performed in adult patients under general anesthesia or in the immediate postoperative period and showed that the ANI measurement was significantly correlated with the severity of pain.[60] To date, very little data is available on the usefulness of ANI in children.

Newborn Infant Parasympathetic Evaluation Index

Newborn Infant Parasympathetic Evaluation Index (NIPE)[61] provides an analysis of the parasympathetic response to a nociceptive stimulus. This indicator of nociception and analgesia effectiveness is also based on an algorithm for evaluating heart rate variability (HRV). As mentioned above, ANI was developed for adults and children over 2 years of age. Newborns and infants up to 2 years of age, due to the immaturity of the autonomic nervous system and the higher initial HR level, require a modified HRV analysis. The NIPE index is a modified version of ANI, and can reach values from 0 to 100. A score close to 100 indicates a higher level of patient comfort. Values below 50 indicate discomfort, stress or pain, which suggests a modification of the analgesic therapy. Few pediatric studies have yet validated this tool, although the NIPE index seems to be related to EDIN (Échelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale), for postoperative neonatal pain.[62]

Principles of pain management in children

It is important that children, regardless of their age, receive effective postoperative analgesia. The type and dosage of analgesics should be selected on the basis of scientific evidence, as well as standards and guidelines developed by local, national and international organizations. In this context, it is important to establish the standards of postoperative pain management in children that they expect from surgical procedures. The administration of basic analgesics (nonsteroidal anti-inflammatory drugs, paracetamol, etc.) intravenously, orally and rectally is crucial for pain management in children, and these drugs are to be found in most medical centers and hospitals around the world, even in resource-limited facilities. In addition, the effective use of basic analgesics has a significant impact on reducing the use of opioids,[63,64] which are reserved for the intraoperative and early postoperative period, in conditions where adequate monitoring is provided and a continuous opioid infusion requires the availability of specially trained personnel 24 h a day.

Table 6. Dosage suggestions for systemic analgesia in children in the postoperative period

Basic level	Intermediate level	Advanced level	Dosage suggestions
Rectal NSAIDs			
ibuprofen	ibuprofen	ibuprofen	10 mg kg^{-1} every 8 h
diclofenac	diclofenac	diclofenac	1 mg kg^{-1} every 8 h
naproxen	naproxen	naproxen	5–7.5 mg kg^{-1} every 12 h
Oral NSAIDs			
ibuprofen	ibuprofen	ibuprofen	10 mg kg^{-1} every 8 h
diclofenac	diclofenac	diclofenac	1 mg kg^{-1} every 8 h
Intravenous NSAIDs			
–		ketorolac	0.5–1 mg kg^{-1} up to 30 mg for a single intraoperative dose of 0.15–0.2 mg kg^{-1} (max 10 mg) every 6 h (short-term therapy, max 48 h)
–		ketoprofen	1 mg kg^{-1} every 8 h
Rectal paracetamol (if rectal NSAID in not available)			
paracetamol	paracetamol	paracetamol	20–40 mg kg^{-1} (15 mg kg^{-1} if <10 kg). Single loading dose in association with anesthesia; the higher dose is due to poor bioavailability from rectal route of administration.
Oral paracetamol			
paracetamol	paracetamol	paracetamol	10–15 mg kg^{-1} every 6 h
Intravenous paracetamol			
–		paracetamol	<10 kg: 7.5 mg kg^{-1} >10 kg: 15 mg kg^{-1} Intravenous preparation: 10 mg mL^{-1}
Intraoperative/postoperative intravenous metamizole			
–		metamizole	10–15 mg kg^{-1} every 8 h. 2.5 mg kg^{-1} h^{-1} (continuous infusion following an intraoperative loading dose). Due to the risk of agranulocytosis after long-term use metamizole is recommended for short term postoperative use in a hospital setting only.

NSAIDs – nonsteroidal anti-inflammatory drugs.
Adapted with a permission from: Vittinghoff M, Lönnqvist PA, Mossetti V, et al. Postoperative pain management in children: Guidance from the pain committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative). *Paediatr Anaesth*. 2018;28(6):493–506.

In 2018, the European Society for Paediatric Anaesthesiology (ESPA) Pain Committee published guidelines[65] to improve postoperative pain management in children. Although these guidelines are primarily aimed at Europe, the authors of the guidelines hope that they can also be used in other countries around the world, and that postoperative pain therapy can be adapted based on the availability of medicines, national recommendations and drug registration rules in different countries. The ESPA consensus on postoperative pain management in children is presented in Table 6. Special precautions should be taken when prescribing opioids in patients with obstructive sleep apnea, due to the increased risk of ventilation disorders in the postoperative period.[66]

Conclusions

Adequate postoperative pain assessment in pediatric patients may significantly improve their comfort and quality of life. Postoperative pain prolongs recovery and hospitalization,[67] so the severity of pain should be assessed routinely, using tools appropriate for the patient's age and disease. The research has been reviewed by selecting the scales most commonly used and validated in the postoperative period (Table 1). In order to establish simple criteria for scale selection, it seems most appropriate to categorize the patient's age into ≤5 years and >5 years of age. For patients up to 5 years of age, the CHEOPS and FLACC scales should be used; they are behavioral scales and do not require self-assessment by the patient. For children over 5 years of age, who are able to describe the severity and intensity of their pain, it is recommended to use mainly pictorial scales – such as the ethnically differentiated Oucher scale, the Wong–Baker FACES® Pain Rating Scale, or the FPS-R – or the most commonly used VAS. Whichever tool is applied to measure pain, it should take into account the child's age, language, ethnicity, and cognitive ability. Without a doubt, more than one tool is required, because no individual scoring system will be appropriate for assessing pain in all children and in all contexts. Only by considering all of these parameters can an objective evaluation of the complex nature of pain be conducted.[68]

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Correlation between skin conductance measurements and subjective pain scales in children after otolaryngological procedures

Original Study

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Abstract

Introduction. Pain assessment in children is crucial in managing postoperative analgesia; it is therefore necessary to determine the most accurate tool for assessing pain in children. The aim of this study was to evaluate the correlation between skin conductance measurements and self-reporting pain scales in children after otolaryngology procedures.
Materials and methods. Thirty-three children (N=33) were assessed for eligibility for the research. Postoperative pain was assessed using the Visual Analogue Scale; the Wong-Baker Faces Pain Rating Scale; the Face, Legs, Activity, Cry, and Consolability scale; and a skin conductance algesimeter. The postoperative pain was measured 1 and 2 hours after the surgery.
Results. There was no statistically significant correlation between self-reported pain scores and the skin conductance fluctuations in the children studied, regardless of gender or age. A statistically significant correlation was found between the existing subjective pain scales in children.
Conclusions. The skin conductance measurements do not provide an additional reliable tool for assessing pain in patients after otolaryngological procedures. The existing self-reported pain scales are sufficient to assess postoperative pain in children.

Keywords

pain • skin conductance • pain scale • postoperative pain • pediatric

Introduction

Surgery is one of the most common causes of acute pain in children [1]. More than 85% of pediatric patients experience postoperative pain [2, 3], which, if inadequately diagnosed and subsequently treated, can lead to chronic pain, even after discharge home from the hospital [4], increased sensitivity to pain, and anxiety about future medical procedures [5]. Postoperative pain management has become one of the major problems in pediatrics [6]. The main reason for insufficient postoperative pain therapy in children is the difficulty in evaluating it [7]. A wide range of pain self-assessment tools have been developed for pediatric patients, of which the most often used in the postoperative period are the Visual Analogue Scale (VAS); the Wong-Baker Faces Pain Rating Scale (WB); and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale [8]. In the last decade, efforts have been directed towards implementing a diagnostic tool that can assess pain intensity as objectively as possible, especially in pediatric patients. These methods include the skin conductance algesimeter (SCA), with which fluctuations in skin amplitude and conductivity frequencies can be measured and used to assess pain [9]. An SCA relies on stimulation of the autonomic nervous system by nociceptive stimuli, which leads to changes in skin conduction caused by the action of acetylcholine – released in the pain response to muscarinic receptors – with the subsequent release of sweat [10]. In the past, skin conductance has also been measured in the postoperative period [11, 12, 13]. However, to our knowledge, it has not been as widely used as the pain self-assessment scales in children. In addition, upon a patient's discharge from the hospital, the burden of pain management is shifted from the medical staff to the parents, making it even more important for parents to be aware of the most ap-

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propriate methods to assess pain in children. The purpose of this study was to evaluate whether an SCA is a useful diagnostic tool for pain assessment in the pediatric postoperative care setting and to demonstrate the correlation between SCA measurements and the widely used pain assessment scales.

1. Materials and methods

Approval was obtained from the Ethical Committee of the Medical University of Wrocław to perform the study from July 2019 to January 2021, under the number KB–459/2018. The authors confirm that all procedures comprising this research conformed to the ethical standards for human experimentation and the World Medical Association Declaration of Helsinki.

The clinical trial included a total of 33 children from the Department of Otolaryngology of the University Clinical Hospital in Wrocław. The inclusion criteria were healthy children between the ages of 3 and 17 years who qualified for surgical treatment in the Department of Otolaryngology and the written informed consent of their parents (or legal guardians). The exclusion criteria were intellectual disability, major coexisting diseases, and pain prior to surgery. All children underwent otolaryngological surgeries (adenoidectomy, adenotonsillotomy, or tonsillectomy). Postoperative pain was assessed using the VAS, the WB scale, the FLACC scale, and an SCA. Postoperative pain was measured 1 and 2 hours after the surgery. The most common VAS is a straight, horizontal line 10cm in length. The ends are defined as the extremes of the parameter being measured – pain, in this case – from 1 (no pain) to 10 (very severe pain). The patient is asked to mark a line on the scale to express the intensity of their pain [14]. The WB is a pain scale that represents a series of faces. There are 6 different faces, representing happy at 0, meaning "no hurt," to crying at 10, meaning "hurts worst." Based on the faces and written descriptions, the patient selects the face that best describes their pain level [15]. The FLAAC scale [16] is an assessment tool that quantifies pain on a score ranging from 0 to 10 using five categories: facial expression, legs, activity, crying, and consolability. It is an observational scale which can be used by parents or, as it was in this study, by a research team. The observation took 5 minutes; each parameter was evaluated on a scale from 0 to 2. The total score is interpreted as follows: 0 = relaxed and comfortable; 1-3 = mild discomfort; 4-6 = moderate pain; and 7-10 = severe discomfort/pain. A score of more than 3 points suggests the presence of pain. The children were asked to score their pain on the VAS and Wong-Baker scale, while the research team used the FLACC scale to assess it. In addition, an SCA was used, measuring skin conductance via a laptop running MedStorm software and a measuring device connected to the child's hand with a cable and 3 electrodes. The "postoperative" mode was selected in the computer application. After the patient's data were entered, a hand was disinfected with an antiseptic and degreaser, the electrodes were connected, and the signal quality was checked. The results were then recorded. The measurement took 5 minutes each time, and the key parameter considered was the average number of peaks per second, because we investigated the pain reaction to a single pain stimulus over a period of time instead of at a single moment. The threshold of less than 0.13 peaks per second can distinguish between no pain or mild pain and moderate or severe pain in the postoperative period [11].

Statistical analysis was performed using the STATISTICA v.13.3 software (TIBCO, Software Inc., USA). For quantitative variables, mean values, median standard deviations, quartile ranges, and extreme values were calculated. The Shapiro-Wilk test was used to assess the normality of the distribution. As the empirical distributions deviated from the normal distribution, nonparametric tests were used in further analysis. The Mann-Whitney U test was

Table 1. Characteristics of the children in the study group

Variable	Statistics
Gender, N (%)	
Female	17 (51.5%)
Male	16 (48.5%)
Age, years	
Mean±SD	6.1±3.0
Me (Q1–Q3)	5 (4–8)
Min–Max	3–17
Otolaryngological procedures	
Adenoidectomy	11 (33.3%)
Adenotonsillotomy	15 (45.5%)
Tonsillectomy	7 (21.2%)

Table 2. Correlation between skin conductance fluctuations and self-reported pain score by gender

	Female (n = 17)	Male (n = 16)	p-value*
PM 1 h	0.07 (0.04–0.12)	0.10 (0.04–0.15)	0.406
PM 2 h	0.09 (0.06–0.18)	0.17 (0.08–0.24)	**0.045**
p-value**	0.156	**0.020**	x
WB 1 h	4 (0–4)	5 (0–8)	0.612
WB 2 h	2 (0–4)	2 (0–4)	0.628
p-value**	0.201	0.182	x
VAS 1 h	3 (1–5)	6.5 (1–9)	0.205
VAS 2 h	1 (1–5)	2.5 (1–5)	0.586
p-value**	0.450	0.052	x
FLACC 1 h	0 (0–1)	3 (0–5)	0.059
FLACC 2 h	0 (0–0)	0 (0–3)	**0.048**
p-value**	0.128	0.094	x

** Mann–Whitney U test; ** Wilcoxon test*

used to estimate the statistical significance of the difference between independent groups. In the case of related groups (results after 1 hour and after 2 hours), the Wilcoxon test was used. The relationship between the parameters was checked by calculating the Rho Spearman correlation coefficient.

2. Results

Data were collected on 33 children (17 girls and 16 boys). Eleven children (33.3%) had undergone adenoidectomy, 15 (45.5%) adenotonsillotomy, and 7 (21.2%) tonsillectomy. The mean age was 6.1 years (SD=3.0; range: 3-17). The groups were properly matched and there were no statistically significant differences between the two research samples: the gender (p=0.869) and age (p=0.186) ratios were similar (Table 1).

The median pain measurements by gender are shown in Table 2. The boys had significantly higher skin conductance measurements 2 hours after surgery. There was no significant correlation between self-reported pain scores and gender.

There was no statistically significant correlation between self-reported pain level and the number of skin conductance fluctuations per second in either the entire study group or in subgroups differentiated by gender (p>0.05) (Tables 3, 4, 5). There was a statistically significant correlation between all subjective self-reported pain scales in the entire study group (p<0.05) (Table 6).

3. Discussion

Assessing postoperative pain in children, especially in the youngest patients, can be challenging. The available pain self-assessment scales, in use for several decades, have been continuously questioned because the child indicates their pain level on their own. A young child does not have a reference for the full spectrum of pain sensations and their experience of pain, often their first, may be influenced by a tendency to mark the highest possible value on the scale. Younger children generally rate their pain experience as higher, even with the same procedure being performed [17, 18]. Therefore, the prospect of creating an objective pain measurement tool, and its subsequent implementation, would facilitate accurate pain management. To date, most clinical studies using an SCA have been based on measuring the acute pain that occurs at the moment of measurement [19, 20, 21]. However, assessing pain in children who do not experience a

Table 3. Spearman correlation between the number of skin conductance fluctuations per second and subjective ratings of perceived pain in a group of 33 children

All (N=33)	WB 1 h	WB 2 h	VAS 1 h	VAS 2 h	FLACC 1 h	FLACC 2 h
PM 1 h	Rho=0.29 P=0.102	-	Rho=0.18 P=0.313	-	Rho=0.33 P=0.064	-
PM 2 h	-	Rho=-0.13 P=0.476	-	Rho=-0.07 P=0.712	-	Rho=0.08 P=0.668
PM (1 and 2 h)	Rho=0.00 P=0.999		Rho=-0.02 P=0.846		Rho=0.10 P=0.429	

Table 4. Spearman correlation between the number of skin conductance fluctuations per second and subjective ratings of perceived pain in females

Females (N=17)	WB 1 h	WB 2 h	VAS 1 h	VAS 2 h	FLACC 1 h	FLACC 2 h
PM 1 h	Rho=0.28 P=0.263	-	Rho=0.32 P=0.195	-	Rho=0.30 P=0.235	-
PM 2 h	-	Rho=-0.23 P=0.351	-	Rho=-0.09 P=0.719	-	Rho=0.19 P=0.453
PM (1 and 2 h)	Rho=-0.03 P=0.875		Rho=0.07 P=0.686		Rho=0.16 P=0.348	

Table 5. Spearman correlation between the number of skin conductance fluctuations per second and subjective ratings of perceived pain in males

Males (N=16)	WB 1 h	WB 2 h	VAS 1 h	VAS 2 h	FLACC 1 h	FLACC 2 h
PM 1 h	Rho=0.32 P=0.216	-	Rho=-0.12 P=0.633	-	Rho=0.29 P=0.237	-
PM 2 h	-	Rho=-0.12 P=0.650	-	Rho=-0.10 P=0.711	-	Rho=-0.14 P=0.577
PM (1 and 2 h)	Rho=-0.04 P=0.808		Rho=-0.25 P=0.170		Rho=-0.07 P=0.682	

Table 6. Rank correlation coefficients (Spearman's rho) between pain scales (in the first and second hours after surgery)

	WB	VAS	FLACC	PM
WB	X	**0.886**	**0.433**	0.000
VAS		X	**0.497**	-0.024
FLACC			X	0.098
PM				´

single pain incident, such as in the postoperative period, is more difficult; previous studies have also failed to conclusively confirm the usefulness of the SCA after surgical procedures [11, 13, 22].

The issue of pain perception by gender has also been the subject of many studies, though scientific reports continue to collate conflicting data between men and women [23, 24]. The current study is the first to compare three subjective pain rating scales with skin conductance measurements in the postoperative period in pediatric patients. Our clinical trial found no statistically significant correlation between self-reported pain scores and the skin conductance fluctuations in the children under study, regardless of gender or age. However, a statistically significant correlation was found between existing subjective pain scales in children. In the study group of 33 children, the number of skin conductance fluctuations per second increased between the first and second hour (0.08 vs. 0.11 Hz; $p = 0.008$) and the subjective pain ratings decreased. Perhaps the children had become accustomed to the pain. This finding suggests that these commonly used scales that are easy to use and – above all – easy for young patients to understand, have been validated and proven reliable. The skin conductance measurements do not provide an additional reliable tool for assessing pain in patients after otolaryngological procedures. The existing self-reported pain scales are sufficient for assessing postoperative pain in children.

The limitations of the present study rest on the fact that it is a single-center study with a small number of patients. It is therefore uncertain whether the results can be replicated in other larger centers, with variable experience and standardization in their practices.

Abbreviations

FLACC – Face, Legs, Activity, Cry, and Consolability scale; SCA – skin conductance algesimeter; VAS – Visual Analogue Scale; WB – Wong-Baker Faces Pain Rating Scale.

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Authors' Contribution

J.Z.: research concept and design; supervising the project; carrying out the experiments; acquisition of data; data analysis and interpretation; writing – original draft preparation; writing – review and editing; visualization; literature review; final proofreading and approval of the version for publication; funding acquisition; **M.M.K.:** research concept and design; supervising the project; literature review; writing – review and editing; final proofreading and approval of the version for publication; **K.D.:** data analysis and interpretation; **T.Z.**: supervising the project; final proofreading and approval of the version for publication.

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Conflict of Interest

The authors have no potential conflicts of interest to declare.

Ethics Approval

Approval was obtained from the Ethical Committee of the Medical University of Wrocław to perform the study, under the number KB–459/2018.

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The Effect of Pre-Emptive Analgesia on the Postoperative Pain in Pediatric Otolaryngology: A Randomized, Controlled Trial

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Abstract: The aim of this randomized, controlled trial was to determine whether children undergoing otolaryngological procedures (adenoidectomy, adenotonsillotomy, or tonsillectomy) benefit from pre-emptive analgesia in the postoperative period. Methods: Fifty-five children were assessed for eligibility for the research. Four children refused to participate during the first stage of the study, leaving fifty-one (n = 51) to be randomly assigned either to receive pre-emptive analgesic acetaminophen (15 mg/kg; n = 26) or a placebo (n = 25) in addition to midazolam (0.5 mg/kg) as premedication. All children were anesthetized with sevoflurane, propofol (2–4 mg/kg), and fentanyl (2 mcg/kg). Postoperative pain was assessed using the Visual Analogue Scale (VAS), the Wong–Baker Faces Pain Rating Scale, and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale. The postoperative pain was measured 1, 2, 4, and 6 h after the surgery. Results: The clinical trial reported a statistically significant correlation between administering pre-emptive analgesia (acetaminophen) and reducing pain in children after otolaryngological procedures compared to placebo. The ratio of boys to girls and age were similar among the groups ($p > 0.05$), so the groups of children were not divided by gender or age. Conclusions: Standard pre-emptive analgesia reduced the severity of pain in the postoperative period after otolaryngological procedures in children. Acetaminophen given before surgery reduces postoperative pain in children undergoing otolaryngological procedures.

Keywords: pain; postoperative pain; children; pain management; pre-emptive analgesia; adenoidectomy; tonsillectomy

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1. Introduction

Adenoidectomy, tonsillectomy, or adenotonsillotomy are some of the most commonly performed surgeries in children all around the world. Tonsillectomy consists of the complete removal of the tonsils [1], but it is very often performed together with adenoidectomy for the treatment of obstructive sleep apnea, sleep-disordered breathing, or chronic tonsillitis [1–3]. It was previously reported that tonsillectomy is an effective treatment tool for obstructive sleep apnea in children [4,5]. The removal of the tonsils triggers inflammatory cascades that improve healing but also leaves an open wound in the oropharynx, which exposes the glossopharyngeal and trigeminal nerves [6]. This combination of factors causes a postoperative wound that is susceptible to mechanical trauma when swallowing. Therefore, this procedure is associated with severe postoperative pain [7]. The pain after tonsil removal begins with local tissue damage and does not subside completely until the

affected lesion is covered with a mucous membrane. Common complications following tonsillectomy include nausea and vomiting, hemorrhage, dehydration, and pain [8].

Postoperative analgesia in pediatric patients undergoing tonsil surgery is a subject that has been widely discussed by ENT (ear, nose, and throat) specialists for years. The basic goals for surgical centers are painless hospitalization with a focus on a short hospital stay, an early home discharge and return to normal activities, and the prevention of re-hospitalization due to complications. Appropriate analgesic therapy requires standard protocols. Increasing awareness and effort to improve the pain management peri- and postoperatively in children have resulted in the development of guidelines in 2018 by the European Society for Paediatric Anaesthesiology (ESPA) Pain Committee [9]. These guidelines were primarily addressed to the European continent, but they can also be used in other countries around the world, according to the availability of medicines, national recommendations, and drug registration rules. In addition, the research into postoperative pain management led to the concept of pre-emptive analgesia [10]. Pre-emptive analgesia is a method that is initiated before the pain stimulus occurs, namely, before the surgery begins, and is continued during the procedure to minimize the physiological consequences of nociceptive transmission induced by the surgery. As a result of this "protective" effect, it may be more effective than similar analgesic treatment initiated after surgery. Pre-emptive analgesia can be used to prevent a pain signal from the surgical wound starting from the very first skin incision. These findings have been confirmed in previously published studies on pre-emptive analgesia in different surgical conditions [11–13]. The aim of this double-blinded, randomized, placebo-controlled trial was to determine whether children undergoing otolaryngological procedures (adenoidectomy, tonsillectomy, or adenotonsillectomy) benefit from pre-emptive analgesia in the postoperative period.

2. Materials and Methods

Approval was obtained from the Ethical Committee of the Medical University of Wrocław to perform the study under the number KB–459/2018. The authors confirm that all procedures comprising this research conformed to ethical standards and institutional guidelines for human experimentation. The study was registered in the ISRCTN registry under the number ISRCTN77862744 and was performed from July 2019 to February 2022. Trial registration: 26 April 2021—retrospectively registered.

The primary outcome of the study was to determine the effect of pre-emptive analgesia on postoperative pain in pediatric otolaryngology. The secondary outcome provides the correlation between pain scores measured with the Visual Analogue Scale (VAS), the Wong–Baker Faces Pain Rating Scale (WB), and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale after surgery. Assuming a probability of first type error (alpha) at $p < 0.05$ and a test power (1—beta) > 0.80 and the expected treatment effect: for the significance test for related variables, the required group size is N = 45.

2.1. Research Participants

The clinical trial initially included a total of 55 children from the Department of Otolaryngology of the University Clinical Hospital in Wrocław. Four children who refused to participate at the very beginning of the study, with a subsequent lack of parental formal consent, were excluded, resulting in an overall number of 51 children (Figure 1). The inclusion criteria were an age of 3–15 years and the written informed consent from the parents (or legal guardians). The exclusion criteria were intellectual disability; major coexisting diseases; allergy to acetaminophen, dexamethasone, or nalbuphine; and pain prior to surgery.

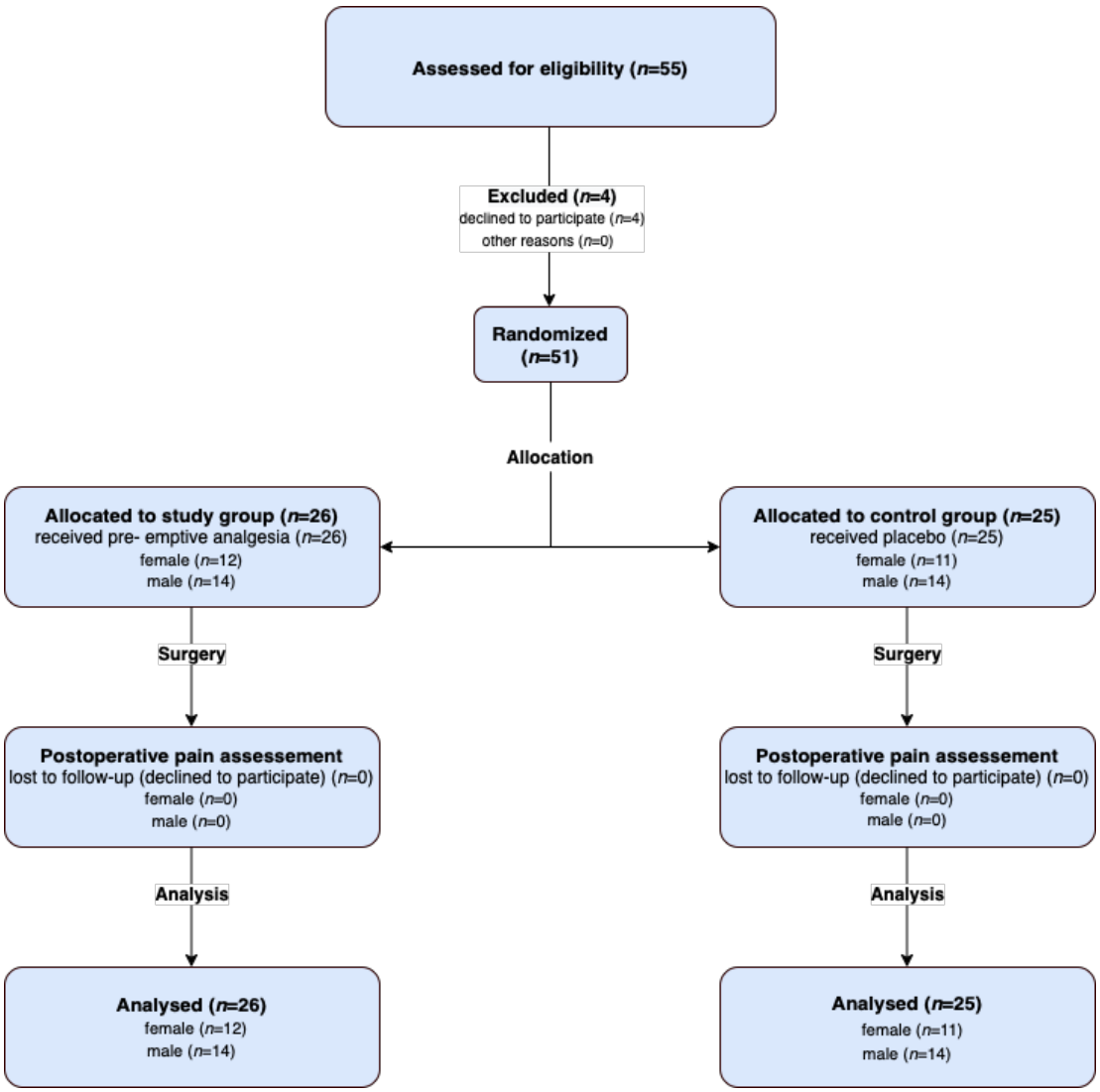

Figure 1. Flow diagram presenting the research participants.

2.2. Randomization and Blinding

To randomly allocate a patient to a study or control group, permuted block randomization was used. The patient, parent, anesthetist, and surgeon were all blinded to the study. Only the nurse delivering the premedication to the child was not blinded. Once the child received their premedication, the group allocation sheet was concealed in an envelope. The exact dose of postoperative analgesics was prescribed every 6 h, based on the child's weight.

2.3. Pain Assessment

Postoperative pain was assessed using the Visual Analogue Scale (VAS), the Wong–Baker Faces Pain Rating Scale (WB), and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale. The FLAAC scale [14] is an assessment tool that is used to quantify pain on a score from 0 to 10 using five categories: facial expression, legs, activity, cry, and consolability. The observation should last 2–5 min. Each parameter is evaluated on a scale from 0 to 2; the total score is interpreted as follows: 0 = Relaxed and comfortable, 1–3 = Mild discomfort, 4–6 = Moderate pain, 7–10 = Severe discomfort/pain. A score of more than 3 points suggests the need for analgesics. The Wong–Baker FACES Pain Rating Scale [15] was the second assessment tool used during the postoperative period. It consists of a series of faces from a 0-value happy face—which represents a lack of pain—to a 10-value crying

face, which suggests the worst possible pain. The patient chooses the face that best reflects their current pain level. The VAS [16] is a line that is often 10 cm long with the markings "1" and "10" at the ends. The "1" represents no pain or discomfort, and "10" indicates very strong pain. The patient is asked to mark a line on the scale to express the intensity of their pain.

2.4. Research Protocol including Anesthesia Protocol

Fifty-one children were randomized to receive either pre-emptive analgesic acetaminophen (Pedicetamol, Laboratorios ERN, Barcelona, Spain) at the dose of 15 mg/kg (n = 26) or a placebo (n = 25), in addition to midazolam (Midanium, WZF Polfa S.A., Warsaw, Poland) at the dose of 0.5 mg/kg (N = 51) as premedication. Only the nurse delivering the premedication to the child was not blinded; the group allocation sheet was concealed in an envelope after the premedication liquid was administered to the child orally. The research documents were stored in a locker at the hospital, which only the investigators had access to.

The premedication mixture with acetaminophen and midazolam was red and strawberry-flavored. To assure that the control group was given a liquid that was the same weight and color, concentrated strawberry juice was added to the midazolam. Approximately 30–45 min after the premedication was given, the child was transported to the operating room.

The induction of anesthesia was performed with propofol (Propofol 1% MCT/LCT, Fresenius Kabi, Bad Homburg, Germany) at the dose of 2–4 mg/kg iv, sevoflurane (Sevoflurane Baxter, Baxter Polska, Warsaw, Poland) as inhalation agent and fentanyl (Fentanyl WZF, WZF Polfa S.A., Warsaw, Poland) at the dose of 2 mcg/kg iv. Sevoflurane was used to maintain anesthesia. At the end of surgical procedures, all patients received intravenous dexamethasone (Dexaven, Bausch Health Ireland Limited, Dublin, Ireland) at the dose of 0.2 mg/kg and nalbuphine (Nalpain, G.L. Pharma GmbH, Vienna, Austria) at the dose of 0.2 mg/kg as standard perioperative analgesia. Postoperatively the patients were transferred to the postop room and then to the otolaryngology ward, which took approximately 45 min.

Postoperative pain was assessed using the Wong–Baker Faces Pain Rating Scale, the VAS, and the FLACC scale. The postoperative pain was measured 1, 2, 4, and 6 h after the surgery. The children were asked to score their pain on the VAS and Wong–Baker scale, while the FLACC scale was used by the research team to assess pain. During the evaluation, the research team and the parent or guardian were present. Only throat pain was included in the pain score analysis. All children in this study received postoperative analgesia. The patients were administered intravenous acetaminophen (Paracetamol B. Braun, B. Braun Melsungen AG, Melsungen, Germany) at the dose of 15 mg/kg every 6 h after the previous dose was given. In case of severe pain, additional intravenous metamizole (Pyralgin, Polpharma S.A, Starogard Gdanski, Poland) at the dose of 15 mg/kg was administered.

2.5. Statistical Analysis

Statistical analysis was performed using the STATISTICA v.13.3 software (TIBCO Software Inc., Palo Alto, CA, USA). Qualitative variables are presented in the contingency tables as numbers and proportions. The independence of the two qualitative variables was verified using the Chi-square test. For quantitative variables, mean values, median standard deviations, quartile ranges, and extreme values were calculated. The Shapiro–Wilk test was used to assess the normality of the distribution. As the empirical distributions deviated from the normal distribution, non-parametric tests were used in further analysis. The Mann–Whitney U test was used to estimate the statistical significance of the difference between independent groups. The relationship between pain scales was checked by calculating Spearman's Rho correlation coefficient. The values of the intra-class correlation coefficients (ICC) and Bland–Altman plots were used to assess the compliance of the results of pain level measurements on the WB, VAS, and FLACC scales. The results were considered statistically significant at $p < 0.05$.

3. Results

3.1. Demographic Data

Data were collected on 51 children (23 girls and 28 boys). The children were divided into two groups. The first one consisted of twenty-six children (51%) who received acetaminophen prior to surgery. The second one consisted of twenty-five children (49%) who received a placebo. The mean age was 5.6 years (SD = 2.8; range: 2–15) (Table 1). Both groups were properly matched, and there were no statistically significant differences between the two research samples: the gender and age ratios were similar. There was no statistically significant correlation between the use of pre-emptive analgesia and gender or age (Table 2).

Table 1. Characteristics of the studied children.

Variable	Statistics
Gender	N (%)
Female	23 (45.1%)
Male	28 (54.9%)
Age (years):	
Mean ± SD	5.6 ± 2.8
Me (Q1–Q3)	5 (4–7)
Min–Max	2–15
Pre-emptive	
Yes	26 (51.0%)
No	25 (49.0%)

Abbreviations: Me—median.

Table 2. Characteristics of children in groups that differ in pain prevention.

Variable	Pre-Emptive Analgesia		*p*-Value
	Yes N = 26	No N = 25	
Gender:			
Female, *n* (%)	12 (46.2)	11 (44.0)	0.877
Male, *n* (%)	14 (53.8)	14 (56.0	
Age, years			
Mean ± SD	6.0 ± 2.7	5.2 ± 2.8	0.258
Me (Q1–Q3)	5 (4–8)	5 (3–6)	
Min–Max	3–13	2–15	
Body weight (kg)			
Mean ± SD	28.0 ± 14.0	23.1 ± 11.1	0.172
Me (Q1–Q3)	23 (20–29)	20 (17–24)	
Min–Max	15–68	13–63	
Height (cm)			
Mean ± SD	123 ± 18	115 ± 17	0.113
Me (Q1–Q3)	120 (107–130)	111 (104–126)	
Min–Max	102–160	85–160	
BMI (kg/m^2)			
Mean ± SD	17.6 ± 3.6	16.9 ± 3.4	0.449
Me (Q1–Q3)	16.4 (15.3–18.8)	15.9 (14.6–19.9)	
Min–Max	13.3–29.4	12.4–24.6	

Abbreviations: Me—median; *p*-value, *p*—level of significance; *n*—number of participants, BMI—body mass index.

3.2. Outcomes

The study showed a statistically significant difference in postoperative pain between the two study groups. The level of pain in children after otolaryngological procedures, who received acetaminophen as pre-emptive analgesia, was significantly lower compared to

those who received placebo, when using Wong–Baker Faces Pain Rating Scale and the VAS, except for the second hour after surgery (Table 3). However, the differences in pain scores on the FLACC scale are not statistically significant ($p > 0.05$). There was no need to provide rescue analgesia for any patients during this trial.

Table 3. Assessment of perceived pain in groups of children differing in pain prophylaxis.

Pain Measurement Scale	Pre-Emptive Analgesia		*p*-Value
	Yes N = 26	No N = 25	
WB 1 h	2 ((0–2)	4 (2–8)	0.001
WB 2 h	2 (0–4)	2 (0–4)	0.401
WB 4 h	2 (0–4)	4 (2–6)	0.002
WB 6 h	0 (0–2)	4 (2–4)	0.003
VAS 1 h	2.5 (1–4)	6 (3–8)	0.001
VAS 2 h	2 (1–5)	3 (1–5)	0.839
VAS 4 h	2 (1–3)	4 (3–6)	0.001
VAS 6 h	1 (1–2)	4 (2–5)	0.002
FLACC 1 h	0 (0–4)	2 (0–4)	0.289
FLACC 2 h	0 (0–2)	0 (0–2)	0.847
FLACC 4 h	0 (0–1)	0 (0–1)	0.779
FLACC 6 h	0 (0–0)	0 (0–0)	1.000

Abbreviations: *n*—number of participants; *p*-value, *p*—level of significance; WB—Wong–Baker Faces Pain Rating Scale; VAS—Visual Analogue Scale (VAS); FLACC—Face, Legs, Activity, Cry, and Consolability Scale.

A statistically significant correlation was found between pain scores measured by WB, VAS, and FLACC scales at the first, second, fourth, and sixth hours after surgery (Table 4).

Table 4. Rank correlation coefficients (Spearman's Rho) between pain scales.

		WB	VAS	FLACC
1st hour	WB	×	0.854 ***	0.474 ***
	VAS		×	0.528 ***
	FLACC			×
2nd hour	WB	×	0.894 ***	0.318 *
	VAS		×	0.328 *
	FLACC			×
4th hour	WB	×	0.956***	0.323 *
	VAS		×	0.327 *
	FLACC			×
6th hour	WB	×	0.915 ***	0.515 ***
	VAS		×	0.511 ***
	FLACC			×

Abbreviations: WB—Wong–Baker Faces Pain Rating Scale; VAS—Visual Analogue Scale (VAS); FLACC—Face, Legs, Activity, Cry, and Consolability Scale. * $p < 0.05$; *** $p < 0.001$.

The highest rate of agreement between pain level assessment scales was between the WB and VAS scales (Table 5). The Bland–Altman index, i.e., the percentage of ratings not falling within the 95% concordance range for the mean difference, was 9.8% for VAS vs. FLACC, and for WB vs. FLACC ratings, it was 11.8% (Figure 2).

Table 5. The values of the intra-class correlation coefficients (ICC) assessing the compliance of the results of pain level measurements on the WB, VAS, and FLACC scales.

Patients	VAS vs. FLACC	WB vs. FLACC	VAS vs. WB
All	0.287	0.324	0.876
Pre-emptive	0.364	0.457	0.851
No pre-emptive	0.249	0.258	0.860

Abbreviations: WB—Wong–Baker Faces Pain Rating Scale; VAS—Visual Analogue Scale (VAS); FLACC—Face, Legs, Activity, Cry, and Consolability Scale.

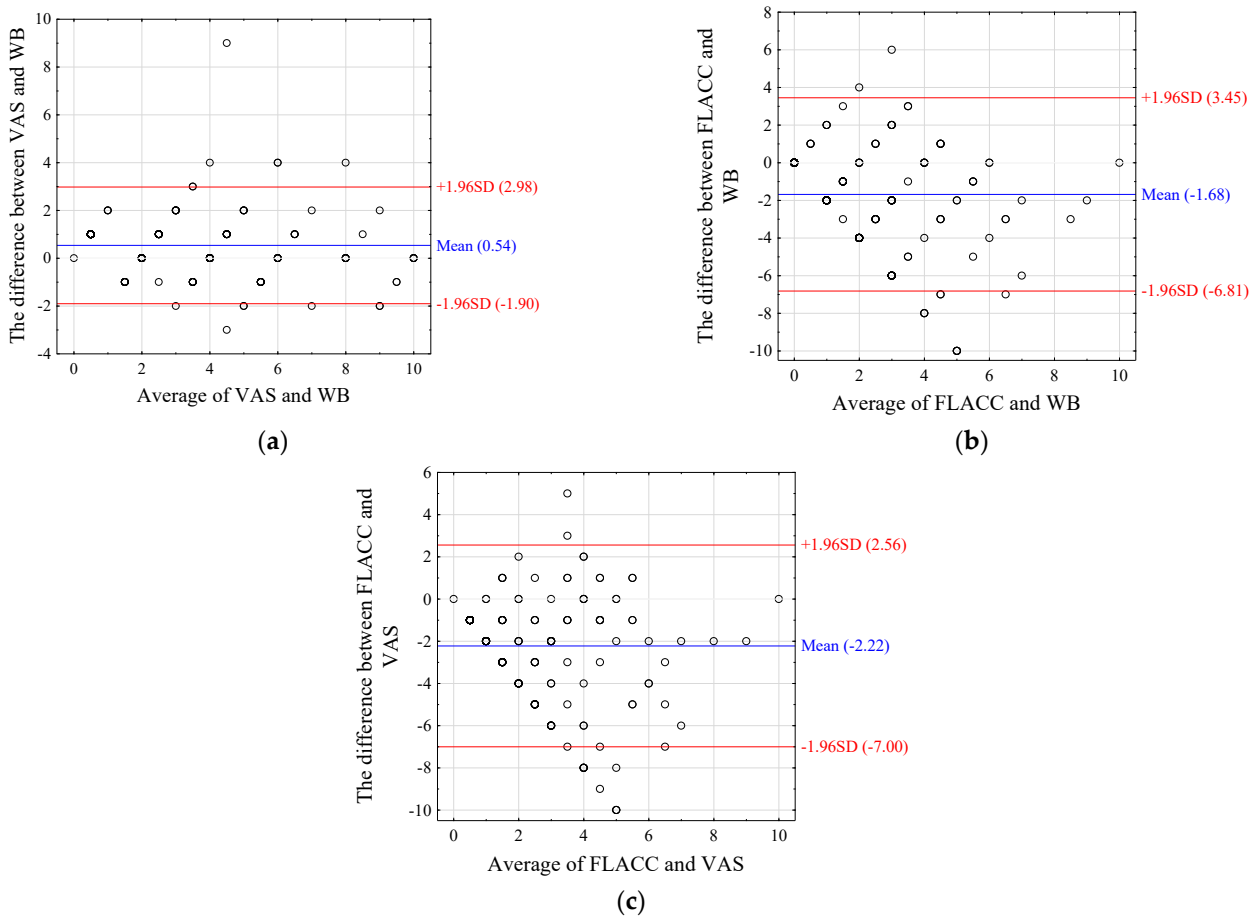

Figure 2. Bland–Altman charts comparing pain levels as assessed by WB, VAS, and FLACC.

4. Discussion

Postoperative pain management in children is challenging, especially after tonsillectomy, which is a painful procedure for most children—much more painful than an adenoidectomy [17]. In recent years, several tools have been applied preoperatively to reduce postoperative pain, including injections of local anesthetics prior to surgery, the application of fibrin glue, pre-emptive peritonsillar infiltration of magnesium sulfate or magnesium, the administration of steroids [18], different surgical approach, and the administration of oral analgesics. Each method has its own benefits, but none has consistently proven to have a statistically significant reduction in postoperative pain in children. Peritonsillar infiltration with ropivacaine [19] or magnesium sulfate [20] did not provide any major postoperative analgesic effect in children after adenotonsillectomy. Additionally, there was no significant beneficial effect of fibrin glue in post-tonsillectomy pain control [21]. In contrast, pre-emptive peritonsillar dexamethasone infiltration reduced post-tonsillectomy pain better than levobupivacaine [22]. Another study did not confirm the hypothesis that tonsillectomy performed with the coblator device would result in lower levels of postoperative pain [23].

This study showed that acetaminophen administered as a part of oral premedication effectively reduced the level of postoperative pain in children and thus demonstrated the effectiveness of pre-emptive analgesia. In order to exclude the influence of other potentially analgesic agents in this study, a uniform anesthetic protocol common to all participating children was established. The use of local anesthesia or other drugs outside the protocol was excluded. The surgery times were similar, and all procedures were performed without complications.

The selection of acetaminophen, among other analgetic drugs commonly used in pain management in the otolaryngological ward, such as ibuprofen, opioids, and steroids for pre-emptive analgesia, was due to its limited side-effect profile. Acetaminophen has been shown to be very safe for use in children [24]. It is an effective analgesic in the postoperative period [25]. Acetaminophen is metabolized in the liver by CYP2E1, and toxicity and mortality occur only when taken in massive quantities [26]. Acetaminophen is well-tolerated and has an adequate analgesic effect in children after tonsillectomy [27]. As a nonsteroidal anti-inflammatory drug (NSAID), ibuprofen remains controversial because of its nonselective inhibition of cyclooxygenase (COX), resulting in limited production of proinflammatory cytokines, and because it leads to blocking the formation of thromboxane (part of platelet aggregation) [28], potentially resulting in an increased risk of bleeding. Nevertheless, several systematic reviews have not substantiated a statistically significant difference in the frequency of bleeding postoperatively when comparing NSAIDs to other analgesics [29,30]. Another review [31], which included only studies that used ibuprofen and looked at the bleeding rates for the entire postoperative period, found a statistically significant 35% increase in post-tonsillectomy hemorrhage with ibuprofen. In addition, NSAIDs manage pain similarly to opioids and other analgesics [32,33], and they reduce the incidence of postoperative vomiting [34].

Another analgesic drug considered was dexamethasone steroid. A single intraoperative dose of intravenous dexamethasone reduces postoperative nausea and pain [35]. It is recommended by the American Academy of Otolaryngology—Head and Neck Surgery, which includes steroids in its clinical practice guideline. Multiple studies have concluded that there is no increased risk of postoperative bleeding associated with a single perioperative dose of steroids [36–38].

Opioids were excluded because special precautions should be taken when prescribing opioids in patients with obstructive sleep apnea due to the increased risk of ventilation disorders in the postoperative period [39]. However, a systematic review [40] concluded that there was not any relevant efficacy advantage between opioids, steroids, ibuprofen, and acetaminophen. For the above discussed reasons, acetaminophen was chosen for this study.

The idea of preemptive analgesia before tonsillectomy is not new. Still, our work advantage and novelty are the use of several pain scales, including those designed especially for children. In work published by El-Fattah and Ramzy [41], the parent-specific pain rating scale was used. Although the caregiver's assessment of pain may be subjective, the effectiveness of pre-emptive analgesia for pain reduction after surgeries in children was demonstrated, as in our study.

Assessing the pain children experience can be problematic because children are unwilling or unable to verbalize. Current standard pain assessment tools mostly rely on self-reporting and behavioral analysis of children, and a wide range of studies have developed methods to accurately assess the intensity of pain in children in the postoperative period. The pain scales most often used in the literature are the FLACC scale, the Wong–Baker FACES Pain Rating Scale, and the VAS [42].

In this clinical trial, the research team concluded that postoperative pain in children should be assessed using the most popular and widely validated scales. Explaining the Wong–Baker and the VAS to the children in the preoperative period improved their understanding and informed pain scale marking in the postoperative period. In addition, children were asked to locate the site of pain in postoperative assessment—which was

throat pain, excluding the intravenous cannula or other reasons. It was easier for both the patient and the research team and led to a better relationship with the child in the postoperative period.

A standard anesthesia protocol was used in this study, including sevoflurane, intravenous propofol (2–4 mg/kg), and fentanyl (2 mcg/kg) induction. During the surgery, all patients received a single intravenous dose of dexamethasone (0.2 mg/kg) and nalbuphine (0.2 mg/kg) as standard perioperative analgesia. Postoperatively, the patient was transferred to the postop room and then to the otolaryngology ward, which took approximately 45 min. Sevoflurane is the most popular gas induction agent; it is tolerated well by patients and is known for its beneficial pharmacokinetic and pharmacodynamic properties [43]. However, it is associated with an increased risk of emergence agitation, which presents as pain-like signs, including crying and moaning, confusion, disorientation, and incoherence [44]. Emergence agitation can last up to 45 min and can occur independently of pain [45]. Therefore, postoperative pain was assessed 1, 2, 4, and 6 h after surgery. In addition, it has been proven that administering fentanyl around the end of surgery reduces the incidence of emergence agitation in children undergoing general anesthesia [46]. Furthermore, propofol also improves analgesia, produces sedation, and results in immediate recovery with hemodynamic stabilization and minimal respiratory depression [47].

Limitations

The limitations of the present study rest on the fact that it is a single-center study with a small number of patients. The reason for this was the fact that the time implementation of the study coincided with the COVID-19 pandemic, and thus, the number of planned procedures performed during that period was limited. The observation and pain recording period was limited to 6 h after the surgery; therefore, it would be worth extending it to 24 h in future studies. This would give an answer to the question of whether pre-emptive analgesia influences the pain level at a later period than only a few hours after the surgery. It is therefore uncertain whether the results can be replicated in other larger centers, with variable experience and standardization in their practices.

5. Conclusions

The clinical trial reported a statistically significant correlation between administering pre-emptive analgesia (acetaminophen) and reducing pain in children after otolaryngological procedures compared to placebo. The majority of children in both study groups did not experience severe postoperative pain regardless of whether or not they received acetaminophen before the procedure. However, the positive effect of pre-emptive analgesia was statistically significant in reducing pain to an absolute minimum. For this reason, it seems that pre-emptive analgesia should be routinely used in children undergoing otolaryngological procedures.

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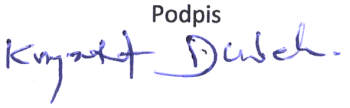

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Uniwersytet Medyczny we Wrocławiu
KATEDRA I KLINIKA OTOLARYNGOLOGII,
CHIRURGII GŁOWY I SZYI
kierownik
dr hab. n. med. Tomasz Zatoński prof. nadzw.

Wrocław, 23.05.2022r.

dr hab. n. med. Tomasz Zatoński, prof. UMW
Katedra i Klinika Otolaryngologii, Chirurgii Głowy i Szyi
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy pt. „Correlation between skin conductance measurements and subjective pain scales in children after otolaryngological procedures" autorów: Jakub Zieliński, Monika Morawska-Kochman, Krzysztof Dudek, Tomasz Zatoński, w czasopiśmie Advances in Hygiene and Experimental Medicine; Vol. 76 Issue 1/2022: 117-121, mój udział polegał na kierowaniu projektem naukowym oraz ostatecznej korekcie i zatwierdzeniu wersji do publikacji w opisanym czasopiśmie.

Podpis

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2. Nota biograficzna

Jakub Zieliński urodził się 16 marca 1990 roku we Wrocławiu. Od najmłodszych lat wykazywał zainteresowanie medycyną, z którą był naturalnie związany. Jego rodzice, również lekarze, z biegiem lat, wychowywali go w atmosferze niesienia pomocy potrzebującym. Już w wieku nastoletnim, wiedział, że chce podążyć ich śladami. W latach 2006-2009 był uczniem klasy o profilu biologiczno- chemicznym w VII Liceum Ogólnokształcącym we Wrocławiu. Zdając maturę w 2009 roku, złożył podanie na studia medyczne, gdzie rozpoczął 6 lat nauki. W roku 2015 ukończył jednolite studia magisterskie na Wydziale Lekarskim Uniwersytetu Medycznego we Wrocławiu, uzyskując tytuł lekarza. Również w 2015 roku rozpoczął studia doktoranckie na Wydziale Lekarskim Kształcenia Podyplomowego, a następnie został asystentem w Katedrze Otolaryngologii, Chirurgii Głowy i Szyi. Obecnie pracuje jako lekarz rezydent w tożsamej Klinice. Pracę na Oddziale Otolaryngologii łączy z pracą naukową oraz kształceniem młodszego pokolenia studentów wydziału lekarskiego. Wolny czas poświęca na dodatkowe staże i kursy oraz stałe poszerzanie swojej wiedzy. Prywatnie interesuje się kinematografią oraz jest pasjonatem podróży.

Wykształcenie i przebieg pracy zawodowej:

- studia wyższe na wydziale lekarskim Uniwersytetu Medycznego we Wrocławiu (2009 – 2015 r.)
- studia doktoranckie na WLKP Uniwersytetu Medycznego we Wrocławiu (2015 – 2021 r.)
- asystent w Katedrze Otolaryngologii, Ch. Głowy i Szyi Uniwersytetu Medycznego we Wrocławiu (od 2020 r.)
- lekarz rezydent na Oddziale Otolaryngologicznym SCM Polanica Zdrój (2017 – 2018 r.)
- lekarz rezydent w Klinice Otolaryngologii, Ch. Głowy i Szyi USK Wrocław (od 2018 r.)