WYDZIAŁ LEKARSKI

GDAŃSKI UNIWERSYTET MEDYCZNY

Wpływ karencji płynowej i podaży płynu wysokowęglowodanowego na wybrane parametry hemodynamiczne i dystrybucję wody w organizmie człowieka

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ROZPRAWA DOKTORSKA

Praca została wykonana w Klinice Anestezjologii i Intensywnej Terapii

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Spis treści

Wykaz skrótów

ASA – (ang. American Society of Anesthesiologists) Amerykańskie Towarzystwo Anestezjologów

ATM – (ang. adipose tissue mass) masa tkanki tłuszczowej

BIA – (ang. Bioelectrical impedance analysis) analiza bioimpedancyjna

CO – (ang. cardiac output) pojemność minutowa serca

ECW – (ang. extracellular water) woda zewnątrzkomórkowa

ERAS – (ang. Enhanced Recovery After Surgery protocol) protokół kompleksowej opieki okołooperacyjnej dla poprawy wyników leczenia

ESPEN – (ang. European Society for Clinical Nutrition and Metabolism) Europejskie Towarzystwo Żywienia Klinicznego i Metabolizmu

ICG – (ang. impedance cardiography) kardiografia impedancyjna

ICW – (ang. intracellular water) woda wewnątrzkomórkowa

LTM – (ang. lean tissue mass) beztłuszczowa masa ciała

PONV – (ang. postoperative nausea and vomiting) pooperacyjne nudności i wymioty

SV – (ang. stroke volume) objętość wyrzutowa serca

SVR – (ang. systemic vascular resistance) systemowy opór naczyniowy

SVV – (ang. stroke volume variation) zmienność objętości wyrzutowej serca

TBW – (ang. total body water) całkowita zawartość wody w ustroju

Wykaz prac wchodzących w skład rozprawy doktorskiej

Kukliński J, Steckiewicz KP, Sekuła B, Aszkiełowicz A, Owczuk R. The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: a volunteer randomized study. *Perioperative Medicine* 2021; **10**.

IF_{2021}: 2,904 MEiN: 100

Kukliński J, Steckiewicz KP, Piwowarczyk SP, Kreczko MJ, Aszkiełowicz A, Owczuk R. Effect of Carbohydrate-Enriched Drink Compared to Fasting on Hemodynamics in Healthy Volunteers. A Randomized Trial. *Journal of Clinical Medicine* 2022; **11**.

IF_{2021}: 4,964 MEiN: 140

Kukliński J, Steckiewicz KP, Owczuk R. Perioperative carbohydrate loading in patients undergoing one-day surgery. A systematic review of randomized controlled trials. *Videosurgery and Other Miniinvasive Techniques* 2022; **17**.

IF_{2021}: 1,627 MEiN: 70

Łączny współczynnik oddziaływania IF: 9,495

Łączna punktacja MEiN: 310

Wprowadzenie

Znieczulenie ogólne umożliwia bezpieczne i bezbolesne wykonanie inwazyjnych procedur diagnostycznych i leczniczych. Jednak jak każda procedura medyczna niesie ryzyko powikłań, ponieważ podczas znieczulenia ogólnego zostają zniesione obronne odruchy organizmu. Brak odruchu wymiotnego, wykrztuśnego oraz połykania stwarza ryzyko okołooperacyjnego zachłyśnięcia treścią żołądkową i jego potencjalnie śmiertelnych powikłań. Co więcej środki stosowane podczas znieczulenia ogólnego, w szczególności opioidy oraz anestetyki wziewne przyczyniają się do występowania pooperacyjnych nudności i wymiotów (PONV) [1]. Stąd też idea ograniczenia przyjmowania pokarmów i płynów przed znieczuleniem ogólnym sięga początków anestezji. Pierwotnie kierowano się troską o zmniejszenie dyskomfortu pacjenta związanego z nieprzyjemnymi skutkami ubocznymi. Nie zalecano całonocnej głodówki, a jedynie kilkugodzinną przerwę od ostatniego posiłku [2]. Podejście to zmieniło się po badaniach Mendelsona opisujących przypadki zachłystowego zapalenia płuc oraz Mortona i Wylie'a analizujących zgony związane z regurgitacją i wymiotami. W zależności od konsystencji treści żołądkowej, jej aspiracja może prowadzić do chemicznego zapalenia płuc (zespołu Mendelsona) lub zamknięcia światła dużych oskrzeli, a w konsekwencji do ostrej niewydolności oddechowej [3,4]. Pomimo stale malejącej liczby incydentów (2-7 na 20000 znieczuleń), pozostaje ona wiodącą przyczyną śmierci związanych z instrumentacją dróg oddechowych (11 z 34 przypadków) [5]. Obecnie wiemy, że u nieprzytomnego człowieka, w zależności od ustawienia głowy, >0,8 $ml\ kg^{-1}\ m.c.$ płynu w żołądku stwarza ryzyko aspiracji [6]. Ponadto sześciogodzinny okres nieprzyjmowania pokarmów stałych i dwugodzinny dla klarownych płynów jest uznany za wystarczający do całkowitego opróżnienia żołądka [7–9]. Mimo to większość pacjentów nie przyjmuje pokarmów stałych przez ponad 12 godzin, a klarownych płynów przez ponad 4 godziny przed planową operacją [10,11].

Nasilenie procesów katabolicznych w okresie ograniczonej dostępności pożywienia zwiększało szansę przeżycia naszych przodków. Niestety, w okresie przedoperacyjnym, te adaptacje skutkują wieloma niekorzystnymi zmianami w metabolizmie [12]. Zmniejszenie stężenia insuliny, nasilona glikogenoliza i glukoneogeneza prowadzą do insulinooporności oraz poprzez zwiększenie stężenia wiążącego go białka, zmniejszenia aktywności insulinopodobnego czynnika wzrostu 1 [13,14]. Jest to szczególnie niekorzystne, ponieważ odpowiedź stresowa ustroju na uraz operacyjny również prowadzi do podobnych zmian poprzez wzrost stężenia amin katecholowych, glukokortykosteroidów oraz prozapalnych cytokin [15]. Powyższe zjawiska prowadzą do hiperglikemii, utrudniają gojenie się ran i zwiększają ryzyko powikłań w okresie pooperacyjnym, a w konsekwencji przedłużają hospitalizację.

W związku z tym zaproponowano stosowanie płynu wysokowęglowodanowego w okresie przedoperacyjnym [16]. Na przestrzeni lat jego korzystny wpływ na poprawę komfortu pacjentów i skrócenie czasu hospitalizacji został potwierdzony w kilku metaanalizach [17–20], a aktualne wytyczne ESPEN [7] oraz protokół ERAS [8] zalecają spożycie 400 ml płynu zawierającego przynajmniej 12,5% węglowodanów na 2 do 3 godzin przed zabiegiem. Jednakże badania dotyczące proponowanego mechanizmu działania poprzez redukcję insulinooporności dostarczają sprzecznych wyników. Podobnie doniesienia dotyczące wpływu na dolegliwości bólowe oraz uczucie głodu, pragnienia czy zmęczenia dostarczają sprzecznych wyników. Wczesne badania opisywały korzystny wpływ płynu wysokowęglowodanowego na zmniejszenie częstości PONV [21], doniesienia te nie znalazły potwierdzenia w nowszych badaniach [22]. Warto jednak zaznaczyć, że stosowanie płynu wysokowęglowodanowego nie spowalnia opróżniania żołądka[23].

Przedłużające się powstrzymywanie od przyjmowania pokarmów i płynów w okresie przedoperacyjnym może doprowadzić do odwodnienia, a w konsekwencji do pogorszenia parametrów hemodynamicznych i nieadekwatnego dowozu tlenu. Trzeba zaznaczyć, że wolemię rutynowo oceniamy w sposób pośredni, na podstawie parametrów takich jak: średnie ciśnienie tętnicze, akcja serca, ośrodkowe ciśnienie żylne, diureza godzinowa. Ich wartości mogą być utrzymane w prawidłowym zakresie dzięki mechanizmom kompensacyjnym, dlatego u większości pacjentów nie obserwujemy cech pośrednich hipowolemii [8,24]. Badania dotyczące zmian w przedziałach wodnych ustroju podczas głodzenia w okresie przedoperacyjnym dostarczają rozbieżnych wyników. Ponadto nie uwzględniają one stosowania płynu wysokowęglowodanowego. Dlatego w badaniach wchodzących w skład mojej pracy doktorskiej ocenialiśmy jego wpływ na przestrzenie wodne ustroju oraz wybrane parametry hemodynamiczne.

Analiza bioimpedancja to metoda analizy składu ciała wykorzystująca różnice w oporze elektrycznym stawianym przez poszczególne tkanki organizmu. Prąd zmienny o wysokiej częstotliwości penetruje błony komórkowe, natomiast o niskiej płynie w przestrzeni zewnątrzkomórkowej [25]. Pierwsze urządzenia (lata 90 XX wieku) korzystały z pojedynczej częstotliwości (ang. single frequency BIA), co umożliwiało ocenę TBW, ale nie ICW. Nowoczesne urządzenia (ang. bioelectrical spectroscopy) korzystają z całego zakresu częstotliwości oraz ulepszonych modeli matematycznych, co zwiększyło dokładność i pozwoliło na ocenę poszczególnych kompartmentów wodnych [25–27]. Kardiografia impedancyjna polega na jednoczasowym pomiarze zmian oporu elektrycznego tkanek klatki piersiowej w czasie oraz monitorowaniu czynności elektrycznej serca. Podobnie jak w bioimpedancji, wykorzystywany jest prąd zmienny o wysokiej częstotliwości. Uzyskane wartości parametrów hemodynamicznych korelują dobrze z inwazyjnymi metodami referencyjnymi oraz echokardiografią [28,29]. Dzięki zastosowaniu powyższych metod W badaniach wchodzących w skład tej pracy, zarówno pomiar przestrzeni wodnych ustroju, jak i parametrów hemodynamicznych mógł odbyć się w sposób nieinwazyjny.

Cel główny

Ocena wpływu stosowania płynu wysokowęglowodanowego na wybrane parametry istotne w opiece okołooperacyjnej.

Cele szczegółowe

Ocena wpływu stosowania płynu wysokowęglowodanowego na przestrzenie wodne ustroju u zdrowych ochotników.

Ocena wpływu stosowania płynu wysokowęglowodanowego na wybrane parametry hemodynamiczne u zdrowych ochotników.

Przegląd systematyczny prac oceniających wpływ stosowania płynu wysokowęglowodanowego na rekonwalescencję pacjentów po operacjach planowych.

Populacja i metody

W pracach oryginalnych będących podstawą do ubiegania się przeze mnie o nadanie mi stopnia doktora, opisano dwa jednoośrodkowe, randomizowane badania kliniczne. Badania zostały pozytywnie zaopiniowane przez Niezależną Komisję Bioetyczną ds. Badań Naukowych przy Gdańskim Uniwersytecie Medycznym: NKBBN/126/2014 oraz NKBBN/562/2021. Protokoły badań zostały zarejestrowane w bazie ClinicalTrials.gov (NCT04665349, NCT04972500).

Uczestnicy

Badania zostały przeprowadzone na pełnoletnich, zdrowych osobach (ocenionych w skali ASA na 1 lub 2). Uczestnicy wyrazili świadomą, pisemną zgodę na udział w badaniu. W badaniach wzięło udział, odpowiednio 81 i 100 ochotników. Przydzielonych po równo do grupy kontrolnej i badanej. Do kryteriów wyłączenia należały:

- przewlekła choroba nerek
- choroby zastawek i niewydolność serca
- epizody hipoglikemii lub inne zaburzenia metabolizmu
- choroby płuc
- wzrost poniżej 120 cm oraz powyżej 230 cm
- masa ciała poniżej 30 kg lub powyżej 155 kg

Celem zapewnienia najwyższej jakości uzyskiwanych pomiarów populacje badaną dostosowano pod standaryzację użytych urządzeń pomiarowych.

Ponadto w skład rozprawy wchodzi praca będąca przeglądem systematycznym badań, które odbyły się na pacjentach poddanych laparoskopowej cholecystektomii zakwalifikowanych do klasy ASA 1 lub 2.

Urządzenia pomiarowe

Analiza składu ciała została wykonana z użyciem urządzenia Body Composition Monitor (Fresenius Medical Care AG & Co. KgaA, Bad Homburg, Niemcy), wykorzystującego zjawisko bioimpedancji elektrycznej. Pomiar odbywał się pozycji leżącej na plecach. Dwie pary elektrod były umieszczane odpowiednio w dystalnym odcinku kończyny górnej oraz dystalnym odcinku tożstronnej kończyny dolnej zgodnie z zaleceniami producenta.

Nieinwazyjny pomiar parametrów hemodynamicznych został wykonany przy użyciu urządzenia Niccomo™ (Medizinische Messtechnik GmbH, Ilmenau, Niemcy), wykorzystującego metodę kardiografii impedancyjnej. Pomiar odbywał się pozycji leżącej na plecach. Zestaw czterech elektrod był umieszczany na uprzednio oczyszczonej skórze szyi i klatki piersiowej zgodnie z zaleceniami producenta.

Napój wysokowęglowodanowy

Nutricia™ PreOp® (Nutricia, Amsterdam, Holandia) to klarowny, izoosmotyczny (240 $mOsmol\ L^{-1}$) napój wysokowęglowodanowy przeznaczony dla osób poddawanych zabiegom w trybie planowym. Jeden mililitr dostarcza 0,5 $kcal$ energii, z czego większość zawarta jest w maltodekstrynie oraz fruktozie. W 100 ml napoju znajdują się następujące makro- i mikroelementy: 50 mg sodu, 122 mg potasu, 6 mg chloru, 6 mg wapnia, 1 mg fosforanów, 1 mg magnezu. W obydwu pracach oryginalnych uczestnicy otrzymywali porcję 400 ml napoju, zawierającą 50,4 g węglowodanów. Jest to zgodne z zaleceniami ESPEN i protokołem ERAS, które rekomendują podaż przynajmniej 45 g węglowodanów.

Analiza statystyczna

Do analizy statystycznej został wykorzystany program Prism 8 lub Prism 9 (GraphPad, San Diego, USA).

Zmienne kategorialne opisano przez liczbę i odsetek osób w każdej kategorii. Zmienne ciągłe o normalnym rozkładzie prawdopodobieństwa przedstawiono jako średnią arytmetyczną z odchyleniem standardowym (SD). Dla zmiennych ciągłych o innym rozkładzie prawdopodobieństwa podano medianę i rozstęp ćwiartkowy (IQR).

Testem D'Agostino-Pearsona oceniono normalność rozkładu wartości ilościowych. Zmienne parametryczne o homogennej wariancji zostały porównane z użyciem testu t-Studenta, natomiast wartości o heterogennej wariancji z użyciem testu t-Welcha. Dla zmiennych niewykazujących tego rozkładu zastosowano test U Manna-Whitneya. Za znamienną statystycznie wartość przyjęto $p < 0,05$.

Strategia wyszukiwania

Prace zakwalifikowane do przeglądu systematycznego zostały wyszukane zgodnie z wytycznymi Prisma, a protokół wyszukania został zarejestrowany w PROSPERO - CRD42021284397. Bazy danych: Medline, EBSCO, Scopus, Web of Science, Cochrane, zostały przeszukane w październiku 2021 r. z użyciem poniższego zapytania:

((Preoperative or perioperative) and (carbohydrate or CHO or nutricia or carbohydrates or maltodextrin or carbohydrate rich) and (drink or treatment or loading or oral or per os or load or administration)) and ((ambulatory or one-day or elective or outpatient or ambu* or electiv* or fast-track) and (surgery or surgical procedures or procedure or sedation or anesthesia or surg* or general anesthesia))

Omówienie prac

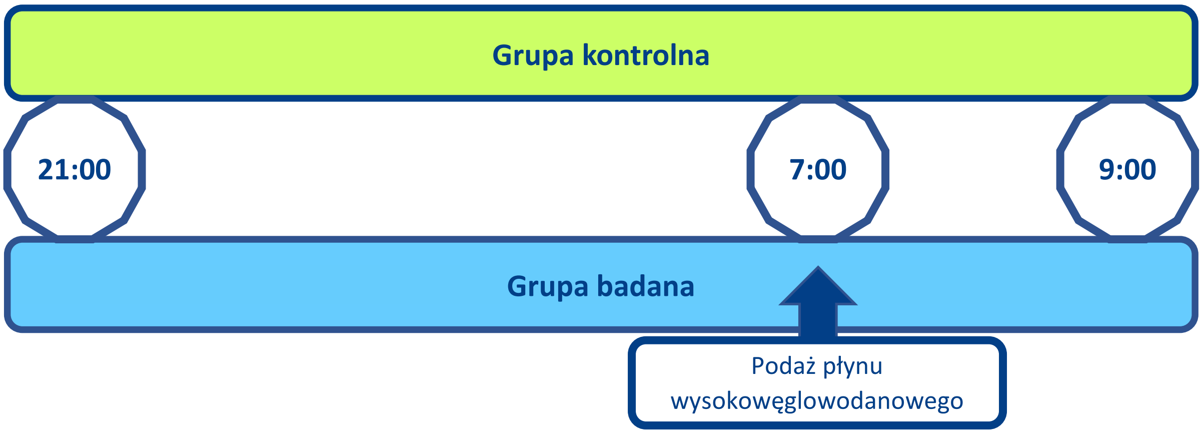
W skład mojej pracy doktorskiej wchodzą trzy prace (dwie oryginalne i jedna praca będąca przeglądem systematycznym) opublikowane w międzynarodowych czasopismach indeksowanych na Liście Filadelfijskiej. Artykuły opisują wpływ płynu wysokowęglowodanowego na wybrane parametry w okresie okołooperacyjnym.

J. Kukliński, K. P. Steckiewicz, B. Sekuła, A. Aszkiełowicz, and R. Owczuk, "The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: a volunteer randomized study"

Uraz operacyjny oraz głodzenie wywołują niekorzystne zmiany w metabolizmie, które obserwujemy głównie pod postacią narastającej insulinooporności. Prowadzi to do upośledzonego gojenia ran, a w konsekwencji przedłuża okres hospitalizacji [12]. Dodatkowo zbyt długi okres nieprzyjmowania pokarmów i płynów może doprowadzić do odwodnienia. Jednak u pacjentów przed planowymi zabiegami rzadko obserwujemy pośrednie objawy hipowolemii, przy czym zwykle oceniamy ją na podstawie pośrednich parametrów, których wartości mogą pozostać w prawidłowym zakresie dzięki mechanizmom kompensacyjnym. Dlatego zdecydowaliśmy się zbadać wpływ głodzenia oraz stosowania płynu wysokowęglowodanowego na objętość i dystrybucję wody w organizmie z wykorzystaniem bioimpedancji. Oczekiwaliśmy obniżenia objętości wody wewnątrzkomórkowej z zachowaniem objętości wody zewnątrzkomórkowej.

Zbadaliśmy 81 zdrowych ochotników, którzy zostali podzieleni na dwie grupy: kontrolną (n=40) oraz badaną (n=41). Pomiary odbywały się w trzech punktach czasowych: 0 godz., +10 godz., +12 godz. Pomiędzy pierwszym, a drugim pomiarem wszyscy uczestnicy mieli powstrzymać się od przyjmowania pokarmów stałych. Po drugim pomiarze druga badana otrzymywała 400 ml preparatu Nutricia™ PreOp®, natomiast grupa kontrolna pościła przez kolejne dwie godziny (Rycina 1). Każdorazowo mierzone były następujące parametry: masa ciała, ciśnienie tętnicze, TBW, ECW, ICW, ATM, LTM. Analiza składu ciała odbywała się z użyciem Body Composition Monitor.

Nasze badanie nie wykazało istotnych zmian w badanych parametrach pomiędzy grupami, ani w różnych punktach czasowych. Nie zaobserwowaliśmy również istotnego odwodnienia podczas trwania badania. Płyn wysokowęglowodanowy wydaje się nie mieć istotnego wpływu na dystrybucję wody w organizmie.



Rycina 1 Uproszczony schemat protokołu badania

J. Kukliński, K. P. Steckiewicz, S. P. Piwowarczyk, M. J. Kreczko, A. Aszkiełowicz, and R. Owczuk, "Effect of Carbohydrate-Enriched Drink Compared to Fasting on Hemodynamics in Healthy Volunteers. A Randomized Trial"

Odpowiednie nawodnienie w okresie okołooperacyjnym jest jednym z kluczowych elementów protokołu ERAS. Niestety rutynowe monitorowanie pozwala jedynie na pośrednią ocenę wolemii, a inwazyjne metody pomiarowe obarczone są istotnym ryzykiem, szczególnie u ciężko chorych pacjentów [30]. Jednakże, dzięki rozwojowi technik kardiografii impedancyjnej możliwe jest monitorowanie parametrów hemodynamicznych w sposób nieinwazyjny, również w trakcie trwania zabiegu.

Badanie miało na celu ocenę wpływu napoju wysokowęglowodanowego na wybrane parametry hemodynamiczne. Zbadaliśmy 100 zdrowych ochotników, przydzielonych po równo do grupy badanej i kontrolnej. Pomiar parametrów hemodynamicznych odbył się nieinwazyjną metodą kardiografii impedancyjnej z użyciem Niccomo™. Przyjęto założenia podobne jak w protokole pierwszego badania, pomiary odbywały się w trzech punktach czasowych: 0 godz., +10 godz., +12 godz. Pomiędzy pierwszym, a drugim pomiarem wszyscy uczestnicy mieli powstrzymać się od przyjmowania pokarmów stałych. Po drugim pomiarze grupa badana otrzymywała 400 ml preparatu Nutricia™ PreOp®, natomiast grupa kontrolna pościła przez kolejne dwie godziny (Rycina 1). Każdorazowo mierzone były masa ciała, ciśnienie tętnicze oraz parametry hemodynamiczne, między innymi: SV, SVV, CO, SVR.

Nie zaobserwowaliśmy istotnych zmian w wartościach ciśnienia tętniczego oraz częstości akcji serca pomiędzy grupami, ani w różnych punktach czasowych. Nie zaobserwowaliśmy zmian w parametrach hemodynamicznych pomiędzy grupami ani w różnych punktach czasowych. Wykazaliśmy brak wpływu głodzenia i stosowania płynu wysokowęglowodanowego na parametry hemodynamiczne u relatywnie zdrowych osób (ASA 1 lub 2).

J. Kukliński, K. P. Steckiewicz, and R. Owczuk, "Perioperative carbohydrate loading in patients undergoing one-day surgery. A systematic review of randomized controlled trials"

Cztery metaanalizy potwierdziły niewielką redukcję czasu hospitalizacji po stosowaniu płynu wysokowęglowodanowego, przy czym dwie z nich nie wykazały różnicy względem placebo. Co więcej wyniki dotyczące drugorzędowych efektów były niejednoznaczne. W naszej pracy poglądowej ocenialiśmy wpływ napoju wysokowęglowodanowego na okres rekonwalescencji po planowych zabiegach „chirurgii jednego dnia". Pozwoliło nam to na skupienie się na aspektach stosowania płynu wysokowęglowodanowego takich jak: wpływ na pragnienie i głód, PONV, ból, zmęczenie, insulinooporność.

Przeszukaliśmy następujące bazy danych: Medline, EBSCO, Scopus, Web of Science oraz Cochrane. Zidentyfikowaliśmy 3467 prac, z których to 6, obejmujących 411 pacjentów, zostało ostatecznie włączonych do przeglądu systematycznego. Wybrane badania odbywały się w latach 2012-2020 i opisywały efekty stosowania płynu wysokowęglowodanowego u pacjentów poddanych laparoskopowej cholecystektomii.

Prace oceniały wpływ stosowania płynu wysokowęglowodanowego na wiele objawów w okresie okołooperacyjnym. Ze względu na ich subiektywny charakter większości z nich posługiwano się wizualnymi skalami analogowymi lub raportowano liczbę incydentów. Wpływ na pragnienie i głód został opisany w trzech pracach, dwie z nich wykazały redukcję głodu i pragnienia zarówno w okresie przed- jak i pooperacyjnym, jednak w trzeciej pracy takie działanie nie zostało opisane. Wyniki dotyczące wpływu na nudności i wymioty dostarczyły sprzecznych wyników. Dwie z prac oceniały subiektywne odczucia bólowe, w pierwszej z nich nie wykazano wpływu płynu wysokowęglowodanowego na odczuwanie bólu w okresie pooperacyjnym. Nie wykazano również różnicy w zapotrzebowaniu na leki przeciwbólowe. Druga praca sugeruje działanie przeciwbólowe płynu wysokowęglowodanowego w pierwszych 12 godzinach po zabiegu. Wpływ na metabolizm był oceniany poprzez pomiar stężenia glukozy, insuliny lub obydwu. W żadnej z prac nie wykazano różnic pomiędzy grupami.

Płyn wysokowęglowodanowy nie miał istotnego wpływu na badane parametry. Dodatkowo w wielu przypadkach nie wykazano jego przewagi nad placebo – najczęściej używana była w tym celu aromatyzowana woda. Podważa to proponowane działanie płynu wysokowęglowodanowego poprzez redukcję insulinooporności.

Podsumowanie

Wstępne badania nad stosowaniem płynu wysokowęglowodanowego w okresie okołooperacyjnym były źródłem obiecujących doniesień co do korzystnych efektów tej interwencji [31,32]. Z biegiem lat udało się potwierdzić niewielką redukcję czasu hospitalizacji dzięki stosowaniu takiej praktyki. Jednak najnowsze badania nie wykazują przewagi napoju wysokowęglowodanowego nad placebo.

Jak ustaliliśmy w pracy poglądowej, wpływ płynu wysokowęglowodanowego na okres rekonwalescencji po zabiegach planowych pozostaje niejednoznaczny. Badania dostarczają sprzecznych wyników co do efektów drugorzędowych tej interwencji. Dodatkowo w przeważającej części są to dowody niskiej jakości.

Jako pierwsi zbadaliśmy wpływ płynu wysokowęglowodanowego na przedziały wodne oraz parametry hemodynamiczne. Nie wykazaliśmy istotnych różnic w badanych parametrach pomiędzy grupami.

Badania wchodzące w skład rozprawy doktorskiej miały następujące ograniczenia. Korzystaliśmy z nieinwazyjnych metod pomiarowych, które choć dostarczają klinicznie istotnych danych, są nieco mniej dokładne niż inwazyjne metody referencyjne. Nie weryfikowaliśmy w sposób obiektywny czy uczestnicy przestrzegają protokołu badania. Nie mierzyliśmy objętości diurezy. Nie porównywaliśmy skuteczności interwencji z placebo. Badania nie były zaślepione.

Impact of fasting and carbohydrate-rich drink administration on chosen hemodynamic parameters and body water distribution in humans

Summary in English

List of abbreviations

ASA – American Society of Anesthesiologists

ATM – adipose tissue mass

BIA – bioelectrical impedance analysis

CO – cardiac output

ECW – extracellular water

ERAS – Enhanced Recovery After Surgery protocol

ESPEN – European Society for Clinical Nutrition and Metabolism

ICG – impedance cardiography

ICW – intracellular water

LTM – lean tissue mass

PONV – postoperative nausea and vomiting

SV – stroke volume

SVR – systemic vascular resistance

SVV – stroke volume variation

TBW – total body water

List of papers included in the doctoral dissertation

Kukliński J, Steckiewicz KP, Sekuła B, Aszkiełowicz A, Owczuk R. The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: a volunteer randomized study. *Perioperative Medicine* 2021; **10**.

IF_{2021}: 2,904

Kukliński J, Steckiewicz KP, Piwowarczyk SP, Kreczko MJ, Aszkiełowicz A, Owczuk R. Effect of Carbohydrate-Enriched Drink Compared to Fasting on Hemodynamics in Healthy Volunteers. A Randomized Trial. *Journal of Clinical Medicine* 2022; **11**.

IF_{2021}: 4,964

Kukliński J, Steckiewicz KP, Owczuk R. Perioperative carbohydrate loading in patients undergoing one-day surgery. A systematic review of randomized controlled trials. *Videosurgery and Other Miniinvasive Techniques* 2022; **17**.

IF_{2021}: 1,627

Cumulative Impact Factor: 9,495

Introduction

Thanks to general anaesthesia, both therapeutic and diagnostic invasive medical procedures can be carried out in safe and painless way. Unfortunately, certain complications may arise during general anaesthesia due to impairment of defensive reflexes. Without cough, gag and swallowing reflexes aspiration of stomach contents can occur perioperatively, leading to severe, potentially fatal complications. Moreover drugs used during general anaesthesia, particularly opioids and inhalational anaesthetics, cause postoperative nausea and vomiting (PONV) [1]. For those reasons the idea to limit intake of solids and liquids prior to general anaesthesia is almost as old as the procedure itself. Initially patients' discomfort due to PONV was the utmost concern and few hours of fasting were deemed sufficient. Overnight fasting was not recommended [2]. This approach shifted after Mendelson's and Morton & Wylie's research regarding aspiration pneumonitis and regurgitation related death respectively. Depending on their consistency, aspiration of gastric contents may cause chemical pneumonitis (Mendelson's syndrome) or airway obstruction, both leading to acute respiratory failure [3,4]. While incidence of aspiration events is decreasing (2-7 per 20000 anaesthetic cases), they remain the most common cause of death related to airway management (11 of 34 cases) [5]. Nowadays it is known, that in unconscious human, more than 0,8 $ml\ kg^{-1}\ bodyweight$ of fluid in stomach may pose a risk of aspiration depending on head position [6]. Additionally refraining from solid foods for 6 hours and from clear liquids for 2 hours is deemed sufficient time for a stomach to empty completely [7–9]. In spite of this evidence most patients refrain from solids for over 12 hours and from clear liquids for over 4 hours before elective surgery [10,11].

Increase in catabolic processes during periods of food scarcity was beneficial to our ancestors' survival. Unfortunately, in preoperative period, such adaptations cause several disadvantageous changes in metabolism [12]. Decreased insulin level, increased glycogenolysis and increased gluconeogenesis lead to insulin resistance and decrease in activity of insulin-like growth factor 1, by increasing concentration of its binding protein [13,14]. This is especially detrimental, as stress response to surgical injury has similar metabolic effects, albeit through increase in catecholamines, glucocortycosteroids and proinflammatory cytokines [15]. Aforementioned phenomena cause hyperglycaemia, impair wound healing, increase risk of complications in postoperative period, and in consequence lengthen hospital stay.

Therefore use of carbohydrate-rich drink in preoperative period was proposed [16]. Over the years its beneficial impact on patients' general well-being and reduction in length of hospital stay was confirmed in several meta-analyses [17–20]. Accordingly, current ESPEN guidelines [7], as well as ERAS protocol [8], recommend intake of 400 ml of fluid containing at least 12,5% of carbohydrates between 2 to 3 hours before surgery. Nonetheless studies regarding proposed rationale of reducing insulin resistance provide conflicting data. Similarly reports regarding impact on pain, hunger, thirst and fatigue are inconclusive. At first studies showed reduction in PONV after carbohydrate loading [21], however this was not confirmed in more recent ones [22]. Regardless, it is important to note that carbohydrate-rich drink does not prolong stomach emptying [23].

Excessive fasting in preoperative period may cause dehydration, and consequently impair hemodynamic parameters and oxygen delivery. It is worth emphasising that volume status is estimated based on parameters such as: mean arterial pressure, heart rate, central venous pressure, hourly urine output. Those parameters can remain within normal range due to compensation mechanisms, therefore indirect signs of hypovolemia are not observed in majority of patients [8,24]. Studies assessing changes in body water composition during preoperative fasting have conflicting results. Moreover, they do not include use of carbohydrate-rich drink. Therefore, studies included in the doctoral dissertation aim to access impact of carbohydrate-rich drink on body water distribution and hemodynamic parameters.

Bioelectrical impedance analysis (BIA) is a method of body composition analysis which utilizes differences in electrical resistance of different tissues. High frequency alternating current penetrates cellular membranes, while lower frequency flows in extracellular space [25]. First devices (1990s) used just a single frequency which facilitated estimation of TBW, but not of ICW. Modern devices use range of frequencies and, in combination with better mathematical models, provide more accurate data regarding each individual compartment [25–27]. Impedance cardiography consists of registering changes in impedance of thorax simultaneously with electrocardiography. Similarly to BIA, high frequency alternating current is applied. Obtained values of hemodynamic parameters correlate well with reference methods and echocardiography [28,29]. Due to use of aforementioned methods in studies included in this dissertation, both body water distribution and hemodynamic parameters could be measured in non-invasive way.

Main aim

Assessment of impact of carbohydrate-rich drink administration on chosen parameters important in perioperative care.

Specific aims

Assessment of impact of carbohydrate-rich drink administration on body water distribution and amount in healthy volunteers.

Assessment of impact of carbohydrate-rich drink administration on hemodynamic parameters in healthy volunteers.

Systematic review of studies assessing impact of carbohydrate-rich drink administration on convalescence after elective surgeries.

Population and methods

Original articles, included in this doctoral dissertation, describe results of two single-centre, randomized controlled trials. Both studies received approval from Independent Bioethics Committee for Scientific Research at Medical University of Gdansk: NKBBN/126/2014 and NKBBN/562/2021. Study protocols were registered at ClinicalTrials.gov database (NCT04665349, NCT04972500).

Participants

Studies were carried out on healthy adults (assessed as ASA 1 or 2). Participants agreed to either study by giving written informed consent. For the respective studies we enrolled 81 and 100 volunteers, who were assigned equally into control and experimental groups. The following exclusion criteria applied:

- chronic kidney disease
- diseases of the heart valves and circulatory failure
- episodes of hypoglycaemia or other metabolic disturbances
- lung diseases
- height less than 120 cm or more than 230 cm
- weight less than 30 kg or more than 155 kg

In order to obtain best quality of measurements studied population was chosen in regard to standardization of the measuring devices.

Furthermore, systematic review included in this dissertation focuses on studies carried out on patients who undergone laparoscopic cholecystectomy and were assessed as ASA 1 or 2.

Measuring devices

Body composition analysis was performed with the help of Body Composition Monitor (Fresenius Medical Care AG & Co. KgaA, Bad Homburg, Germany), which utilizes bioelectrical impedance analysis. Measurements were carried out in prone position. Two pairs of electrodes were placed unilaterally on distal parts of upper and lower limb as per manufacturer's guidelines.

Non-invasive measurement of hemodynamic parameters was performed with the help of Niccomo™ (Medizinische Messtechnik GmbH, Ilmenau, Germany), which utilizes impedance cardiography. Measurements were carried out in prone position. Set of four electrodes was placed on previously cleaned skin of neck and chest as per manufacturer's guidelines.

Carbohydrate-rich drink

Nutricia™ PreOp® (Nutricia, Amsterdam, Netherlands) is a clear, isosmotic (240 $mOsmol\,L^{-1}$), carbohydrate-rich drink specifically formulated for patients undergoing elective surgeries. One millilitre provides 0,5 $kcal$ of energy, most of which is contained in maltodextrin and fructose. Following micro- and macro-elements are present in 100 ml of this drink: 50 mg of sodium, 122 mg of potassium, 6 mg of chloride, 6 mg of calcium, 1 mg of phosphate, 1 mg of magnesium. In both original studies participants were given 400 ml of this drink, containing 50,4 g of carbohydrates. This is compliant with both ESPEN guidelines and ERAS protocol, which recommend at least 45 g of carbohydrates.

Statistical analysis

For the purpose of statistical analysis Prism 8 or Prism 9 software was used (GraphPad, San Diego, USA).

Categorical variables were presented as number and percentage of subjects in each category. Continuous variables with a normal probability distribution were presented as arithmetic mean and standard deviation. For continuous variables with a different probability distribution, median and interquartile range were given.

D'Agostino & Pearson test was used to assess normality of continuous variables. Variables with normal distribution and homogenous variance were compared with Student's t-test, those with heterogenous variance were compared with Welch's t-test instead. Variables with non-normal distribution were compared with Mann-Whitney U test. The p-value of less than 0,05 was considered statistically significant.

Search query

Studies included in systematic review were identified in accordance with Prisma guidelines and the search protocol was registered at PROSPERO - CRD42021284397.
In October 2021 following data bases were searched: Medline, EBSCO, Scopus, Web of Science, Cochrane, using undermentioned query:

((Preoperative or perioperative) and (carbohydrate or CHO or nutricia or carbohydrates or maltodextrin or carbohydrate rich) and (drink or treatment or loading or oral or per os or load or administration)) and ((ambulatory or one-day or elective or outpatient or ambu* or electiv* or fast-track) and (surgery or surgical procedures or procedure or sedation or anesthesia or surg* or general anesthesia))

Summary of publications

There are three papers included in my doctoral thesis (two original articles and one systematic review) each published in international, ISI indexed journal. Articles focus on impact of carbohydrate-rich drink administration on chosen parameters in perioperative period.

J. Kukliński, K. P. Steckiewicz, B. Sekuła, A. Aszkiełowicz, and R. Owczuk, "The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: a volunteer randomized study"

Both surgical injury and fasting cause detrimental changes in metabolism, which can be observed as increase in insulin resistance. This impairs wound healing and in consequence lengthens hospital stay [12]. Additionally, prolonged fasting can lead to dehydration. Despite this hypovolemia is rarely observed in patients undergoing elective surgery as their volume status is assessed indirectly with the help of parameters which can remain within normal range due to compensation mechanisms. Therefore we decided to study the effects of fasting and carbohydrate-rich drink administration on body water amount and distribution using bioelectrical impedance analysis. We expected decrease in intracellular water while maintaining extracellular water.

We examined 81 healthy volunteers, divided into control (n=40) and experimental (n=41) groups. Measurements were carried out at three time points: 0 hours, 10 hours and 12 hours. Between first and second measurement all subjects refrained from solid foods. After second measurement experimental group was given 400 ml of Nutricia™ PreOp®, while control group kept fasting for another two hours (Figure 1). At each time point following parameters were measured: weight, blood pressure, TBW, ECW, ICW, ATM, LTM. Body composition analysis was performed with the help of Body Composition Monitor.

Our study showed no significant changes in the measured parameters between groups nor at different time points. We did not observe significant dehydration throughout the course of the study. Carbohydrate-rich drink seems not to have significant effect on body water amount and distribution.

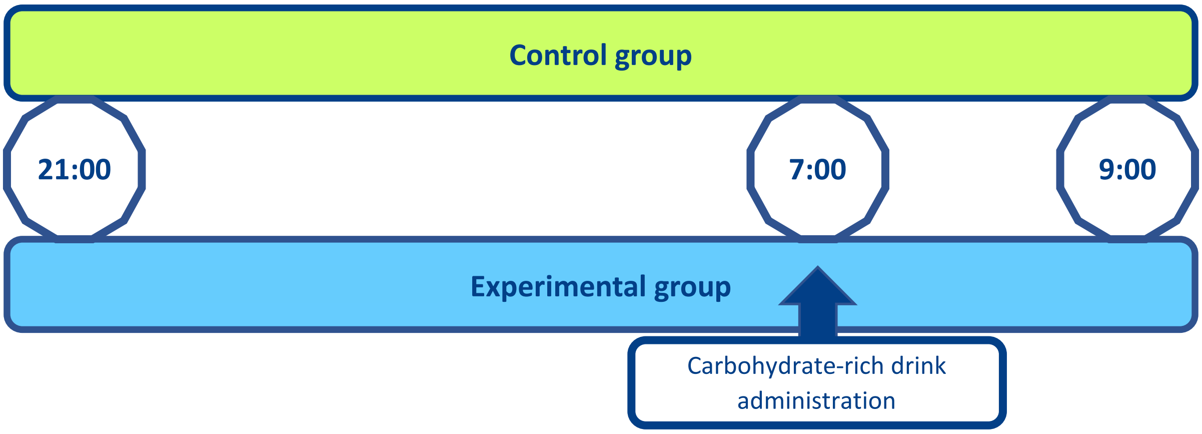


Figure 1 Simplified diagram of study protocol

J. Kukliński, K. P. Steckiewicz, S. P. Piwowarczyk, M. J. Kreczko, A. Aszkiełowicz, and R. Owczuk, "Effect of Carbohydrate-Enriched Drink Compared to Fasting on Hemodynamics in Healthy Volunteers. A Randomized Trial"

Adequate fluid management is one of the main components of ERAS protocol. Unfortunately routine monitoring allows only for indirect assessment of volume status, while direct, invasive methods pose considerable risks, especially for critically ill patients [30]. However, thanks to the improvements in impedance cardiography it is possible to monitor hemodynamic parameters in a non-invasive way, even during surgery.

The study aimed to assess impact of carbohydrate-rich drink on chosen hemodynamic parameters. We examined 100 healthy volunteers, divided evenly into experimental and control groups. Hemodynamic parameters were measured non-invasively using impedance cardiography device Niccomo™. With similar assumptions and protocol as in the previous study, measurements were carried out at three time points: 0 hours, 10 hours, 12 hours. Between first and second measurement all subjects refrained from solid foods. After second measurement experimental group was given 400 ml of Nutricia™ PreOp®, while control group kept fasting for another two hours (Figure 1). Each time weight, blood pressure and hemodynamic parameters, such as SV, SVV, CO, SVR, were measured.

We did not observe significant changes in blood pressure and heart rate values between groups nor at different time points. We did not observe changes in hemodynamic parameters between groups nor at different time points. We showed that fasting and carbohydrate-rich drink administration have no effect on hemodynamic parameters in relatively healthy adults (ASA 1 or 2).

J. Kukliński, K. P. Steckiewicz, and R. Owczuk, "Perioperative carbohydrate loading in patients undergoing one-day surgery. A systematic review of randomized controlled trials"

Four meta-analyses confirmed small reduction in length of hospital stay after carbohydrate-rich drink administration, albeit two of them showed no difference when compared to placebo. Moreover, results regarding secondary outcomes were inconclusive. in our systematic review we assessed impact of carbohydrate-rich drink administration on convalescence after elective, day-care surgeries. This allowed us to focus on effects of carbohydrate loading on symptoms such as: thirst, hunger, PONV, pain, tiredness, insulin resistance.

We searched following data bases: Medline, EBSCO, Scopus, Web of Science, Cochrane. We identified 3467 papers, of which 6, encompassing 411 patients, were included in the review. Included studies took place in the years 2012-2020 and reported effects of carbohydrate-rich drink administration in adults undergoing laparoscopic cholecystectomy.

Studies assessed impact of carbohydrate-rich drink administration on several symptoms in perioperative period. As most of them were subjective visual analogue scales or incidence reporting were used. Impact on thirst and hunger was examined in three studies. Two of them showed decrease in both during pre- and postoperative periods. However, this was not confirmed in the third one. Results regarding effects on nausea and vomiting were conflicting. Two studies described impact on pain level post-operatively. One of them showed no changes in pain intensity nor painkillers usage, while other suggested pain alleviation in the first 12 hours after surgery. Effect on metabolism was assessed by measuring either or both glucose and insulin levels. None of the studies showed significant differences between groups.

Carbohydrate-rich drink had little to no impact on studied outcomes. Moreover, in most cases studies showed no benefits over placebo – usually artificially flavoured water was used in this purpose. This undermines proposed rationale of carbohydrate-rich drink administration reducing insulin resistance.

Conclusion

Early studies about the use of carbohydrate-rich drink in perioperative period brought promising findings regarding its effectiveness [31,32]. Over the years small reduction in length of hospital stay was confirmed. However most recent studies show no difference when comparing carbohydrate-rich drink to placebo.

As shown in the systematic review, impact of carbohydrate-rich drink administration on convalescence after elective surgeries remains inconclusive. Studies regarding secondary outcomes of this intervention report conflicting results. Moreover, quality of evidence is relatively low.

We were first to examine effects of carbohydrate-rich drink administration on body water and hemodynamic parameters. We did not observe any significant differences in measured parameters between groups.

Studies included in the doctoral dissertation had following limitations. We used non-invasive measuring devices, which provide clinically relevant data, but their measurements are less accurate compared to invasive, reference methods. We had no objective method of assuring obedience to the study protocol, so we relied on participants' compliance. We did not measure urine secretion. Carbohydrate-rich drink was not compared to placebo. Studies were not blinded.

Bibliografia (References)

1. Shaikh SI, Nagarekha D, Hegade G, Marutheesh M. Postoperative nausea and vomiting: A simple yet complex problem. *Anesthesia, Essays and Researches* 2016; **10**: 388.

2. Maltby JR. Fasting from midnight - the history behind the dogma. *Best Practice and Research: Clinical Anaesthesiology* 2006; **20**: 363–78.

3. MENDELSON CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. *American journal of obstetrics and gynecology* 1946; **52**: 191–205.

4. MORTON HJV, WYLIE WD. Anaesthetic deaths due to regurgitation or vomiting. *Anaesthesia* 1951; **6**: 190–201.

5. Zdravkovic M, Berger-Estilita J, Kovacec JW, Sorbello M, Mekis D. A way forward in pulmonary aspiration incidence reduction: ultrasound, mathematics, and worldwide data collection. *Brazilian Journal of Anesthesiology (English Edition)*2022; doi 10.1016/J.BJANE.2021.05.004.

6. Bouvet L, Stevic N, Cercueil E, Drevet G, Chassard D. Effect of patient head position on the aspirated volume of regurgitated clear fluid. A fresh human cadaver study. *Anestezjologia Intensywna Terapia* 2020: 399–403.

7. Weimann A, Braga M, Carli F et al. ESPEN practical guideline: Clinical nutrition in surgery. *Clinical Nutrition* 2021; **40**: 4745–61.

8. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). *Canadian Journal of Anesthesia* 2015; **62**: 158–68.

9. Anesthesiologists AS. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures. *ANESTHESIOLOGY* 2017; **126**: 376–93.

10. El-Sharkawy AM, Daliya P, Lewis-Lloyd C et al. Fasting and surgery timing (FaST) audit. *Clinical Nutrition* 2021; **40**: 1405–12.

11. Aguilar-Nascimento JE de. Reducing preoperative fasting time: A trend based on evidence. *World Journal of Gastrointestinal Surgery* 2010; **2**: 57.

12. Nygren J. The metabolic effects of fasting and surgery. *Best Practice and Research: Clinical Anaesthesiology*, 2006.

13. Nygren J, Carlsson-Skwirut C, Brismar K, Thorell A, Ljungqvist O, Bang P. Insulin infusion increases levels of free IGF-I and IGFBP-3 proteolytic activity in patients after surgery. *American journal of physiology. Endocrinology and metabolism* 2001; **281**.

14. Nygren J, Thorell A, Brismar K, Karpe F, Ljungqvist O. Short-term hypocaloric nutrition but not bed rest decrease insulin sensitivity and IGF-I bioavailability in healthy subjects: The importance of glucagon. *Nutrition* 1997; **13**: 945–51.

15. Thorell A, Loftenius A, Andersson B, Ljungqvist O. Postoperative insulin resistance and circulating concentrations of stress hormones and cytokines. *Clinical nutrition (Edinburgh, Scotland)* 1996; **15**: 75–9.

16. Ljungqvist O, Søreide E. Preoperative fasting. *British Journal of Surgery* 2003; **90**: 400–6.

17. Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. *Clinical nutrition (Edinburgh, Scotland)* 2013; **32**: 34–44.

18. Li L, Wang Z, Ying X et al. Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis. *Surgery today* 2012; **42**: 613–24.

19. Smith MD, Mccall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database of Systematic Reviews*, 2014. https://pubmed.ncbi.nlm.nih.gov/25121931/ (accessed October 29, 2020).

20. Amer MA, Smith MD, Herbison GP, Plank LD, McCall JL. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. *British Journal of Surgery* 2017; **104**: 187–97.

21. Hausel J, Nygren J, Thorell A, Lagerkranser M, Ljungqvist O. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. *The British journal of surgery* 2005; **92**: 415–21.

22. Mathur S, Plank LD, McCall JL et al. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. *The British journal of surgery* 2010; **97**: 485–94.

23. Nygren J, Thorell A, Jacobsson H et al. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. *Annals of surgery* 1995; **222**: 728–34.

24. Li Y, He R, Ying X, Hahn RG. Dehydration, hemodynamics and fluid volume optimization after induction of general anesthesia. *Clinics* 2014; **69**: 809.

25. Kyle UG, Bosaeus I, De Lorenzo AD et al. Bioelectrical impedance analysis - Part I: Review of principles and methods. *Clinical Nutrition* 2004; **23**: 1226–43.

26. Kyle UG, Bosaeus I, De Lorenzo AD et al. Bioelectrical impedance analysis - Part II: Utilization in clinical practice. *Clinical Nutrition* 2004; **23**: 1430–53.

27. Song IK, Kim DH, Kim EH, Lee JH, Kim JT, Kim HS. Efficacy of bioelectrical impedance analysis during the perioperative period in children. *Journal of Clinical Monitoring and Computing* 2017; **31**: 625–30.

28. Mansouri S, Alhadidi T, Chabchoub S, Salah R Ben. Impedance cardiography: recent applications and developments. *Biomedical Research* 2018; **29**: 3542–52.

29. Cleymaet R, Scheinok T, Maes H et al. Prognostic value of bioelectrical impedance analysis for assessment of fluid overload in ICU patients: a pilot study. *Anestezjologia Intensywna Terapia* 2021; **53**: 10–7.

30. Pang Q, Hendrickx J, Liu HL, Poelaert J. Contemporary perioperative haemodynamic monitoring. *Anaesthesiology Intensive Therapy* 2019; **51**: 147–58.

31. Soop M, Nygren J, Thorell A et al. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. *Clinical Nutrition* 2004; **23**: 733–41.

32. Hausel J, Nygren J, Lagerkranser M et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesthesia and Analgesia* 2001; **93**: 1344–50.

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Perioperative Medicine

RESEARCH Open Access

The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: a volunteer randomized study

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Abstract

Background: Fasting prior to anesthesia is considered aspiration prophylaxis. However, prolonged food and drink restrictions may increase the risk of other complications. The aim of this study was to assess whether a carbohydrate-enriched drink (Nutricia™ preOp®), recommended by the enhanced recovery after surgery (ERAS) protocol, can improve body hydration in fasting healthy individuals.

Methods: Measurements were done with the bioelectric impedance analysis with a Fresenius body composition monitor. Body composition, total body water, water distribution, and hemodynamic parameters were measured at the beginning of the study and after 10 h and 12 h of fasting. Patients fasted for 10 h and then were divided into two groups: the control (n = 40) and the pre-op group (n = 41). The pre-op group received 400 mL of Nutricia™ preOp®, as suggested in the ERAS guidance. The two-tailed Student's t test was used to compare two groups with normally distributed data and homogenous variances; if variances were heterogeneous, Welch's test was used. The Mann-Whitney U test was used to compare two groups with non-normal data distribution. $p <$ 0.05 was considered statistically significant.

Results: We found no significant differences between the control and pre-op groups regarding body water distribution and body composition. We did not observe significant losses in the total body water after fasting. Also, blood pressure was not affected by fasting.

Conclusion: We have proven that pre-op did not impact either body composition or body water.

Trial registration: ClinicalTrials.gov, NCT04665349. Registered on 11 December 2020—retrospectively registered.

Keywords: Fasting, Bioelectrical impedance analysis, Total body water, Pre-op, Perioperative patient management, Enhanced recovery after surgery (ERAS), Intracellular water, Extracellular water, Dehydration

Introduction

The current American Society of Anesthesiologists (ASA) guidelines recommend that patients should fast for 6 h and refrain from drinking clear liquids for 2 h before elective surgery (Warner et al. 1999). Excessive fasting is not recommended; however, in many hospitals, patients are required to not eat from the evening before surgery (Chin et al. 2006). Even short-term fasting causes insulin resistance, which leads to hyperglycemia and increases the risk of complications in the postoperative period, and lowers the level of insulin-like growth factor (IGF-1), which impairs wound healing (Nygren

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2006). This is particularly disadvantageous because the stress response to surgical injury has similar metabolic effects to starvation (Nygren 2006). Moreover, withholding liquid administration may cause dehydration in patients, which increases the risk of hypotension during induction of anesthesia. Unfortunately, direct monitoring of hydration is impossible in the operating room, and only indirect hemodynamic parameters may be used to estimate patient hydration (Pang et al. 2019; Szczepańska et al. 2020). On the other hand, food and fluid restriction causes the stomach to empty, reducing the risk of pulmonary aspiration of gastric contents. It was proven that ≥ 1 mL kg^{-1} of fluid in the stomach may cause a clinically significant risk of aspiration (Bouvet et al. 2019). Thus, intravenous liquids are administered.

There is no consensus on perioperative fluid management among anesthesia providers (Jacob et al. 2008). It is clear that crystalloids are superior to colloids in perioperative fluid therapy (Jacob et al. 2008). In the past, 5% glucose and 0.9% sodium chloride solution (named normal saline) were commonly used. It was suggested that 5% glucose may be beneficial in overcoming insulin resistance, and 5% glucose was thought to increase intracellular water content; however, these speculations were never confirmed (Chin et al. 2006). Due to their significant disadvantages, these fluids lost their primacy to balanced crystalloids. Although normal saline is isotonic, it is considered a non-balanced crystalloid (Corrêa et al. 2015). It has 154 mEq L^{-1} of chloride, which is 1.5 times higher than the level in human serum (Corrêa et al. 2015). Additionally, the strong ion difference (SID) of normal saline is much lower than that of serum: 0 mEq L^{-1} vs. 40 mEq L^{-1} (Corrêa et al. 2015). In summary, a large volume infusion of normal saline will reduce SID and may cause hyperchloremic acidosis (Corrêa et al. 2015). However, 5% glucose is an isotonic solution, glucose is rapidly metabolized to water and carbon dioxide after intravenous administration (Chin et al. 2006). Thus, administration of 5% glucose is equal to the administration of pure water.

Therefore, the enhanced recovery after surgery (ERAS) protocol has been established to increase patient's well-being after surgery. One of the important aspects of ERAS is rational fluid and food restriction prior to anesthesia (Borys et al. 2020; Kaye et al. 2020; Taniguchi et al. 2012). Both ERAS and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend oral intake of a carbohydrate-rich drink prior to surgery (Nygren et al. 2013; Weimann et al. 2017).

The aim of this study was to assess whether a carbohydrate-enriched drink (Nutricia™ preOp®), recommended in ERAS protocols improves body hydration in fasting healthy individuals. We hypothesized that pre-op would improve body hydration and will not impact body composition. Measurements were done with the bioelectric impedance analysis. To the best of our knowledge, this is the first study of the kind.

Materials and methods

The study was conducted as a single-center randomized controlled open-label study with balanced randomization conducted in Poland. Study protocol was accepted by Independent Bioethics Committee for Scientific Research at Medical University of Gdansk (resolution 126/2014, from 27th May 2014). The study was carried out according to Good Clinical Practice Guidance (GCP), all precipitants signed written consent. The study took place at the Department of Anesthesiology and Intensive Care of Medical University of Gdansk, Gdansk, Poland, from September 2019 to October 2020. Study design does not contain follow-up. Full study protocol is available from the corresponding author upon request. Study was retrospectively registered at ClinicalTrials.gov (NCT04665349) at 11 December 2020

Participants

Following approval by the institutional ethics committee and obtaining written informed consent, we recruited 81 adult volunteers of ASA physical status 1 or 2. The study was performed on healthy individuals. The exclusion criteria were chronic kidney disease, heart failure, phenylketonuria, episodes of hypoglycemia, or other carbohydrate metabolism disorders. The first measurements were taken at 8:00 pm. Body composition was measured in the supine position using two sets of electrodes for unilateral hand and foot measurements. Body mass and blood pressure were also measured. Participants were asked to abstain from food for the next 10 h. They were allowed to drink clear liquids for the next 2 h, after which they had to abstain from all liquids. Second measurements were taken at 6:00 am. Then, participants were divided into two groups, the control and pre-op group, using a computer-generated randomization plan (www.randomization.com). Allocation ratio was 1:1. The control group was not allowed to drink for the next 2 hours, while the pre-op group was given 400 mL of Nutricia™ preOp®. Both groups had to refrain from eating and drinking for the next 2 h. The final measurements were taken at 8:00 am, concluding a 12-h fasting period. Due to lack of norms for body water distribution parameters we were unable to calculate groups sizes ex ante.

Bioelectrical impedance analysis

Body composition was measured using a Body Composition Monitor (Fresenius Medical Care AG & Co. KGaA, Germany), which uses non-invasive bioimpedance spectroscopy techniques (Kyle et al. 2004a; Kyle et al. 2004b). Electrodes were placed on the extremities, and an alternating current was applied. High-frequency current penetrates cell membranes, while low-frequency current does not. This phenomenon allowed the measurement of electrical resistances of total body water (TBW) and extracellular water (ECW). Those values were then used to calculate clinically relevant parameters, such as ECW, TBW, intracellular water (ICW), adipose tissue mass (ATM), and lean tissue mass (LTM) using two advanced physiological models. All output parameters were validated against reference methods.

Carbohydrate drink

Nutricia™ preOp® is a 0.5-kcal mL^{-1}, clear, carbohydrate drink for patients undergoing elective surgery. All of its energy content comes from carbohydrates, namely, maltodextrin and fructose. A 400 mL serving contains 50.4 g of carbohydrates, which is more than the 45 g recommended by the enhanced recovery after surgery (ERAS) protocol. The drink is isosmotic, with an osmolarity of 240 mOsmol L^{-1}. It contains the following micro- and macro-elements per 100 mL: 50 mg of sodium, 122 mg of potassium, 6 mg of chloride, 6 mg of calcium, 1 mg of phosphate, and 1 mg of magnesium.

Statistical analysis

No interim analyses for efficacy or futility were done. The primary endpoint was changes in the extracellular to intercellular water and the amount of total body water. Outcomes were measured after the study has ended.

Categorical variables are reported by the number and percentage of patients in each category. Continuous variables with a normal probability distribution are presented as the arithmetic mean with standard deviation. For the continuous variables with a different probability distribution, the median and the interquartile range (IQR) are given.

Fisher's exact test was used for the comparison of categorical data. The D'Agostino & Pearson test was used to assess the normality of the data. For variables with a normal distribution, parametric tests were used; if the normality of the distribution was not confirmed, non-parametric tests were used. The two-tailed Student's t test was used to compare two groups with normally distributed data and homogenous variances; if variances were heterogeneous, Welch's test was used. The Mann-Whitney U test was used to compare two groups with non-normal data distribution. $p < 0.05$ was considered statistically significant.

Data were analyzed with Prism 8 software (GraphPad, USA).

Table 1 Patient characteristics at the beginning of the study. Values are number [%], median (IQR [range]), or mean (SD)

Variable	Control (*n* = 40)	Pre-op (*n* = 41)	*p*
Female	22 [55%]	25 [61%]	0.67
Age (years)	24.5 [23.3–26.0]	25 [24.0–28.0]	0.069
Height (cm)	171.2 (9.3)	171.7 (8.7)	0.82
Body mass (kg)	67.0 (13.9)	66.8 (9.8)	0.93

Results

Participant characteristics

Eighty-one participants were recruited into the study, and all of them completed the study protocol. Forty participants were randomized into the control group, and forty-one people received carbohydrate drink after 10 h of fasting. There were no significant differences between groups (Table 1).

Hemodynamic parameters of the participants

There were no significant differences between systolic blood pressure (SBP) and diastolic blood pressure (DPB) at any of the time points (Table 2). We observed a significant difference in heart rate (HR) between the control and the pre-op group after 12 h of fasting (p = 0.0271). HR was higher in the pre-op group (Table 2).

Body composition of the participants

There were no significant differences between any measured parameters at the 0-hour and 10-hour time points. After randomization and carbohydrate-enriched drink administration, there were no significant differences between the pre-op and control group (Table 3).

Body water distribution of the participants

There were no significant differences between body water distribution at the 0-hour and 10-hour time points. After randomization and carbohydrate-enriched drink administration, there were no significant differences between the pre-op and control group (Fig. 1). We did not observe significant dehydration of participants over the course of the study.

Table 2 Comparison of blood pressure and heart rate between groups. Values are median (IQR [range]) or mean (SD)

Variable	0 h	10 h	12 h		*p*
			Control (*n* = 40)	Pre-op (*n* = 41)	
SBP (mmHg)	123 [115.5–135]	117 [108–125]	117.5 [103.8–125.8]	114 [105.6–127.0]	0.77
DBP (mmHg)	79 [73.5–86.0]	77 [71.5–81.5]	75 [71.0–80.8]	75 [69.5–82.0]	0.67
HR (bmp)	78 [70.0–84.0]	71 [64.0–78.5]	66.5 [59.0–74.0]	72 [66.0–79.0]	**0.03**

Table 3 Comparison of body composition between groups. Values are median (IQR [range]) or mean (SD)

Variable	0 h	10 h	12 h Control (n = 40)	12 h Pre-op (n = 41)	p (control vs pre-op)
BMI (kg m^{-2})	22.6 (2.8)	22.4 (2.7)	22.3 (2.9)	22.4 (2.5)	0.90
LTI (kg m^{-2})	14.5 [12.4–17.7]	14.3 [12.5–17.1]	15.3 [13.1–17.1]	13.4 [12.1–17.8]	0.23
LTM (kg)	41.1 [33.8–56.0]	41.1 [33.4–54.8]	43.5 [34.0–55.3]	40.2 [32.9–55.2]	0.43
Fat (kg)	15.5 [11.7–21.3]	15.3 [11.3–20.5]	13.9 [11.2–20.5]	17.3 [11.4–21.1]	0.21
FTI (kg m^{-2})	7.2 [5.8–9.5]	7.1 [5.5–9.9]	6.75 [5.5–9.4]	7.7 [5.6–10.2]	0.30
ATM (kg)	20.6 [15.9–23.4]	20.9 [15.3–27.9]	18.9 [15.3–27.9]	23.5 [15.5–28.7]	0.22
BCM (kg)	25.3 (8.3)	24.6 (8.1)	25.7 (8.5)	24.1 (8.4)	0.39

Discussion

We aimed to assess whether the administration of a carbohydrate-enriched drink impacts body water distribution in healthy fasting individuals in this study. Measurements were made with the bioelectrical impedance analysis, which is commonly used for such purposes (Kyle et al. 2004a; Kyle et al. 2004b; Song et al. 2017; Taniguchi et al. 2012; Tsukamoto et al. 2017). Participants were fasted for 10 h and the randomized into two groups: the control group, which fasted for 2 more hours, and the pre-op group, which received-carbohydrate enriched drink. The baseline hydration of our participants is worth emphasizing, as the majority of the population had E/I ratio values on the higher side of values expected for young adults (Gligoroska et al. 2016). We found no significant differences between the

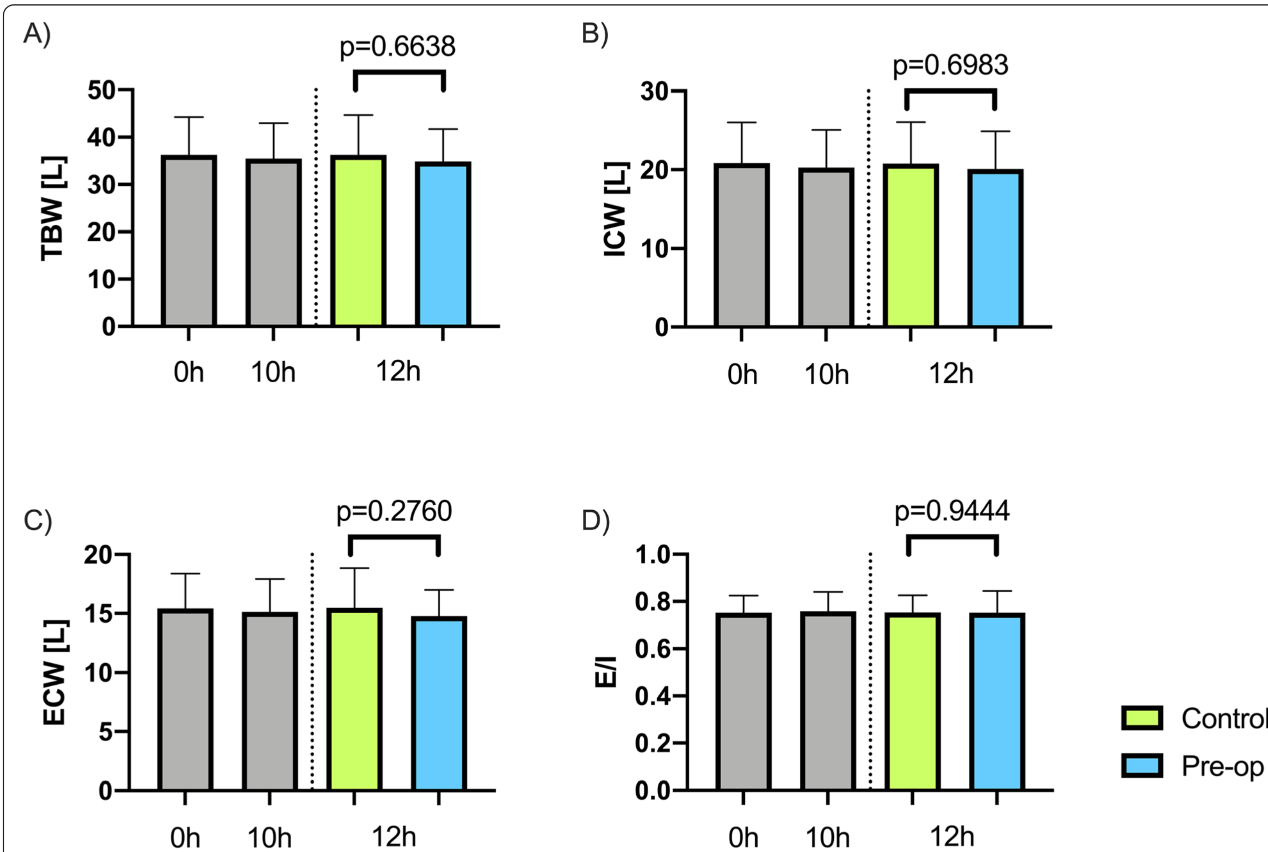

Fig. 1 Comparison of body water distribution between groups. **A** Total body water. **B** Intracellular water. **C** Extracellular water. **D** Extracellular to intracellular water ratio

control and pre-op groups regarding body water distribution and body composition. We did not observe significant losses in TBW after fasting.

Other studies also aimed to understand the impact of fasting on body water distribution. Tsukamoto et al. [17] found that there were no differences in TBW, ECW, and ICW in patients with different perioperative fasting periods. In contrast, Taniguchi et al. found that patients with a shortened perioperative fasting time had a smaller decrease in TBW than patients with conventional fasting time (Taniguchi et al. 2012).

Although the carbohydrate drink did not cause any changes in water distribution, there are detrimental metabolic effects of fasting on surgery (Nygren 2006), such as insulin resistance (Soop et al. 2004) and muscle loss (Yuill et al. 2005), that can be alleviated with carbohydrate treatment. Those are associated with prolonged hospital stay, which can be shortened with carbohydrate treatment (Smith et al. 2014). Other beneficial effects include reduction of thirst, hunger, and anxiety (Hausel et al. 2001).

This study has the following limitations. First, we had no actual control of participants' food and fluid intake and had to rely on their compliance, which may have caused alterations in fasting time. Second, we did not forbid smoking; while nicotine causes the release of antidiuretic hormone (Burn 1951), it has no effect on TBW (Vio et al. 1995). Last, we did not measure urine volume. We were unable to perform the power analysis. Ex ante analysis requires precise defined norms for the parameters, and post hoc analysis is biased.

Further studies should focus on the metabolic effects of preoperative carbohydrate treatment, the value of carbohydrates other than maltodextrin, and different routes of administration.

Conclusion

We determined the impact of a carbohydrate-enriched drink (Nutricia™ preOp®) on body composition and body water in fasting healthy individuals. We have proven that pre-op did not impact either body composition or body water.

Abbreviations

ASA: American Society of Anesthesiologists; ATM: Adipose tissue mass; BCM: Body cell mass; BMI: Body mass index; DBP: Diastolic blood pressure; E/I: Extracellular water to intracellular water ratio; ECW: Extracellular water; ERAS: Enhanced recovery after surgery; ESPEN: European Society for Clinical Nutrition and Metabolism; FTI: Fat tissue index; HR: Heart rate; ICW: Intracellular water; LTI: Lean tissue index; LTM: Lean tissue mas; SBP: Systolic blood pressure; SD: Standard deviation; TBW: Total body water

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Authors' contributions

Study design and conceptualization: AA, RO; data acquisition: JK, KPS, BS; statistical analysis and visualization: KPS; data interpretation: JK, KPS, RO; writing – original draft preparation: JK, KPS; writing – critical review and editing: JK, KPS, BS, AA, RO; supervision and funding: AA, RO. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data used to support the findings of this study are included within the article or are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (approval no. NKBBN/126/2014). The study was performed in accordance with the ethical standards as laid down in 1964 Declaration of Helsinki and its later amendments. All participates gave informed written consent before enrolment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

Borys M, Żurek S, Kurowicki A, Horeczy B, Bielina B, Sejboth J, et al. Implementation of enhanced recovery after surgery (ERAS) protocol in off-pump coronary artery bypass graft surgery. A prospective cohort feasibility study. Anaesthesiol Intensive Ther. 2020;52(1):10–4. https://doi.org/10.5114/ait.2020.93160.

Bouvet L, Cercueil E, Barnoud S, Lilot M, Desgranges FP, Chassard D. Relationship between the regurgitated and the aspirated volume of water. A manikin study. Anaesthesiol Intensive Ther. 2019;51(2):121–5. https://doi.org/10.5114/ait.2019.85953.

Burn JH. Antidiuretic effect of nicotine and its implications. Br Med J. 1951; 2(4725):199–201. https://doi.org/10.1136/bmj.2.4725.199.

Chin KJ, Macachor J, Ong KC, Ong BC. A comparison of 5% dextrose in 0.9% normal saline versus non-dextrose-containing crystalloids as the initial intravenous replacement fluid in elective surgery. Anaesth Intensive Care. 2006;34(5):613–7.

Corrêa TD, Rocha LL, Pessoa CMS, Silva E, de Assuncao MSC. Fluid therapy for septic shock resuscitation: which fluid should be used? Einstein (Sao Paulo). 2015:462–8 Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1679-45082015000300462&lng=en&nrm=iso&tlng=en. Instituto Israelita de Ensino e Pesquisa Albert Einstein. Cited 2020 Oct 31.

Gligoroska JP, Todorovska L, Mancevska S, Karagjozova I, Petrovska S. Bioelectrical impedance analysis in karate athletes: BIA parameters obtained with INBODY720 regarding the age. Res Phys Educ Sport Health. 2016;5(2):117–21 Available from: https://go.openathens.net/redirector/leedsmet.ac.uk?url=http%3A%2F%2Fsearch.ebscohost.com%2Flogin.aspx%3Fdirect%3Dtrue%26db%3Ds3h%26AN%3D120814808%26site%3Deds-live%26scope%3Dsite%26authtype%3Dathens.

Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almström C, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001;93(5):1344–50. https://doi.org/10.1097/00000539-200111000-00063 Lippincott Williams and Wilkins.

Jacob M, Chappell D, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. Anesthesiology. 2008;109(4):723–40.
Kaye A, Renschler J, Cramer K, Klein K, Granier A, Hart B, et al. The role of clinical pharmacology in enhanced recovery after surgery protocols: a comprehensive review. Anaesthesiol Intensive Ther. 2020;52(2):154–64. https://doi.org/10.5114/ait.2020.95020.
Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis - Part I: Review of principles and methods. Clin Nutr. 2004a;23(5):1226–43 Available from: https://pubmed.ncbi.nlm.nih.gov/15380917/. Churchill Livingstone. Cited 2020 Nov 1.
Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis - Part II: Utilization in clinical practice. Clin Nutr. 2004b;23(6):1430–53 Available from: https://pubmed.ncbi.nlm.nih.gov/15556267/. Churchill Livingstone. Cited 2020 Nov 1.
Nygren J. The metabolic effects of fasting and surgery. Best Pract Res Clin Anaesthesiol. 2006;20(3):429–38.
Nygren J, Thacker J, Carli F, Fearon KCH, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced recovery after surgery (ERAS®) society recommendations. World J Surg. 2013:285–305 Available from: https://pubmed.ncbi.nlm.nih.gov/23052796/. Cited 2020 Nov 1.
Pang Q, Hendrickx J, Liu HL, Poelaert J. Contemporary perioperative haemodynamic monitoring. Anaesthesiol Intensive Ther. 2019;51(2):147–58. https://doi.org/10.5114/ait.2019.86279.
Smith MD, Mccall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. Cochrane Database Syst Rev. 2014 Aug 14;(8):CD009161. https://doi.org/10.1002/14651858.CD009161.pub2.
Song IK, Kim DH, Kim EH, Lee JH, Kim JT, Kim HS. Efficacy of bioelectrical impedance analysis during the perioperative period in children. J Clin Monit Comput. 2017;31(3):625–30. https://doi.org/10.1007/s10877-016-9881-1 Springer Netherlands.
Soop M, Nygren J, Thorell A, Weidenhielm L, Lundberg M, Hammarqvist F, et al. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. Clin Nutr. 2004;23(4):733–41. https://doi.org/10.1016/j.clnu.2003.12.007.
Szczepańska A, Pluta M, Krzych Ł. Clinical practice in intraoperative haemodynamic monitoring in Poland: a point prevalence study in 31 Polish hospitals. Anaesthesiol Intensive Ther. 2020;52(2):97–104. https://doi.org/10.5114/ait.2020.95168.
Taniguchi H, Sasaki T, Fujita H. Preoperative management of surgical patients by "Shortened fasting time": A study on the amount of total body water by multi-frequency impedance method. Int J Med Sci. 2012;9(7):567–74. https://doi.org/10.7150/ijms.4616. Ivyspring International Publisher. Cited 2020 Nov 1.
Tsukamoto M, Hitosugi T, Yokoyama T. Influence of fasting duration on body fluid and hemodynamics. Anesth Prog. 2017;64(4):226–9. https://doi.org/10.2344/anpr-65-01-01.
Vio F, Salazar G, Yanez M, Pollastri A, Aguirre E, Albala C. Smoking and its effects on maternal body composition in late pregnancy. Eur J Clin Nutr. 1995;49(4):267–73.
Warner MA, Caplan RA, Epstein BS, Gibbs CP, Keller CE, Leak JA, et al. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: Application to healthy patients undergoing elective procedures: a report by the american society of anesthesiologists task force o. Anesthesiology. 1999:896–905 Available from: http://pubs.asahq.org/anesthesiology/article-pdf/90/3/896/396690/0000542-199903000-00034.pdf. Lippincott Williams and Wilkins. Cited 2020 Oct 31.
Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50. https://doi.org/10.1016/j.clnu.2017.02.013 Cited 2020 Nov 1.
Yuill KA, Richardson RA, Davidson HIM, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively - a randomised clinical trial. Clin Nutr. 2005;24(1):32–7. https://doi.org/10.1016/j.clnu.2004.06.009.

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Effect of Carbohydrate-Enriched Drink Compared to Fasting on Hemodynamics in Healthy Volunteers. A Randomized Trial

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Abstract: Fasting prior to surgery can cause dehydration and alter hemodynamics. This study aimed to determine the impact of a carbohydrate-enriched drink (Nutricia™ Pre-op®) on selected hemodynamical parameters, measured in a non-invasive manner. We enrolled 100 healthy volunteers and measured their weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), thoracic fluid content (TFC), thoracic fluid index (TFCI), stroke volume (SV), stroke volume variation (SVV), stroke index (SI), cardiac output (CO), cardiac index (CI), heather index (HI), systolic time ration (STR), systemic time ratio index (STRI), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI) by a Niccomo™ device, implementing the impedance cardiography (ICG) method. Measurements were performed at the beginning of the study, and after 10 h and 12 h. We randomly allocated participants to the control group and the pre-op group. The pre-op group received 400 mL of Nutricia™ preOp®, as suggested in the ERAS guidelines, within 10 h of the study. Student's *t*-test or the Mann–Whitney U test were used to compare the two groups, and $p < 0.05$ was considered significant. We did not observe any changes in hemodynamical parameters, blood pressure, and heart rate between the groups. We have proven that carbohydrate-enriched drink administration did not have a significant impact on the hemodynamical parameters of healthy volunteers.

Keywords: impedance cardiography (ICG); fasting; enhanced recovery after surgery (ERAS); hemodynamics; cardiac index (CI); systemic vascular resistance index (SVRI); pre-op; perioperative patient management; NICCOMO

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1. Introduction

Preoperative, overnight fasting is a decades-old idea, introduced as prophylaxis for Mendelson syndrome, which is aspiration pneumonia with a poor prognosis [1]. Over the years, new evidence has come to light, and current guidelines recommend patients do not eat solid foods for 6 h and do not drink clear liquids for 2 h before surgery [2,3]. However old habits prove difficult to change, as fasting time still remains excessive in many hospitals (even up to 16 h) [4,5]. This can lead to dehydration, which has adverse effects on hemodynamic parameters, and in consequence, impairs oxygen delivery [6,7]. It is worth emphasising that a patient's hydration is not routinely measured in the operating theatre, as neither heart rate nor blood pressure are sensitive indicators [8]. Fasting can also cause unwanted metabolic changes, which can increase the complication ratio, and thus preoperative carbohydrate treatment in the form of carbohydrate-rich drinks (so-called pre-op) are recommended by both enhanced recovery after surgery (ERAS) protocol and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [2,9]. This can reduce patients' anxiety and improve general well-being [10]. Surgical injury and fasting increase insulin resistance, causing complications in the postoperative period [11], carbohydrate treatment can alleviate this to some degree [10], and decrease the length of hospital stay [12]. Oppositely, a more recent meta-analysis shows no benefit of pre-op over placebo or water [13]. Due to inconsistent data, it is important to gather new evidence regarding this matter.

In our previous study, we measured changes in body water (total body water, intracellular water, extracellular water) and body composition in fasting individuals. We did not observe significant dehydration during overnight fasting, but nonetheless there was a significant difference in heart rate [14]. This prompted us to take a closer look at changes in hemodynamic parameters. While they are rarely measured directly in the operating theatre [15], improvements in bioelectrical impedance analysis may change this in the near future [16–18]. Although not a new concept, impedance cardiography (ICG) is becoming more and more accurate as new hardware and calculation algorithms are developed. It is already comparable to reference methods [19–21], providing a non-invasive alternative for hemodynamic monitoring.

In this study, we assessed the impact of a carbohydrate drink on cardiac output and systemic vascular resistance after overnight fasting using the ICG device. The study aimed to determine the impact of the carbohydrate-enriched drink (Nutricia™ Pre-op®, Nutricia, Warsaw, Poland) on selected hemodynamical parameters measured in a non-invasive manner. We hypothesized that the administration of liquid recommended by ERAS guidelines would improve the hemodynamical status of fasting healthy volunteers. According to our best knowledge, this relationship has not been previously studied. Furthermore, we were interested in determining the impact of fasting on hemodynamics.

2. Materials and Methods

This was an open label randomized controlled study conducted in Gdansk, Poland. The study was designed according to the regulation of Good Clinical Practice (GCP) and the 1964 Declaration of Helsinki and its amendments. Study protocol revied approval from the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (NKBBN/562/2021). The study was prospectively registered at ClinicalTraials.gov (NCT04972500) on 9 July 2021.

2.1. Participants

The study was performed on healthy individuals. Between 12 July 2021 and 4 November 2021, we enrolled 100 adult volunteers from the American Society of Anesthesiologists (ASA) status 1 and 2. Due to lack of literature data, the ex-ante calculation of groups sizes was impossible. Volunteers' height had to be within a 120–230 cm range and the weight between 30 and 155 kg. Exclusion criteria were chronic kidney disease, circulatory failure, lung diseases, diseases of the heart valves, history of hypoglycaemic episodes, or any carbohydrate disturbance. For each participant, the study started at 9 p.m. when the first measurements were taken. Firstly, body mass and blood pressure were measured. Then, the skin was cleaned with alcohol to make skin-to-electrode impedance as low as possible. Two electrodes were placed on the thorax along the midaxillary line, and another two electrodes were placed on the neck. Hemodynamic parameters were measured in a supine position. Measurement was conducted according to manufacturer guidelines. After measurements, participants were asked to fast for 10 h; however, they could drink clear liquids for 2 h. The second and third measurements took place at 7.00 a.m. and 9.00 a.m. The measurements procedure was the same for all timepoints. After the second measurement, the participants were divided into two groups. A computer-generated randomization plan (www.randomization.com (accessed on 8 July 2021)) with allocation ratio 1:1 was implemented. The control group had to restrain from drinking till the third measurement, whereas the pre-op group received 400 mL of Nutricia™ PreOp® per os. The study protocol did not include follow up. Study protocol is presented in Figure 1.

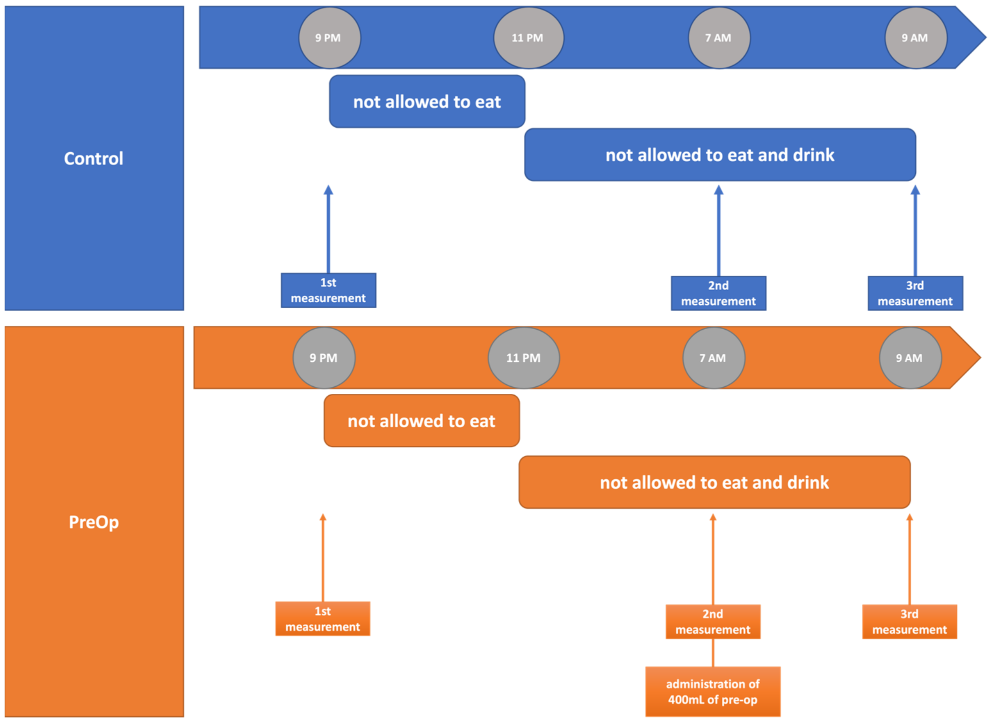

Figure 1. Study protocol summary.

2.2. *Impedance Cardiography*

Niccomo™ device (Medizinische Messtechnik GmbH, Ilmenau, Germany) was used to non-invasively measure hemodynamical parameters. The special algorithm allowed Niccomo™ to calculate hemodynamic-related parameters based on a variation of thoracic bio-impedance caused by changes in volume and velocity of blood in the aorta. Thoracic fluid content (TFC), thoracic fluid index (TFCI), stroke volume (SV), stroke volume variation (SVV), stroke index (SI), cardiac output (CO), cardiac index (CI), heather index (HI), systolic time ration (STR), systemic time ratio index (STRI), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI) were measured. A Signal Quality Indicator, which shows the quality of the beats used in the calculation, was used as a validation tool. All measurements had a high-quality index (>95%).

2.3. *Carbohydrate Drink*

Nutricia™ PreOp® was used in the study. Participants received 400 mL of liquid (50.4 g of carbohydrates), according to the recommendation of enhanced recovery after surgery (ERAS) protocol.

2.4. *Statistical Analysis*

The primary endpoints were changes in CI, SVRI, SV, and heart rate (HR). No interim analyses were performed. Data were analyzed with Prism 9 software (GraphPad Software, San Diego, CA, USA). Categorical variables are reported by the number and percentage of patients in each category. Continuous variables with a normal probability distribution are presented as the arithmetic mean with standard deviation. For the continuous variables with a different probability distribution, the median and the interquartile range (IQR) are given. The D'Agosition and Person test was used as a normality test. Fisher's exact test, a two-tailed *t*-Student test or the Mann–Whitney U test were used to compare two groups regarding the data type and characteristic. Results were considered to be statistically significant if $p < 0.05$. The detailed protocol for statistical analysis was previously described by our team [14].

3. Results

One hundred volunteers were enrolled in the study. All participants completed the study protocol. The allocation ratio was 1:1, each study group (control and pre-op) consisted of 50 people. No significant differences between control and pre-op groups were found (Table 1).

Table 1. Patients' characteristics at the beginning of the study. Values are number [%], or mean (SD).

Variable	Control (*n* = 50) Number [%] Mean (SD)	Pre-op (*n* = 50) Number [%] Mean (SD)	*p* Value
Female	27 (54%)	32 (64%)	0.4162
Age (y)	23.70 (3.51)	23.72 (3.12)	0.9761
Height (cm)	173.50 (10.12)	173.30 (9.26)	0.9263
Weight (kg)	72.45 (15.86)	67.53 (11.84)	0.0819

We did not observe any differences in systolic (SBP) and diastolic (DBP) pressure or heart rate (HR) between groups. SBP and DBP were significant lower at the 10 h time point (Table 2).

Table 2. Comparison of blood pressure and heart rate between groups. Values are median (IQR range), or mean (SD).

Variable	0 h Median (IQR) Mean (SD)	10 h Median (IQR) Mean (SD)	12 h Median (IQR) Mean (SD)		*p* Value (0 h vs. 10 h)	*p* Value (Control vs. Pre-op)
			Control	Pre-op		
SBP (mmHg)	119.50 (12.21)	114.80 (11.04)	112.90 (10.99)	111.30 (10.35)	0.0052	0.4386
DBP (mmHg)	72.37 (7.76)	68.77 (6.32)	68.70 (6.81)	68.60 (6.82)	0.0004	0.9417
HR (bmp)	69.50 (63.00–77.00)	67.91 (11.95)	62.18 (9.81)	63.60 (10.22)	0.1466	0.4802

SBP—systolic blood pressure; DBP—diastolic blood pressure; HR—heart rate.

No significant differences were observed between all measured hemodynamical parameters at the 0 h and 10 h time points. No significant differences between the pre-op and control groups were found at 12 h of the study (after randomization and carbohydrate-enrich drink administration) (Table 3). Additional parameters reported by Niccomo™ are presented in Table S1.

Table 3. Comparison of hemodynamical parameters. Values are median (IQR range) or mean (SD).

Variable	0 h Median (IQR) Mean (SD)	10 h Median (IQR) Mean (SD)	12 h Median (IQR) Mean (SD)		*p* Value (0 h vs. 10 h)	*p* Value (Control vs. Pre-op)
			Control	Pre-op		
SVV (%)	15 (11–18)	14.5 (11–19)	14.5 (11–21)	14 (11.75–17)	0.6982	0.6167
SV (mL)	104 (23.85)	102.9 (23.33)	110 (23.61)	105.3 (21.72)	0.7419	0.3007
SI (mL m^{-2})	56.45 (9.47)	56.15 (8.9)	58 (54–63)	57.5 (53–62.25)	0.8177	0.5035
CO (L min^{-1})	7.28 (1.76)	6.87 (1.51)	6.77 (1.47)	6.61 (1.39)	0.0776	0.5766
CI (L min^{-1} m^{-2})	3.94 (0.67)	3.76 (0.65)	3.65 (0.56)	3.68 (0.64)	0.0569	0.8815
SVRI (dyn s cm^{-5} m^2)	1640 (1423–1847)	1661 (314.2)	1688 (269)	1681 (306.2)	0.9985	0.9036
SVR (dyn s cm^{-5})	893 (740–1120)	904 (784.3–1064)	931.7 (198.4)	943.6 (184.8)	0.9441	0.7588

SVV—stroke volume variation; SV—stroke volume; SI—stroke index; CO—cardiac output; CI—cardiac index; SVRI—systemic vascular resistance index; SVR—systemic vascular resistance.

4. Discussion

Our goal was to access the impact of carbohydrate-rich drink on haemodynamic parameters in fasting, healthy individuals. We used the ICG device Niccomo™, which has been proven as a viable method for the non-invasive measurement of haemodynamic parameters when compared with thermodilution-derived methods [19–21]. The accuracy of the ICG method depended strictly on clinical scenario. Performed meta-analysis demonstrated good values of correlation coefficient; however, it must be noted that dose data were relatively old [22–24]. Generally, the correlation of ICG and reference method were the highest in healthy individuals (r^2 around 0.7–0.8), and much lower in ICU patients and individuals with impaired cardiac function [22,24]. The indisputable advantage of the ICG method was its non-invasive character, which allowed it to be used on patients without indication to invasive monitoring. This approach minimalized the risks while providing useful clinical data. Transthoracic Doppler echocardiography (TTE) can also be used to measure haemodynamic parameters in a non-invasive way, and generally there is no significant difference in CO compared with the thermodilution. However, when structural changes are present in the heart, TTE accuracy is questionable [25]. Interestingly, Daralammouri et al. managed to overcome this shortcoming with the use of the ICG. They used both methods in tandem to measure the aortic valve area in patients with aortic valve stenosis; this hybrid approach significantly correlated to thermodilution method [26]. Liu et al. used the ICG device during cardiopulmonary exercise testing and six-minute walk test to improve peak oxygen uptake assessment in healthy volunteers [27]. ICG proved useful in assessing the impact of postural changes on haemodynamic parameters in healthy adults [28], infants [29–31], and surgery patients [32].

Several factors can contribute to perioperative hemodynamic changes. Firstly, fasting prior to surgery can cause dehydration [33]. Intubation itself causes changes in HR, SBP, and DBP [34]. Moreover, the drugs used during general anaesthesia are cardiodepressants, and hypotension during induction is a common complication [35]. Typically, the decreased mean arterial pressure and CI, as well as increased SVRI, are observed after the induction of general anaesthesia. SV can be lower, even by 62%, in comparison with the values before anaesthesia [6]. Unfortunately, conventional monitoring used in the operating theatre cannot adequately represent changes in hemodynamics; thus, these changes can be easily omitted [36]. Fortunately, appropriate intravenous fluid management can reverse this trend [6]; however, there are no data regarding if *per os* fluid administration can also be beneficial. Given that the perioperative administration of carbohydrate-rich drink has established a role in preventing other complications such as nausea, insulin resistance, and muscle loss [37–39], the question raised in our study is important and covers gaps in current knowledge.

We determined no significant differences between the pre-op and control groups regarding changes in haemodynamic parameters in fasting volunteers. Similarly, Alves et al. showed no changes in haemodynamic parameters after fasting in healthy (ASA I/II) volunteers as well. Although they used echocardiographic methods instead, their population was older (26–67 years old) and they did not examine the carbohydrate-rich drink impact on those changes [40]. Interestingly, in healthy males during physical activity, carbohydrate rich-drink could increase CO and decrease SVR in comparison to protein-rich drinks and water [41]. Even though fasting did not influence the hemodynamic parameters in healthy individuals, it is vital to provide proper fluid therapy as both hypo- and hypervolemia have detrimental effects on surgery outcome. It has to be emphasised that goal-directed fluid therapy is part of ERAS protocol [8,33].

We are aware of several limitations of this study. This is a single-centre study, in which healthy volunteers were included. We used non-invasive methods for hemodynamic assessment, which may be less reliable than invasive methods. We also did not perform this study in a crossover design. We did not have direct control over volunteers' compliance; rather, we relied on their confirmation that they obeyed the study protocol. We also did not measure urine secretion.

5. Conclusions

We determined the impact of a carbohydrate-enriched drink (NutriciaTM Pre-op®) on hemodynamical parameters in fasting healthy individuals. We have proven that consuming this drink did not impact the volunteers' hemodynamic status.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11030825/s1, Table S1: Comparison of impedance cardiography (ICG) parameters.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data used to support the findings of this study are included within the article or are available from the corresponding author upon request.

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References

1. Maltby, J.R. Fasting from midnight—The history behind the dogma. *Best Pract. Res. Clin. Anaesthesiol.* **2006**, *20*, 363–378. [CrossRef] [PubMed]
2. Weimann, A.; Braga, M.; Carli, F.; Higashiguchi, T.; Hübner, M.; Klek, S.; Laviano, A.; Ljungqvist, O.; Lobo, D.N.; Martindale, R.G.; et al. ESPEN practical guideline: Clinical nutrition in surgery. *Clin. Nutr.* **2021**, *40*, 4745–4761. [CrossRef] [PubMed]
3. Anesthesiologists, A.S. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures. *Anesthesiology* **2017**, *126*, 376–393.
4. El-Sharkawy, A.M.; Daliya, P.; Lewis-Lloyd, C.; Adiamah, A.; Malcolm, F.L.; Boyd-Carson, H.; Couch, D.; Herrod, P.J.; Hossain, T.; Couch, J.; et al. Fasting and surgery timing (FaST) audit. *Clin. Nutr.* **2021**, *40*, 1405–1412. [CrossRef]
5. de Aguilar-Nascimento, J.E. Reducing preoperative fasting time: A trend based on evidence. *World J. Gastrointest. Surg.* **2010**, *2*, 57. [CrossRef]
6. Li, Y.; He, R.; Ying, X.; Hahn, R.G. Dehydration, Hemodynamics and fluid volume optimization after induction of general anesthesia. *Clinics* **2014**, *69*, 809–816. [CrossRef]
7. Gutierrez, D.S.G.; Gutiérrez, J.J.V.; Ruiz-Villa, J.O. Cardiac output estimation based on arterial and venous blood gas analysis: Proposal of a monitoring method. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 179–183. [CrossRef]
8. Miller, T.E.; Roche, A.M.; Mythen, M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery after Surgery (ERAS). *Can. J. Anesth.* **2015**, *62*, 158–168. [CrossRef]
9. Nygren, J.; Thacker, J.; Carli, F.; Fearon, K.C.; Norderval, S.; Lobo, D.N.; Ljungqvist, O.; Soop, M.; Ramirez, J. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced recovery after surgery (ERAS®) society recommendations. *World J. Surg.* **2013**, *31*, 801–816. Available online: https://pubmed.ncbi.nlm.nih.gov/23052796/ (accessed on 1 November 2020). [CrossRef]
10. Nygren, J.; Thorell, A.; Ljungqvist, O. Preoperative oral carbohydrate therapy. *Curr. Opin. Anaesthesiol.* **2015**, *28*, 364–369. [CrossRef]
11. Nygren, J. The metabolic effects of fasting and surgery. *Best Pract. Res. Clin. Anaesthesiol.* **2006**, *20*, 429–438. Available online: https://pubmed.ncbi.nlm.nih.gov/17080694/ (accessed on 31 October 2020). [CrossRef]
12. Smith, M.D.; Mccall, J.; Plank, L.; Herbison, G.P.; Soop, M.; Nygren, J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst. Rev.* **2014**, *14*, CD009161. [CrossRef] [PubMed]

13. Amer, M.A.; Smith, M.D.; Herbison, G.P.; Plank, L.D.; McCall, J.L. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. *Br. J. Surg.* **2017**, *104*, 187–197. [CrossRef] [PubMed]
14. Kukliński, J.; Steckiewicz, K.P.; Sekuła, B.; Aszkiełowicz, A.; Owczuk, R. The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: A volunteer randomized study. *Perioper. Med.* **2021**, *10*, 27. [CrossRef] [PubMed]
15. Pang, Q.; Hendrickx, J.; Liu, H.L.; Poelaert, J. Contemporary perioperative haemodynamic monitoring. *Anaesthesiol. Intensive Ther.* **2019**, *51*, 147–158. [CrossRef]
16. Mansouri, S.; Alhadidi, T.; Chabchoub, S.; Ben Salah, R. Impedance cardiography: Recent applications and developments. *Biomed. Res.* **2018**, *29*, 3542–3552. [CrossRef]
17. Cleymaet, R.; Scheinok, T.; Maes, H.; Stas, A.; Malbrain, L.; De Laet, I.; Schoonheydt, K.; Dits, H.; van Regenmortel, N.; Mekeirele, M.; et al. Prognostic value of bioelectrical impedance analysis for assessment of fluid overload in ICU patients: A pilot study. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 10–17. [CrossRef]
18. Gijsen, M.; Simons, E.; de Cock, P.; Malbrain, M.L.N.G.; Wauters, J.; Spriet, I. Reproducibility of fluid status measured by bioelectrical impedance analysis in healthy volunteers: A key requirement to monitor fluid status in the intensive care unit. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 193–199. [CrossRef]
19. Kim, J.-Y.; Kim, B.-R.; Lee, K.-H.; Kim, K.-W.; Kim, J.-H.; Lee, S.-Y.; Kim, K.-T.; Choe, W.-J.; Park, J.-S.; Kim, J.-W. Comparison of cardiac output derived from FloTracTM/VigileoTM and impedance cardiography during major abdominal surgery. *J. Int. Med. Res.* **2013**, *41*, 1342–1349. [CrossRef]
20. Scherhag, A.; Kaden, J.J.; Kentschke, E.; Sueselbeck, T.; Borggrefe, M. Comparison of impedance cardiography and thermodilution-derived measurements of stroke volume and cardiac output at rest and during exercise testing. *Cardiovasc. Drugs Ther.* **2005**, *19*, 141–147. [CrossRef]
21. Kim, G.E.; Kim, S.Y.; Kim, S.J.; Yun, S.Y.; Jung, H.H.; Kang, Y.S.; Koo, B.N. Accuracy and efficacy of impedance cardiography as a non-invasive cardiac function monitor. *Yonsei Med. J.* **2019**, *60*, 735–741. [CrossRef] [PubMed]
22. Fuller, H.D. The validity of cardiac output measurment by thoracic impedance: A meta-analysis. *Clin. Investig. Med.* **1992**, *15*, 103–112.
23. Raaijmakers, E.; Faes, T.J.C.; Scholten, R.J.P.M.; Goovaerts, H.G.; Heethaar, R.M. A meta-analysis of three decades of validating thoracic impedance cardiography. *Crit. Care Med.* **1999**, *27*, 1203–1213. [CrossRef] [PubMed]
24. Peyton, P.J.; Chong, S.W. Minimally invasive measurement of cardiac output during surgery and critical care: A meta-analysis of accuracy and precision. *Anesthesiology* **2010**, *113*, 1220–1235. Available online: http://pubs.asahq.org/anesthesiology/article-pdf/113/5/1220/252362/0000542-201011000-00037.pdf (accessed on 26 January 2022). [CrossRef]
25. Zhang, Y.; Wang, Y.; Shi, J.; Hua, Z.; Xu, J. Cardiac output measurements via echocardiography versus thermodilution: A systematic review and meta-analysis. *PLoS ONE* **2019**, *14*, e0222105. [CrossRef]
26. Daralammouri, Y.; Ayoub, K.; Badrieh, N.; Lauer, B. A hybrid approach for quantifying aortic valve stenosis using impedance cardiography and echocardiography. *BMC Cardiovasc. Disord.* **2016**, *16*, 19. [CrossRef] [PubMed]
27. Liu, F.; Tsang, R.C.C.; Jones, A.Y.M.; Zhou, M.; Xue, K.; Chen, M.; Wang, Y. Cardiodynamic variables measured by impedance cardiography during a 6-minute walk test are reliable predictors of peak oxygen consumption in young healthy adults. *PLoS ONE* **2021**, *16*, e0252219. [CrossRef]
28. Kubota, S.; Endo, Y.; Kubota, M.; Ishizuka, Y.; Furudate, T. Effects of trunk posture in Fowler's position on hemodynamics. *Auton. Neurosci. Basic Clin.* **2015**, *189*, 56–59. [CrossRef]
29. Wu, T.W.; Lien, R.I.; Seri, I.; Noori, S. Changes in cardiac output and cerebral oxygenation during prone and supine sleep positioning in healthy term infants. *Arch. Dis. Child. Fetal Neonatal Ed.* **2017**, *102*, F483–F489. [CrossRef]
30. Ma, M.; Noori, S.; Maarek, J.M.; Holschneider, D.P.; Rubinstein, E.H.; Seri, I. Prone positioning decreases cardiac output and increases systemic vascular resistance in neonates. *J. Perinatol.* **2015**, *35*, 424–427. [CrossRef]
31. Paviotti, G.; Todero, S.; Demarini, S. Cardiac output decreases and systemic vascular resistance increases in newborns placed in the left-lateral position. *J. Perinatol.* **2017**, *37*, 563–565. [CrossRef] [PubMed]
32. Borodiciene, J.; Gudaityte, J.; Macas, A. Lithotomy versus jack-knife position on haemodynamic parameters assessed by impedance cardiography during anorectal surgery under low dose spinal anaesthesia: A randomized controlled trial. *BMC Anesthesiol.* **2015**, *15*, 74. [CrossRef] [PubMed]
33. Kendrick, J.B.; Kaye, A.D.; Tong, Y.; Belani, K.; Urman, R.D.; Hoffman, C.; Liu, H. Goal-directed fluid therapy in the perioperative setting. *J. Anaesthesiol. Clin. Pharmacol.* **2019**, *35*, S29–S34. [PubMed]
34. Anandraja, R.; Ranjith Karthekeyan, B. A comparative study of haemodynamic effects of single-blinded orotracheal intubations with intubating laryngeal mask airway, Macintosh and McGrath video laryngoscopes. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 30–36. [CrossRef] [PubMed]
35. Bijker, J.B.; Van Klei, W.A.; Kappen, T.H.; Van Wolfswinkel, L.; Moons, K.G.M.; Kalkman, C.J. Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* **2007**, *107*, 213–220. [CrossRef]
36. Zepeda-Najar, C.; Palacios-Astudillo, R.X.; Chávez-Hernández, J.D.; Lino-Silva, L.S.; Salcedo-Hernández, R.A. Prognostic impact of microsatellite instability in gastric cancer. *Wspolczesna Onkol.* **2021**, *25*, 68–71. [CrossRef]

37. Soop, M.; Nygren, J.; Thorell, A.; Weidenhielm, L.; Lundberg, M.; Hammarqvist, F.; Ljungqvist, O. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. *Clin. Nutr.* **2004**, *23*, 733–741. [CrossRef]
38. Yuill, K.A.; Richardson, R.A.; Davidson, H.I.M.; Garden, O.J.; Parks, R.W. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively—A randomised clinical trial. *Clin. Nutr.* **2005**, *24*, 32–37. [CrossRef]
39. Hausel, J.; Nygren, J.; Lagerkranser, M.; Hellström, P.M.; Hammarqvist, F.; Almström, C.; Lindh, A.; Thorell, A.; Ljungqvist, O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth. Analg.* **2001**, *93*, 1344–1350. [CrossRef]
40. Alves, D.R.; Ribeiras, R. Does fasting influence preload responsiveness in ASA 1 and 2 volunteers? *Braz. J. Anesthesiol.* **2017**, *67*, 172–179. [CrossRef]
41. Rontoyanni, V.G.; Werner, K.; Sanders, T.A.B.; Hall, W.L. Differential acute effects of carbohydrate- and protein-rich drinks compared with water on cardiac output during rest and exercise in healthy young men. *Appl. Physiol. Nutr. Metab.* **2015**, *40*, 803–810. [CrossRef] [PubMed]

Perioperative carbohydrate loading in patients undergoing one-day surgery. A systematic review of randomized controlled trials

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Abstract

Introduction: *It is suggested that preoperative carbohydrate loading may have beneficial effects, which is emphasised in Enhanced Recovery After Surgery protocols (ERAS). Recent data confirmed that carbohydrate loading shortens length of hospital stay.*
Aim: *In this systematic review we aimed to determine whether carbohydrate loading have positive effects in patients undergoing 1-day surgery.*
Material and methods: *We searched 5 databases and identified some randomized controlled trials which were reviewed independently by two reviewers. In the end 6 RCTs were included, involving 411 patients. Studies compared effects of carbohydrate loading vs. fasting and/or placebo on the following outcomes: thirst, hunger, postoperative nausea and vomiting (PONV), fatigue, pain and postoperative insulin resistance. In most cases data are inconclusive as studies reported opposite results.*
Conclusions: *It seems that carbohydrate loading did not have a significant impact when compared to fasting or placebo. Preoperative carbohydrate loading seems not to have significant benefits over fasting or placebo in patients qualified for 1-day surgery.*

Key words: *enhanced recovery after surgery, carbohydrate loading, pre-op, fasting, 1-day surgery, laparoscopic cholecystectomy.*

Introduction

One of many aspects of Enhanced Recovery After Surgery protocols (ERAS) is perioperative nutrition and fluid management. Preoperative fasting and surgical injury increases insulin resistance leading to postoperative hyperglycaemia and further complications, such as impaired wound healing. This lengthens hospital stay [1]. However those detrimental metabolic effects can be alleviated to some degree with preoperative administration of a carbohydrate-rich drink [2], which is recommended by both ERAS and ESPEN guidelines [3, 4]. Postoperative nausea and vomiting is another factor known for delaying discharge after surgery, fortunately it can be lessened with a carbohydrate rich drink as well [5, 6]. The carbohydrate drink also improves general well-being after surgery [6, 7].

There are four meta-analyses assessing benefits of the preoperative carbohydrate drink [8–11], each proving that carbohydrate loading reduces length of hospital stay. However two of them, including the most recent one, show no difference compared to placebo [10, 11]. We have chosen to focus on day-care surgery to take a closer look on secondary outcomes as those previously mentioned reviews were inconclusive in that regard.

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Aim

The aim of this review was to determine how preoperative carbohydrate treatment impacts on recovery after elective ambulatory surgery compared to placebo.

Material and methods

Search strategy

The Medline, EBSCO, Scopus, Web of Science (WoS) and Cochrane databases were systematically and comprehensively searched in October 2021 according to Prisma guidelines. The search protocol was prospectively registered in the International prospective register of systematic reviews (PROSPERO) – CRD42021284397. Two reviewers (JK, KPS) independently evaluated each paper. If any disagreement occurred, the third reviewer (RO) was involved. The following data were extracted: title, first author, publication year, number of patients, patient age, sex, body mass index (BMI) and ASA status, inclusion criteria, exclusion criteria, intervention type, allocation, measured outcomes, amount of carbohydrates administered, type of surgery, duration of anaesthesia and surgery.

Search query

The following search query was used to extract articles from databases: ((preoperative or perioperative) and (carbohydrate or CHO or nutricia/nutrition or carbohydrates or maltodextrin or carbohydrate rich) and (drink or treatment or loading or oral or per os or load or administration)) and ((ambulatory or 1-day or elective or outpatient or ambu* or electiv* or fast-track) and (surgery or surgical procedures or procedure or sedation or anesthesia or surg* or general anesthesia)).

Type of studies

We included randomised clinical trials comparing carbohydrate loading with controls in patients over 18 years old undergoing elective ambulatory surgery. Patients undergoing ambulatory surgery receiving clear liquid or nothing were treated as controls.

Inclusion criteria

- randomised controlled trial,
- results published in English,
- participants not younger than 18 years old,
- general anaesthesia or general anaesthesia combined with regional anaesthesia,
- any ambulatory or 1-day surgery,
- elective surgery,
- subjects received at least 45 g of the carbohydrate drink *per os* before surgery; controls received other clear liquid or nothing,
- hospitalisation under 24 h,
- results published in a reviewed journal.

Exclusion criteria

- not fulfilling inclusion criteria,
- basic science research,
- single-arm studies.

Main outcome

Comparison of the effectiveness of preoperative oral carbohydrate and fasting.

Additional outcomes

1. Metabolic effect
2. Impact on fatigue and general well-being
3. Impact on nausea and vomiting
4. Other outcomes: as defined and measured by trials' authors.

Results

Search results

Databases yielded 3467 results, from those 2385 were screened for eligibility criteria based on the titles which gave 240 papers. Those were screened for eligibility criteria based on abstracts which have left 74 papers which were read in full text. After careful consideration against inclusion criteria, 6 papers were included in the review. Prisma flow diagram presents study search in detail (Figure 1).

Characteristics of included studies

Six studies published in 2012–2020 were included in the study [12–17]. The studies were conducted in Finland, Turkey, India and Brazil. Majority of patients were females under 50 years old who underwent elective laparoscopic cholecystectomy. Patients had ASA status I–II. In all studies patients received the amount of carbohydrates recommended by ERAS guidelines. The comparator was either fasting place-

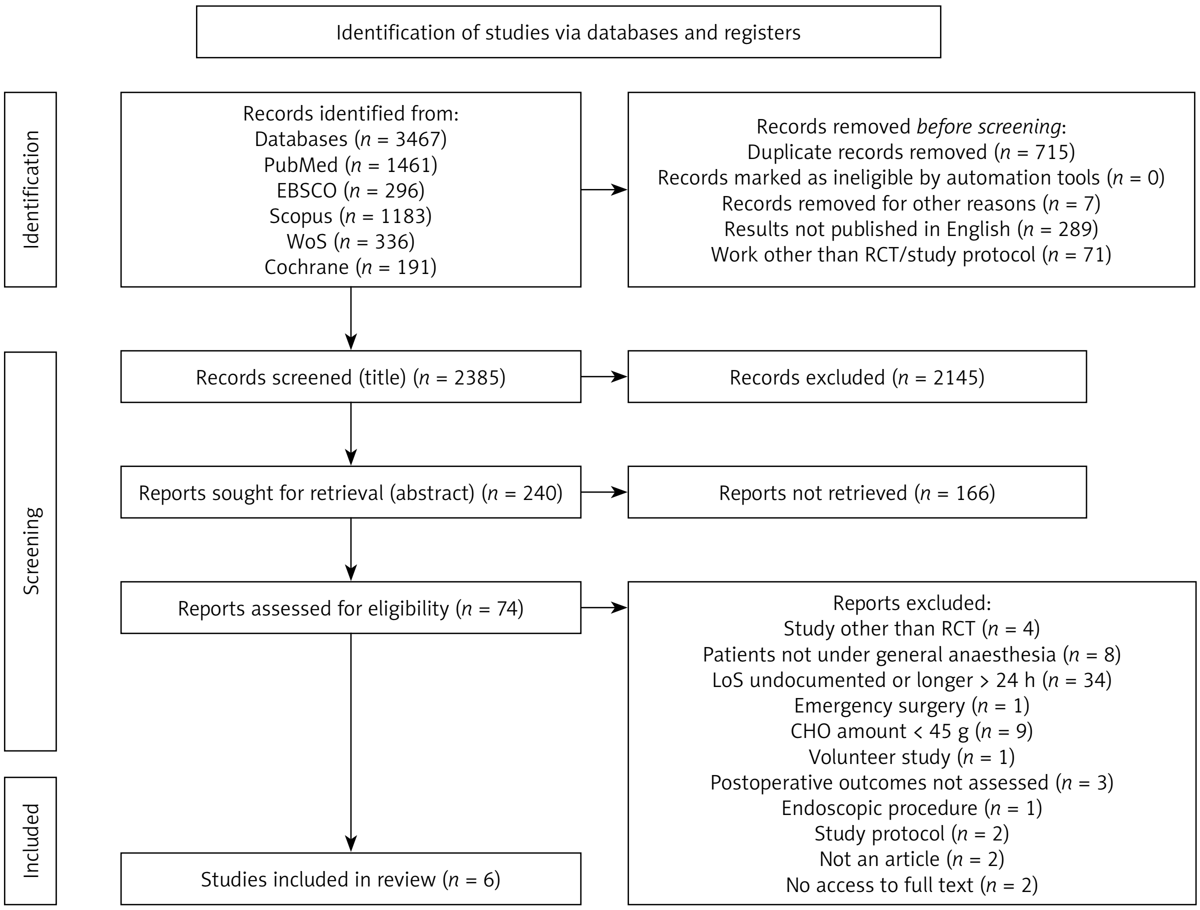

Figure 1. Prisma flow diagram

CHO – carbohydrates, LOS – length of stay, RCT – randomised controlled trial, WoS – Web of Science.

bo or carbohydrates + glycine (GLN group). Detailed characteristics of the studies are presented in Table I.

Quality assessment

We followed Cochrane Collaboration guidelines regarding bias assessment. Each paper was assessed independently by two reviewers. Five databases were searched to ensure that all matching papers were included. In risk of bias assessment, several parameters were included: (I) random sequence generation, (II) allocation concealment, (III) blinding of participants and personnel, (IV) blinding of outcome assessment, (V) incomplete outcome data, (VI) selective reporting, (VII) other potential threats to validity. All studies have met baseline criteria for quality assessment. Typically, there were no issues regarding random sequence generation, however in most cases allocation concealment was not described. Unfortunately majority of the studies were single blinded, or blinding was not reported, also only one study by Helminen *et al.* published the protocol. We have not found other potential risks within the studies. A summary of biased assessment for each study is presented in Table II.

Thirst and hunger

Three studies examined whether carbohydrate loading can alleviate thirst and hunger [14–16]. Helminen *et al.* used VAS scale (0–100) while Gok *et al.* and Yildiz *et al.* measured nausea incidence. In studies by Gök *et al.* and Yildiz *et al.*, the carbohydrate-rich drink decreased thirst preoperatively or preoperatively and postoperatively. However, Helminen et al. did not support that result (Table III).

In studies by Gök *et al.* and Yildiz *et al.*, administration of a carbohydrate-rich drink decreased hunger preoperatively or preoperatively and postoperatively. However, Helminen *et al.* did not support that result (Table IV).

Table I. Characteristics of included studies

Authors	Location	Group	Participants	Total amount of carbohydrates administered [g]	Amount of carbohydrates administered 2 h before surgery	Age (SD) [IQR]	Females [%]	ASA scale	Type of surgery	Reference
Helminen *et al.*	Oulu, Finland	CHO	*n* = 57	67	67	47 (13)	84	I–II	Laparoscopic cholecystectomy	[16]
		Fasting	*n* = 56	0	0	46 (11)	77			
Singh *et al.*	Chandigarh, India	CHO	*n* = 40	75	25	43.2 (15.85)	85	Not reported	Laparoscopic cholecystectomy	[17]
		Placebo	*n* = 40	0	0	43.72 (15.4)	75			
		Fasting	*n* = 40	0	0	44.4 (11.45)	75			
Gök *et al.*	Turkey	CHO	*n* = 21	125	25	46.76 (11.1)	86	I–II	Laparoscopic cholecystectomy	[15]
		Placebo	*n* = 21	0	0	50 (14.24)	95			
Dock-Nascimento *et al.*	Cuiaba, Brazil	Control	*n* = 12	0	0	40 (3.3)	100	I–II	Laparoscopic cholecystectomy	[12]
		Placebo	*n* = 12	0	0	40 (3.3)	100			
		CHO	*n* = 12	75	25	35 (4.1)	100			
		GLN	*n* = 12	75	25	43 (3.9)	100			
Dock-Nascimento *et al.*	Cuiaba, Brazil	Fasting	*n* = 9	0	0	42* [18–62]	Not reported	I–II	Laparoscopic cholecystectomy	[13]
		CHO	*n* = 10	75	25					
		GLN	*n* = 9	75	25					
Yildiz *et al.*	Ankara, Turkey	CHO	*n* = 30	150	50	47.63 (8.83)	83	I–II	Laparoscopic cholecystectomy	[14]
		Fasting	*n* = 30	0	0	43.56 (9.82)	73			

**Age was reported for the whole cohort without distinguishing between groups. ASA – American Society of Anaesthesiologists, CHO – patients receiving carbohydrates, GLN – patients receiving carbohydrates and glycine, IQR – interquartile range, SD – standard deviation.*

Nausea and vomiting

For studies including nausea as examined outcomes [14–17], Helminen *et al.* and Singh *et al.* used VAS scale while Gök *et al.* and Yildiz *et al.* measured nausea incidence. Data are inconsistent as Helminen *et al.* and Yildiz *et al.* did not observe any significant changes in nausea intensity. Meanwhile Singh *et al.* reported that in the early postoperative period nausea was less intensive in the group which received carbohydrates preoperatively, oppositely Gök *et al.* determined that nausea was more frequent in the pre-op group. Detailed results are presented in Table V.

Singh *et al.* and Gök *et al.* examined impact of carbohydrate administration on emesis occurrence [15, 17]. Singh *et al.* determined that vomiting occurred less frequently only in the first 4 h postoperatively, however this observation was not supported by the study of Gök *et al.* It seems that pre-op carbohydrate loading does not have a significant impact on vomiting occurrence more than 4 h after surgery. Moreover, Helminen *et al.* reported that there were no differences regarding need for antiemetics administration between carbohydrates and fasting group ($p = 0.84$). Results are presented in Table VI.

Pain

Two studies included in the analysis determined the effect of carbohydrates administration on the pain level post-operatively [16, 17]. Helminen *et al.*

Table II. Risk of biases in selected studies

Authors	Random sequence generation	Allocation conceal-ment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other risks	Reference
Helminen *et al*.	Low risk	Low risk	High risk – single blinded	Unclear –not described	Low risk – balanced dropouts	Low risk	Low risk	[16]
Singh *et al*.	Low risk	Unclear – not described	Unclear – not described	Unclear – not described	Unclear – no information regarding dropouts	Unclear – protocol not published	Low risk	[17]
Gök *et al*.	Low risk	Unclear – not described	Unclear – not described	Unclear – not described	Unclear – no information regarding dropouts	Unclear – protocol not published	Low risk	[15]
Dock-Nasci-mento *et al*.	Low risk	Unclear – not described	High risk – surgeons were not blinded	Unclear – not described	Low risk – balanced dropouts	Unclear – protocol not published	Low risk	[12]
Dock-Nasci-mento *et al*.	Unclear – not described	Unclear – not described	High risk – single blinded	Unclear – not described	Low risk – balanced dropouts	Unclear – protocol not published	Low risk	[13]
Yildiz *et al*.	Low risk	Unclear – not described	High risk – single blinded	Unclear – not described	Low risk – no dropouts	Unclear – protocol not published	Low risk	[14]

measured pain with a visual analog scale (VAS; 0–100), Singh *et al.* also used VAS, however with a span of 0–10. In the study of Helminen *et al*., no changes between groups had been found. They also did not observe differences in demand for pain medication and opioids between groups (p = 0.94 and p = 0.95, respectively). Contrarily Singh *et al*. reported that pain intensity was lower in the CHO group in the first 12 h postoperatively. Based on those two studies it cannot be concluded whether the carbohydrate-rich drink administration has beneficial effects on pain alleviation. Detailed results of included studies are presented in Table VII.

Tiredness

Two studies included tiredness in their outcomes [14, 16]. Helminen *et al.* used the VAS scale (0–100), whereas Yildiz *et al.* measured tiredness incidence. It seems that the carbohydrate-rich drink did not impact tiredness after surgery. Data regarding the preoperative period are inconclusive as studies reported opposite results (Table VIII).

Impact on metabolism

Three studies measured impact of pre-op carbohydrate loading on glucose and/or insulin levels [12, 13, 16]. In all studies no differences between groups were found (Table IX).

Other outcomes

Some outcomes have been described only in one study, here we discuss the selected few. Helminen *et al.* did not observe any significant changes between groups regarding mouth dryness, time to be able to drink, eat, ambulate or discharge [16]. Dock-Nascimento *et al.* investigated selected biochemical parameters and they found significant differences between the groups in HOMA-IR, albumin, C-reactive protein and interleukin 6 levels [12]. Another study by Dock-Nascimento *et al.* found that there are no differences in gastric residual volume between groups [13]. Yildiz *et al.* have found that weakness, malaise and concentration difficulty are less prominent in patients receiving a carbohydrate-rich drink [14].

Table III. Summary of the results regarding thirst occurrence and intensity

Study	Group	Partici-pants	Thirst pre-op. *n* (%) Median [IQR]	Thirst 0-4 h post-op. *n* (%) Median [IQR]	Thirst 4–12 h post-op. *n* (%) Median [IQR]	Thirst 12–24 h post-op. *n* (%) Median [IQR]	*P*-values	Reference
Helminen *et al.*	CHO	*n* = 57	22 [6–50]	41 [20–60]	28 [9–61]	12 [0–50]	0.682	[16]
	Fasting	*n* = 56	40 [8–63]	46 [24–70]	20 [0–50]	10 [0–50]		
Gök *et al.*	CHO	*n* = 21	12 (57.1%)	n/a	n/a	n/a	0.032	[15]
	Placebo	*n* = 21	19 (90.5%)	n/a	n/a	n/a		
Yildiz *et al.*	CHO	*n* = 30	3 (10%)	13 (43.3%)	n/a	4 (13.3%)	< 0.05 (preoperatively) < 0.05 (0–4 h) > 0.05 (12–24 h)	[14]
	Fasting	*n* = 30	26 (86.7%)	30 (100%)	n/a	10 (33.3%)		

CHO – patients receiving carbohydrates, IQR – interquartile range, pre-op. – preoperatively, post-op. – postoperatively.

Table IV. Summary of the results regarding hunger occurrence and intensity

Study	Group	Partici-pants	Hunger pre-operatively *n* (%) Median [IQR]	Hunger 0–4 h post-op. *n* (%) Median [IQR]	Hunger 4–12 h post-op. *n* (%) Median [IQR]	Hunger 12–24 h post-op. *n* (%) Median [IQR]	*P*-values	Reference
Helminen *et al.*	CHO	*n* = 57	26 [2–48]	10 [0–34]	10 [0–34]	0 [0–8]	0.529	[16]
	Fasting	*n* = 56	30 [19–55]	5 [0–30]	5 [0–30]	0 [0–11]		
Gök *et al.*	CHO	*n* = 21	9 (42.9)	n/a	n/a	n/a	0.003	[15]
	Placebo	*n* = 21	19 (90.5%)	n/a	n/a	n/a		
Yildiz *et al.*	CHO	*n* = 30	1 (3.3%)	5 (16.7%)	n/a	4 (13.3)	< 0.05 (preoperatively) < 0.05 (0–4 h) > 0.05 (12–24 h)	[14]
	Fasting	*n* = 30	19 (63.3%)	26 (86.7%)	n/a	9 (30%)		

CHO – patients receiving carbohydrates, GLN – patients receiving carbohydrates and glycine, IQR – interquartile range, pre-op. – preoperatively, post-op. – postoperatively.

Discussion

In this review we included 6 studies with a total of 411 patients undergoing elective 1-day surgery. We aimed to determine whether perioperative carbohydrate-rich drink administration may be beneficial in this group. The results are inconclusive as some of the studies had opposite results.

Preoperative carbohydrate treatment is over 20-year-old idea, with first findings reported in the late 1990s [18, 19]. Over the years reduction in length of hospital stay caused by carbohydrate loading was confirmed in several meta-analyses [8–11]. However the exact mechanism of action remains uncertain as studies provide conflicting data regarding proposed rationale of increasing postoperative insulin sensitivity [8–11]. We chose to restrict the scope of this review to day-care surgery in order to improve homogeneity, allowing us to focus on outcomes considered as secondary in previous studies. Also, there is a significant gap in knowledge whether carbohydrate loading can be beneficial in relatively healthy individuals who are typically qualified to be 1-day cases. This proved futile as inconsistent findings across all the studies suggest that carbohydrate loading has little to no impact on measured parameters.

Table V. Summary of the results regarding nausea occurrence and intensity

Study	Group	Partici-pants	Nausea 0–4 h post-op. *n* (%) Median [IQR] Mean (SD)	Nausea 4–12 h post-op. *n* (%) Median [IQR] Mean (SD)	Nausea 12–24 h post-op. *n* (%) Median [IQR] Mean (SD)	*P*-values	Reference
Helminen *et al.*	CHO	*n* = 57	0 [0–14]	0 [0–4]	0 [0–3]	0.476	[16]
	Fasting	*n* = 56	0 [0–6]	0 [0–10]	0 [0–3]		
Singh *et al.*	CHO	*n* = 40	0.65 (0.7)	0.7 (0.823)	0.25 (0.439)	0.001 (0–4 h) 0.066 (4–12 h) 0.357 (12–24 h)	[17]
	Placebo	*n* = 40	1.3 (0.853)	0.83 (0.636)	0.43 (0.501)		
	Fasting	*n* = 40	1.23 (1.097)	1.05 (0.815)	0.35 (0.483)		
Gök *et al.*	CHO	*n* = 21	21 (100%)	15 (71.4%)	6 (28.6%)	0.048 (0–4 h) 0.014 (4–12 h) 0.093 (12–24 h)	[15]
	Placebo	*n* = 21	16 (76.25%)	6 (28.6%)	1 (4.8%)		
Yildiz *et al.*	CHO	*n* = 30	17 (56.7%)	n/a	1 (3.3%)	> 0.05 (4–12 h) > 0.05 (12–24 h)	[14]
	Fasting	*n* = 30	17 (56.7%)	n/a	(6.7%)		

CHO – patients receiving carbohydrates, IQR – interquartile range, SD – standard deviation, pre-op. – preoperatively, post-op. – postoperatively.

Table VI. Summary of the results regarding emesis occurrence

Study	Group	Participants	Vomiting 0–4 h post-op. *n* (%)	Vomiting 4–12 h post-op. *n* (%)	Vomiting 12–24 h post-op. *n* (%)	*P*-values	Reference
Singh *et al.*	CHO	*n* = 40	7 (17.5%)	3 (7.5%)	0 (0%)	0.0006 (0–4 h) 0.459 (4–12 h) 0.314 (12–24 h)	[17]
	Placebo	*n* = 40	17 (42.5%)	5 (12.5%)	1 (2.5%)		
	Fasting	*n* = 40	19 (47.5)	13 (32.5%)	1 (2.5)		
Gök *et al.*	CHO	*n* = 21	13 (61.9%)	7 (33.3%)	0 (0%)	0.122 (0–4 h) 0.130 (4–12 h) 0.999 (12–24 h)	[15]
	Placebo	*n* = 21	7 (33.3%)	2 (9.5%)	0 (0%)		

CHO – patients receiving carbohydrates, IQR – interquartile range, SD – standard deviation, pre-op. – preoperatively, post-op. – postoperatively.

Table VII. Summary of the results regarding pain intensity

Study	Group	Pain 0–4 h post-op. Median [IQR] Mean (SD)	Pain 4–12 h post-op. Median [IQR] Mean (SD)	Pain 12–24 h post-op. Median [IQR] Mean (SD)	*P*-values	Reference
Helminen *et al.*	CHO	35 [14–38]	20 [2–40]	20 [8–38]	0.012	[16]
	Fasting	30 [11–50]	23 [8–40]	20 [3–40]		
Singh *et al.*	CHO	5.75 (1.918)	3.53 (1.633)	1.95 (0.714)	0.001 (0–4 h) 0.005 (4–12 h) 0.223 (12–24 h)	[17]
	Placebo	7.13 (1.067)	4.08 (1.289)	2.08 (0.656)		
	Fasting	6.95 (0.959)	4.65 (1.442)	2.25 (0.809)		

CHO – patients receiving carbohydrates, IQR – interquartile range, SD – standard deviation, pre-op. – preoperatively, post-op. – postoperatively.

The studies included in this review seem to demonstrate that the carbohydrate-rich drink did not have a significant impact on thirst and hunger. Similarly, Li *et al*. showed inconsistent results regarding hunger. As for thirst, they observed a significant difference when compared to fasting but not when compared to placebo [9]. With postoperative nausea and vomiting being one of the most common side effects of general anaesthesia [20] early findings about carbohydrate treatment seemed promising [21]. However, our results did not support this as no significant differences were found. This is consistent

Table VIII. Summary of the results regarding tiredness

Study	Group	Participants	Tiredness pre-operatively *n* (%) Median [IQR]	Tiredness 0–4 h post-op. *n* (%) Median [IQR]	Tiredness 4–12 h post-op. *n* (%) Median [IQR]	Tiredness 12–24 h post-op. *n* (%) Median [IQR]	*P*-values	Reference
Helminen *et al.*	CHO	*n* = 57	30 [10–56]	49 [20–70]	42 [8–70]	20 [4–48]	0.582	[16]
	Fasting	*n* = 56	20 [5–46]	53 [30–61]	40 [10–50]	25 [0–46]		
Yildiz *et al.*	CHO	*n* = 30	4 (13.3%)	19 (63.3%)	n/a	9 (42.9%)	< 0.05 (preoperatively) > 0.05 (0–4 h) > 0.05 (12–24 h)	[14]
	Fasting	*n* = 30	14 (46.7%)	21 (70%)	n/a	13 (43.3%)		

CHO – patients receiving carbohydrates, GLN – patients receiving carbohydrates and glycine, IQR – interquartile range, SD – standard deviation, pre-op. – preoperatively, post-op. – postoperatively.

Table IX. Summary of the results regarding pre- and post-operative levels of glucose and insulin

Study	Group	Pre-op. glucose [mmol] Mean (SD)	Post-op. glucose [mmol] Mean (SD)	*P*-values for glucose	Pre-op. insulin [IU/ml] Mean (SD)	Post-op. [IU/ml] Mean (SD)	*P*-values for insulin	Reference
Helminen *et al.*	CHO	6.0 (1.6)	6.4 (1.1)	0.1 (preoperative) 0.37 (postoperative)	n/a	n/a	n/a	[16]
	Fasting	5.4 (0.5)	6.4 (1.1)		n/a	n/a	n/a	
Dock-Nascimento *et al.*	Control	4.4 (0.06)	6.1 (0.3)	0.16 (preoperative)	10.6 (2.1)	9.7 (2.4)	0.17 (preoperative)	[12]
	Placebo	4.3 (0.11)	5.8 (0.2)		8.1 (1.0)	6.4 (0.9)		
	CHO	4.3 (0.2)	5.9 (0.3)		13.3 (4.5)	8.5 (1.2)		
	GLN	4.3 (0.2)	5.7 (0.3)		9.6 (1.0)	9.9 (1.9)		
Dock-Nascimento *et al.*	Fasting	4.5 (0.1)	6.6 (0.2)	> 0.05 for all comparisons between groups	12.0 (3.2)	13.0 (3.6)	> 0.05 for all comparisons between groups	[13]
	CHO	4.3 (0.2)	6.0 (0.4)		18.6 (5.3)	8.6 (1.4)		
	GLN	4.3 (0.2)	5.4 (0.4)		8.0 (0.8)	6.5 (0.7)		

with previous analyses [8–11] and guidelines [22]. Considering that safe, effective painkillers are readily available and routinely administered during and after general anaesthesia, it is difficult to assess whether carbohydrate loading has any impact on pain response. Consequently, no significant difference in pain response was found. To the best of our knowledge, it is the first comprehensive assessment of such kind. Moreover, carbohydrate loading has no impact on either glucose or insulin levels. This is unexpected as alleviating postoperative insulin resistance was one of reasons to consider preoperative carbohydrate treatment in the first place [2, 18, 23]. Those results fall in line with previous works [8–11]. Lastly carbohydrate treatment did not affect postoperative tiredness, which is coherent with previous findings [10, 11].

Our work, being a review, is only as good as the included studies and while they met baseline quality criteria, several limitations should be mentioned. The amount of carbohydrates used differs between studies (67–150 g), though all studies fulfilled ERAS guidelines in this matter. Authors used visual analog scales and incidence reporting, as one could expect when working with parameters of such subjective nature. Those methods rely heavily on patients' compliance, which in itself is a source of discrepancies, even more so considering side effects of general anaesthesia. As for postoperative insulin resistance, none of the studies used hyperinsulinemic-euglycemic clamp method. Considering the short hospital stay there were no follow-up; nonetheless no readmissions were reported.

Interestingly, there seems to be no advantages of using the carbohydrate-rich drink over placebo for several outcomes. Usually artificially flavoured water was used for this purpose. Given the fact that the carbohydrate-rich drink affects neither hydration [24] nor hemodynamic parameters [25], nor causes significant metabolic changes, any beneficial findings could be associated with a psychosomatic effect. However carbohydrates have been proven not to alter mood in any significant way in healthy adults [26]. While current guidelines recommend carbohydrate loading, any clear liquid, with or without carbohydrate content, is allowed for up to 2 h before surgery [3]. This gives an opportunity to pursue a more cost-effective alternative to meticulously manufactured carbohydrate-rich drinks. However, this idea should be further examined and confirmed.

Conclusions

The quality of evidence regarding preoperative carbohydrate loading in patients qualified for one-day case is relatively low. However, it seems that this procedure does not have beneficial effects.

Conflict of interest

The authors declare no conflict of interest.

References

1. Nygren J. The metabolic effects of fasting and surgery. Best Practice and Research: Clinical Anaesthesiology, 2006. https://pubmed.ncbi.nlm.nih.gov/17080694/ (accessed October 31, 2020).
2. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. Proc Nutr Soc 2002; 61: 329-36.
3. Weimann A, Braga M, Carli F, et al. ESPEN practical guideline: clinical nutrition in surgery. Clin Nutr 2021; 40: 4745-61.
4. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). Canad J Anesth 2015; 62: 158-68.
5. Hausel J, Nygren J, Thorell A, et al. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg 2005; 92: 415-21.
6. Sarin A, Chen LL, Wick EC. Enhanced recovery after surgery – preoperative fasting and glucose loading – a review. J Surg Oncol 2017; 116: 578-82.
7. Nygren JTA, Ljungqvist O, Nygren J, et al. Are there any benefits from minimizing fasting and optimization of nutrition and fluid management for patients undergoing day surgery? Curr Opin Anaesthesiol 2007; 20: 540-4.
8. Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr 2013; 32: 34-44.
9. Li L, Wang Z, Ying X, et al. Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis. Surg Today 2012; 42: 613-24.
10. Smith MDD, Mccall J, Plank L, et al. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. Cochrane Database Syst Rev 2014; 8: CD009161.
11. Amer MA, Smith MD, Herbison GP, et al. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. Br J Surg 2017; 104: 187-97.
12. Dock-Nascimento DB, De Aguilar-Nascimento JE, Magalhaes Faria MS, et al. Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: a controlled randomized trial. J Parent Enteral Nutr 2012; 36: 43-52.
13. Dock-Nascimento DB, Aguilar-Nascimento JE de, Linetzky Waitzberg D. Ingestion of glutamine and maltodextrin two hours preoperatively improves insulin sensitivity after surgery: a randomized, double blind, controlled trial. Rev Col Bras Cir 2012; 39: 449-55.
14. Yildiz H, Gunal SE, Yilmaz G, Yucel S. Oral carbohydrate supplementation reduces preoperative discomfort in laparoscopic cholecystectomy. J Investig Surg 2013; 26: 89-95.
15. Gök MA, Kafadar MT, Gok MA, et al. Effects of preoperative oral carbohydrate loading on preoperative and postoperative comfort in patients planned to undergo elective cholecystectomy: a prospective randomized controlled clinical trial. Iran Red Cresc Med J 2020; 22. https://doi.org/10.32592/ircmj.2020.22.11.107.
16. Helminen H, Branders H, Ohtonen P, Saarnio J. Effect of pre-operative oral carbohydrate loading on recovery after day-case cholecystectomy: a randomised controlled trial. Eur J Anaesthesiol 2019; 36: 605-11.
17. Singh B, Dahiya D, Bagaria D, et al. Effects of preoperative carbohydrates drinks on immediate postoperative outcome after day care laparoscopic cholecystectomy. Surg Endosc 2015; 29: 3267-72.
18. Nygren J, Soop M, Thorell A, et al. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. Clin Nutr 1998; 17: 65-71.
19. Nygren JO, Thorell A, Soop M, et al. Perioperative insulin and glucose infusion maintains normal insulin sensitivity after surgery. Am J Physiol 1998; 275: E140-8.
20. Öbrink E, Jildenstål P, Oddby E, Jakobsson JG. Post-operative nausea and vomiting: update on predicting the probability and ways to minimize its occurrence, with focus on ambulatory surgery. Int J Surg 2015; 15: 100-6.
21. Hausel J, Nygren J, Thorell A, et al. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg 2005; 92: 415-21.

22. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014; 118: 85-113.
23. Soop M, Nygren J, Thorell A, et al. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. Clin Nutr 2004; 23: 733-41.
24. Kukliński J, Steckiewicz KP, Sekuła B, et al. The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: a volunteer randomized study. Periop Med 2021; 10: 27.
25. Kukliński J, Steckiewicz KP, Piwowarczyk SP, et al. Effect of carbohydrate-enriched drink compared to fasting on hemodynamics in healthy volunteers. a randomized trial. J Clin Med 2022; 11: 825.
26. Mantantzis K, Schlaghecken F, Sünram-Lea SI, Maylor EA. Sugar rush or sugar crash? A meta-analysis of carbohydrate effects on mood. Neurosci Biobehav Rev 2019; 101: 45-67.

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