

High Flow Nasal Cannula Therapy in the Emergency Department: Main Benefits in Adults, Pediatric Population and against COVID-19: A Narrative Review

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ABSTRACT

This review aims to summarize the literature's main results about high flow nasal cannula therapy (HFNC) HFNC benefits in the Emergency Department (ED) in adults and pediatrics, including new Coronavirus Disease (COVID-19). HFNC has recently been established as the usual treatment in the ED to provide oxygen support. Its use has been generalized due to its advantages over traditional oxygen therapy devices, including decreased nasopharyngeal resistance, washing out of the nasopharyngeal dead space, generation of positive pressure, increasing alveolar recruitment, easy adaptation due to the humidification of the airways, increased fraction of inspired oxygen and improved mucociliary clearance. A wide range of pathologies has been studied to evaluate the potential benefits of HFNC; some examples are heart failure, pneumonia, chronic pulmonary obstructive disease, asthma, and bronchiolitis. The regular use of this oxygen treatment is not established yet due to the literature's controversial results. However, several authors suggest that it could be useful in several pathologies that generate acute respiratory failure. Consequently, the COVID-19 irruption has generated the question of HFNC as a safety and effective treatment. Our results suggested that HFNC seems to be a useful tool in the ED, especially in patients affected by acute hypoxemic respiratory failure, acute heart failure, pneumonia, bronchiolitis, asthma and acute respiratory distress syndrome in patients affected by COVID-19. Its benefits in hypercapnic respiratory failure are more discussed, being only observed benefits in patients with mild-moderate disease. These results are based in clinical as well as cost-effectiveness outcomes. Future studies with largest populations are required to confirm these results as well as establish a practical guideline to use this device.

KEYWORDS

emergency; oxygen; respiratory diseases; high flow nasal cannula; pediatrics; COVID-19

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INTRODUCTION

Respiratory support is applied in the Emergency Department (ED) in several situations to provide adequate oxygenation and alveolar ventilation. Oxygen therapy (OT) consists of administering oxygen at a higher concentration than atmospheric. These concentration values are directly proportional to the altitude. Its indications include both acute and chronic pathologies in children and adults. The main objectives of oxygen therapy are: a) to treat and/or prevent hypoxemia; b) decrease myocardial demand; c) decrease respiratory effort, and d) treating pulmonary hypertension (1, 2). Historically, these situations have been treated with conventional oxygen therapy (COT), which flow is limited to less than 15 L/min. Besides, this system has other limitations, including poor precision of exact oxygen delivery, insufficient heating and humidifying, and poor tolerance (3).

Several authors have demonstrated the adverse effects of breathing dry air in a clinical and physiopathological way. In these situations, the nasal mucosa generates excessive water reducing the nasal mucociliary clearance (4). Cold air is also known to induce bronchoconstriction in patients with asthma and increased airway resistance in the upper airway to protect the lungs (5, 6). Also, it is observed that poor humidified gas cause acute damage and inflammation

in epithelial cells (7). Finally, unwarmed oxygen support is associated with mask discomfort, nasal and oral dryness, eye irritation, nasal and eye trauma, and gastric distention (8). However, these subjective clinical effects are not apparent, being discussed by several authors recently (9, 10).

High flow nasal cannula therapy (HFNC) was created to avoid all the COT limitations in respiratory failure treatment. This system may provide a gas flow up to 60 L/min, allowing a precise FiO_2 (11). This system consists of the administration of high oxygen flows through nasal cannulas and increased use in recent years due to its excellent tolerance and ease of use (12). The air is administered humidified (humidity between 95–100%) and warm (34–40 °C). This system's benefits are due to the gas's humidification and temperature, which reduces metabolic expenditure, improves compliance and lung elasticity and facilitates tolerance and comfort. Furthermore, other advantages of these systems are decreasing the nasopharyngeal dead space, lowering the inspiratory resistance, and providing a certain degree of pulmonary distension pressure (CPAP). Which is neither measurable nor adjustable, but has numerous benefits (decreases atelectasis, improves the ventilation/pulmonary perfusion (V/Q) ratio, and, in premature patients, reduces apnea) (2, 13). Table 1 summarizes the advantages, disadvantages, indications and contraindications of HFNC.

Tab. 1 Advantages, disadvantages, indications and contraindications of high flow nasal cannula therapy.

Advantages	Humidification and heat of the administered gas <ul style="list-style-type: none"> - Improves ciliary movement and clearance of secretions - Improves lung compliance and elasticity - Reduces metabolic work - Improves patient tolerance and comfort - Prevents dryness and damage to the nasal mucosa - Prevents reflex bronchoconstriction Nasopharyngeal dead space lavage <ul style="list-style-type: none"> - Displaces expired air from the naso and oropharynx <ul style="list-style-type: none"> • Reservoir for inspiration • Anatomical oxygen reservoirs - The total volume that the patient must move is less, reducing the work of breathing - Better control of (FiO_2 set = FiO_2 delivered) Decreases inspiratory resistance, thus decreasing the work of breathing Provides some degree of lung distending pressure (alveolar recruitment) <ul style="list-style-type: none"> - Variable, unpredictable, not adjustable - Reduces atelectasis - Improves ventilation/perfusion ratio - Reduces apneas in premature babies
Disadvantages	Side effects <ul style="list-style-type: none"> - Mild: runny nose, facial erosions, condensation of nasal prongs with low flows, meteorism and abdominal distention (assess nasogastric tube) - Severe: barotrauma (uncommon) if very high flows are generated or nostrils are obstructed by cannulae (special care in neonates and preterm newborns), nosocomial infection (system contamination)
Indications	Hypoxemic respiratory failure Mild-moderate hypercapnic respiratory failure Respiratory failure in immunocompromised Acute heart failure Asthma, bronchiolitis, pneumonia Withdrawal of invasive and non-invasive mechanical ventilation Preoxygenation and passive oxygenation in orotracheal intubation Patients in palliative situation
Contraindications	Uncooperative patient Agitated patient Recent nasal surgery or trauma Need to preserve airway

According to age, the flow rate of high-flow oxygen therapy differs, varying from 2–8 L/min in infants and range up to 60 L/min in adolescents and adults. This system's indications have increased in recent years, being accepted generically in moderate acute respiratory failure cases or in cases of hypoxemia that do not respond to conventional oxygen treatment (2, 14).

This review aims to summarize the primary uses of HFNC in both the pediatric and adult populations. The manuscript will be divided into the main pathologies where this system has been studied.

ACUTE HEART FAILURE

Acute heart failure (AHF) is a prevalent and life-threatening medical condition requiring hospital admission and adequate oxygen therapy (15). In the United States, one million ED admissions are due to this pathology every year (16). It has been found that 90% of these patients suffer dyspnea (17), observing in almost 50% hypoxemia, hypercapnia, acidosis, or a combination of these (18). In different AHF syndromes, respiratory failure is most frequently seen in acute cardiogenic pulmonary edema (CPO), in cardiogenic shock, and cases associated to other lung alterations, including respiratory infections, bronchial hyperresponsiveness, and exacerbation of chronic obstructive pulmonary disease (COPD) (19). The potential benefits of this technique in this entity are based in two mechanisms: a) due to the low level of positive end-expiratory pressure (PEEP) provided (<5 cmH₂O), which improves alveolar recruitment and tidal volume, contributing to alveoli clearance and to PaCO₂ decrease. However, this effect depends on airflow as well as on a closed mouth, being the last one often difficult to maintain in severe respiratory failure (20); and b) the capacity of HFNC to provide continuous washout of dead space in the upper airways, preventing the rebreathing of CO₂. Therefore, it is obtained a functional reduction in dead space and reducing minute ventilation by slowing down the breathing frequency and reducing work of breathing (21).

The benefits of HFNC in AHF in the ED have been studied, especially in the recent years. A preliminary study revealed that this oxygen device system reduces dyspnea and refractory hypoxemia compared to COT in patients affected by AHF due to CPO after 24 hours of treatment (22). This data was confirmed in a similar situation by the same authors after 1, 2, and 24 hours, revealing an improvement in pH without significant increases in PaCO₂. Increased tolerance and fewer side effects were also observed (23). Similarly, Ko et al. observed a significant improvement after 30 of the respiratory rate, lactate clearance, and arterial blood gas parameters, in comparison with conventional oxygen therapy (24). However, these results do not agree with recent studies, where COT showed similar effects to HFNC after 72 h attending to N-terminal pro-brain-type natriuretic peptide variations, dyspnoea by visual analog scale, peak expiratory flow, and clinical outcomes up to 30 days following hospital discharge (25).

It is well known that non-invasive ventilation reduces the rate of intubation and mortality in patients with acute

heart failure (26). However, recent studies studied the potential benefits of HFNC in these patients. It has been observed that 30-day mortality is not increased in patients treated with HFNC compared to CPAP in GPO in the ED (27). However, these authors observed a non-significant increase in treatment failure secondary to respiratory worsening due to the less control of PEEP, reducing the effects over compliance, alveolar recruitment, decrease of left ventricular afterload and right ventricular preload. These results agree with a recent study performed by Marjanovic et al. (28), observing a similar effect in PaCO₂ levels after treatment for 1 h as well as pH, breathing frequency and signs of work of breathing.

HFNC has also been compared with invasive ventilation (IV). A study performed by Kang et al. (29) divided refractory patients to COT in the in two groups: HFNC and intubation treatment groups. The study showed that the first group had a similar result of improved oxygen saturation and in-hospital clinical outcomes than the intubation group in AHF. Mean arterial pressure, heart rate, and pulse oxygen saturation during the first 6 hours were evaluated. In addition, 86.8% of the patients were successfully recovered from progressive hypoxemia without endotracheal intubation.

As a result, the European Society of Cardiology included the HFNC as a therapeutic option in patients with moderate AHF. They do not respond to conventional oxygenation or in those with an indication for non-invasive ventilation (NIV) and intolerance (30).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD affects 15–20% of the adult population, being the fourth leading cause of death in the United States (31). This pathology is characterized by airflow limitation leading to dyspnea, cough, and sputum production. Exacerbations can be defined as a worsening of chronic respiratory symptoms and acute respiratory failure. Most of them are produced due to respiratory tract infections, being necessary COT or different oxygen therapy support systems if respiratory acidosis is observed (32). Classically, patients with refractory results in COT treatment or respiratory acidosis are treated with NIV or IV. However, in recent years, HFNC has been introduced in daily practice. The clinical and physiological support is based on: 1) The heated and humidified air diminish injuries to ciliary motion, reduces the inflammatory response and epithelial cell cilia damage, and decrease the airway water loss; 2) HFNC determines a washout from CO₂ from the dead pharyngeal space; The PEEP effect generated, and 4) The more stable FiO₂ provided compared to COT (33).

The literature has been observed in several manuscripts recently about the potential benefits of HFNC in COPD exacerbations. Preliminary studies compared HFNC and COT in COPD exacerbations (34). The authors observed a decrease of PaCO₂ in HFNC treated patients compared to COT treatments. However, non-significant differences have been observed in PaO₂ and respiratory rate. This study agrees with Bräunlich and Wirtz (35),

where authors observed that PaCO₂ and pH levels were significantly improved after HFNC moderate acidotic and non-acidotic hypercapnic COPD exacerbations. However, the limitation of this study was the non-comparison with a control group. These studies were performed in exacerbated COPD patients during the admission, providing the possibility to apply this technique in the ED.

High-flow therapy has also been compared with NIV, one of the main treatments in acidotic hypercapnic COPD exacerbations. Cortegiani et al. (36) observed that HFNC was no inferior to NIV in COPD patients affected by mild-moderate hypercapnic respiratory failure in the ED. Besides, this treatment was more comfortable. NIV was applied with a PEEP of 3–5 cmH₂O, and results were assessed 2 and 6 hours after the beginning of the treatment. A similar study was performed by Sun et al. (37) in the Intensive Care Unit (ICU), found that the mortality rates after 28 days did not differ from NIV treated patients. In addition, HFNC was observed to generate fewer complications, including a significant decrease in the number of nursing airway care interventions and a minor skin breakdown. Similar results have been observed by Cong et al. (38) in the Respiratory Department, observing that HFNC and NIV treated patients showed improved blood gas parameters, revealing better comfort, fewer complications, and increased nursing satisfaction in the HFNC group. All these studies were performed in exacerbated patients, including in the ED, suggesting the potential benefits of this technique in the ED.

Avoid IV treatment is also a central objective of the treatment of COPD exacerbations. HFNC has been observed to do not increase the intubation rate and 30-day mortality compared to NIV treatment (39).

Bronchiectasis, a common comorbidity in patients affected by chronic airway diseases (40), causes the severe phenotype of asthma (41) as well as COPD (42). A single-arm study observed that HFNC effectively improved dyspnoea, decreased respiratory rate, improved gas exchange, and increased mucus production in patients with acute exacerbation of COPD and coexisting bronchiectasis. However, due to the characteristics of the study's design, these results may not be extrapolated (43).

ASTHMA

Asthma is a common obstructive airway disorder in children and adults. This disease is characterized by cough, paroxysmal wheezing, and chest tightness. Approximately 300 million patients suffer from this illness around the world (44). The mortality rate is 0.16–0.21 death per 100,000 habitants, with a rate of intubation in asthma attacks of 0.04% (45, 46).

There are few research studies about the benefits of HFNC in adults in asthma attacks in adults. Moreover, all the studies have been compared with COT. It has been observed that forced expiratory volume in one second (FEV₁), dyspnoea, PaO₂, and O₂ saturation improved significantly in asthma exacerbations after 24 h of treatment in a study performed in the ED. However, these results were similar to COT (47). These results have been confirmed in severe

bronchial asthma patients complicated with respiratory failure in the ED (48). HFNC and COT treated patients presented a significant improvement at 2, 8, 24, and 48 h after admission in terms of PaO₂ and PaCO₂ levels, heart rate, and respiratory rate. There were no significant differences in both groups. However, a higher improvement trend was observed in the HFNC treated group, considering the authors a promising treatment for this type of patient.

As an adult population, the benefits of HFNC in the pediatric population are still unclear, with few literature reports. Compared to NIV, HFNC has been observed to do not increase the length of stay in a Pediatric Intensive Care Unit (PICU) (49). However, 40% of patients treated with HFNC required an escalation to NIV, increasing the length of stay 3-fold longer in this subgroup. Consequently, the authors conclude that HFNC may delay NIV support and potentially cause more extended respiratory support and longer length of stay.

Whereas the benefits of HFNC compared to NIV are controversial, it is suggested that this treatment could be better than COT in severe asthma (50). The authors observed that heart rate, respiratory rate, blood gas results, and acidosis are increased in HFNC treated via nasal compared to COT. However, the length of stay was higher, being suggested to be due to the nasal high flow group's increased complexity. These results agree with recent studies performed in the ED, observing benefits after 2 hours of treatment (attending to Pulmonary Score). In addition, no adverse effects were founded (51). González Martínez et al. (52) obtained similar results in a pediatric hospital ward population, founding that child with higher Pulmonary Score values and a more significant number of previous admissions required HFNC more frequently. However, some studies suggest that HFNC did not have any beneficial effects compared to COT, observing not clinical benefits as well as a diminished time of stay (53). Due to that, future studies should be focused on selecting a better population to apply this treatment.

PNEUMONIA

The evidence of HFNC in both adult and pediatric age is short. Pneumonia is the leading cause of death in children between one month and six years old (54). There is only a study developed in children (55). The authors compared COT, HFNC, and bubble continuous positive airway pressure (bCPAP). Until the clinical trial stop due to the worse results observed in COT treated patients, HFNC did not have statistical differences compared to bCPAP. However, these results may not be generalized due to the early end of the study.

In the adult population, there are not reports explicitly about HFNC and pneumonia. It has been observed that HFNC is associated with less dyspnea and mouth dryness, and was more comfortable compared to the face mask. It is also observed to improve PaO₂ levels with a lower respiratory rate (56). Previous observation states that HFNC does not show an increased risk of tracheal intubation than NIV and COT. It is observed a decreased mortality-ratio after 90 days (57). Potential benefits of HFNC in acute respira-

tory failure in patients affected by pneumonia have also been observed in the ED, observing an improvement of oxygenation compared to COT (58). These results agree with a previous study where HFNC was not compared with a different treatment. The authors observed an improvement in respiratory rate, breath per minute, oxygen saturation, and increased PaO₂ levels (59).

To select patients who may be most benefited from HFNC treatment, some authors have suggested an index denominated ROX (Respiratory rate-Oxygenation). This easy-to-use index is defined as the ratio of SatO₂/FiO₂ (60).

BRONCHIOLITIS

Acute bronchiolitis is the most common cause of hospitalization in infants younger than 12 months of age. Between 50 and 82,000 infants diagnosed with acute bronchiolitis are admitted in United States hospitals each year, mainly due to respiratory syncytial virus (RSV). Likewise, between 10 and 16% require admission to the (PICU). This illness's management represents a significant economic impact between 365 and 585 million dollars per year (61, 62).

Traditionally, these patients' respiratory support has been performed with NIV, demonstrating an essential improvement of the clinical severity scales and decreased respiratory rate and difficulty. However, this treatment is poorly tolerated by infants (63).

In the literature exists little evidence about HFNC benefits in bronchiolitis. The first study reported concluded that HFNC therapy achieved a significant improvement in heart rate, respiratory rate, and scale of severity in patients with bronchiolitis in a pediatric ward. It was observed a few adverse effects. Finally, a decrease in the use of resources due to the decrease in length of stay and PICU admissions (64). These promising results were not confirmed in a study including 1,937 patients, where HFNC used on the general pediatric wards did not provide a significant change in total hospital length of stay, PICU length of stay and transfer rate, intubation rate, or 30-day readmission for patients with bronchiolitis (65).

The benefits of HFNC compared to COT in bronchiolitis still unclear. It is observed that HFNC had significantly lower rates of escalation of care due to treatment failure than those in the group that received standard. Patients who suffered treatment failure with COT were benefited from HFNC rescue therapy. However, these promising results did not reflect significant differences in the duration of hospital stay or oxygen therapy (66). It is also suggested that HFNC may also reduce respiratory rate (67). A rescue therapy's role in reducing the proportion of children requiring high-cost intensive care has been observed previously. As previously showed in the ED, the authors did not find a modification in the underlying disease process and length of oxygen therapy (68). Whereas these studies were developed in the pediatric ward and the ED, Ergul et al. (69) performed a randomized controlled study in ICU. Authors observed that HFNC use decreased the treatment failure rate and the duration of both oxygen therapy and ICU treatment COT provided by diffuser mask, suggesting

that HFNC should be the first choice for treating patients admitted to the ICU with severe bronchiolitis.

Comparing HFNC with NIV in bronchiolitis treatment, it is observed that the first one is increasing its use in the clinical practice (70). However, the benefits of this treatment still not clear. It is suggested that HFNC treatment is non-inferior to NIV attending to respiratory rate, pCO₂, or Modified Woods Clinical Asthma Score (M-WCAS). It could also be more comfortable due to the fewer score in the Neonatal Infant Pain Score (NIPS). Finally, attending to the length of stay, it was not observed statically significant differences, concluding the authors that these results must be confirmed in large multicenter studies (71).

ACUTE RESPIRATORY FAILURE SECONDARY TO CORONAVIRUS DISEASE (COVID-19)

COVID-19 has quickly spread and has now become a global public health problem. As of May 9, 2021, globally, 157,362,408 cases and 3,277,834 deaths have been reported (72). Clinical manifestations include respiratory failure, pneumonia, and acute respiratory distress syndrome (ARDS), which may be observed in 25–34% of cases (73). Oxygen support is required in all these cases; it is necessary to know which treatment is better in each moment to avoid the delay of invasive treatments (74). Consequently, HFNC has been considered a potential treatment of these patients due to the possibility of providing high flow concentration of oxygen with a short effect of PEEP. However, the usage of HFNC is much controversial due to concerns about the benefits and risks of aerosol-dispersion (75).

There are few studies about HFNC benefits in COVID-19 respiratory symptoms. Favorable results were observed by Geng et al. in an 8 case series attending to PaO₂/FiO₂ results. After 24 h of treatment, this value increased from 259.88 ± 58.15 mmHg to 280–450 mmHg, being all discharged without NIV requirements during the admission (76). It is suggested that beneficial results of HFNC are increased if the PaO₂/FiO₂ ratio is higher than 200 mmHg, observing significant differences compared to those where this value is lower. In these patients, NIV could be considered as a rescue therapy showing promising results (77). It has been associated that HFNC decreases in the intubation rate. It also showed a decrease in mortality due to less hospital-associated/ventilator-associated pneumonia in the HFO group than in the intubation group (78). These results agree with recent studies with large number of patients, observing that the ROX index after 6h initiating HFNC had good predictive capacity for HFNC outcomes (79). In addition, this index as well as SOFA has been observed to help to identify patients with higher likelihood of intubation (80).

It is well known that COVID-19 infection affected especially to elderly population. Due to the difficulty of accept these patients with several comorbidities in ICU, HFNC has been purposed to be an effective treatment reducing mortality rate (81).

However, these promising results attending to mortality has been not observed in other result; where HFNC significantly reduces intubation and subsequent invasive

mechanical ventilation but does not affect case fatality (82–84). Authors suggest that these results may be generated due to the complexity and no typical features of ARDS developed by COVID-19 patients (85, 86).

Prone position (PP), which improves the mismatch of ventilation-perfusion and opens the atelectatic lungs by adequate sputum drainage, has been established as therapeutic management of COVID-19 patients in ICU (87). It is observed that in severe patients affected by COVID-19, early PP with HFNC therapy improves the PaO₂/FiO₂ ratio. In addition, in the ten patients used, the demand for medical staff was reduced, being safe for patients and professionals (88), like previously reported (89). Similar results were observed in a 9 cases series with severe ARDS with PaO₂/FiO₂ lower than 150 mmHg. The mean blood oxygen saturation and the mean blood oxygen partial pressure increased significantly, whereas the mean partial pressure of carbon dioxide decreased significantly. Only two patients required invasive mechanical ventilation (90). These results have also been observed in other case series, showing that the efficacy of early PP combined with HFNC is higher than those who received COT (91). In addition, it is also noted that dexmedetomidine, a potent anti-inflammatory proposed as a novel therapeutic strategy to attenuate multi-organ dysfunction of COVID-19 patients (92), may be useful with HFNC facilitating the acceptance of long periods of awake PP (93).

According to this data, it could be considered HFNC as a promising treatment in ARDS due to COVID-19. However, these results must be confirmed, focusing on which type of patients will benefit more from HFNC. There are some cases reports in the literature where, after improvement with NIV, begin the HFNC generated a sharp decrease of PaO₂/FiO₂, requiring invasive treatment (94).

CONCLUSIONS

HFNC seems to be a useful tool in the ED, especially in patients affected by acute hypoxemic respiratory failure, acute heart failure, pneumonia, bronchiolitis, asthma and ARDS in patients affected by COVID-19. Its benefits in hypercapnic respiratory failure are more discussed, being only observed benefits in patients with mild-moderate disease. If we analyze these results attending to the population age, these theories have a strongest evidence in pediatric patients affected by bronchiolitis. Attending the adult population, the strongest evidence could be observed in acute hypoxemic respiratory failure secondary to acute heart failure. It is necessary to remark than all the studies are performed in small number of populations, and mainly in ICU as well as ward patients, requiring in the future large clinical trials to confirm these results, especially in the ED. However, due to the severity as well as type of patients (patients with acute exacerbation of a chronic pathology, including COPD or health failure), it could be proposed that this device could be an important treatment in the ED.

The positive results of this therapy are based in the capacity to provide high flow rates, as well as the heating and humidification of gas. Due to that, it has been found to be more tolerable and comfortable than other devices,

including COT and NIV, avoiding the risk of skin lesions in the last device. In addition, HFNC promote a PEEP effect (<5 cmH₂O), which improves alveolar recruitment and tidal volume, contributing to alveoli clearance and to PaCO₂ decrease.

It is necessary to develop clinical practice guidelines regarding how and when initiate HFNC, protocols for titration and weaning, type and frequency of serial clinical assessment, and clear definitions as to what constitutes treatment failure and the need to escalate to NIV or IV. In the literature has been suggested a potential delay on escalation in adults' patients treated with HFNC, leading to worsening outcomes [95]. Similar results have been observed in children, observing a difference between failure time in HFNC (7–14 hours) compared to NIV (less than 2 hours), remarking the need for continual monitoring beyond the ED [96].

Finally, it is important to evaluate the cost-effectiveness outcomes of HFNC compared to COT and NIV. In the United Kingdom, is estimated to save £469 (USD \$608) per patient compared to standard oxygen therapy and £611 (USD \$793) per patient compared to NIV [97]. A similar study has been developed in Finland, observing that the treatment cost of an episode of acute bronchiolitis is between €1,312–2,644 (USD \$1,786–3,600) if HFNC is applied, compared to €1,598–3,764 (USD \$2,175–5,125) if the patient is treated with COT [98]. These results are related with a decreased number of patients admitted in the PICU, remarking the need to develop clinical practice guidelines about the application of this treatment.

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Comparison of Efficacy and Safety of Non-Regenerated and Regenerated Oxidized Cellulose Based Fibrous Haemostats

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ABSTRACT

Purpose: Various forms of local haemostats are increasingly used routinely in surgical procedures. Our work is the first comparison of the efficacy and safety of non-regenerated and regenerated oxidized cellulose based fibrous haemostats.

Methods: The haemostatic efficacy and safety of fibrous haemostats based on ONRC and ORC were compared in a randomized multicenter study. The primary endpoint was successful haemostasis within 3 minutes of application and no need for surgical revision within 12 hours after the procedure for recurrent bleeding.

Results: There was a significant difference in the rate of successful haemostasis in 3 minutes that was achieved in 82% and 55% in the ONRC and ORC groups, respectively (confidence interval 99%; $p = 0.009$). Mean time to haemostasis was 133.9 ± 53.95 seconds and 178.0 ± 82.33 seconds, in the ONRC, and ORC group, respectively ($p = 0.002$). Revision surgery for re-bleeding was necessary in 0 (0%), and 1 (2%) of patients in the ONRC, and ORC group, respectively. No adverse events were reported.

Conclusion: Fibrous haemostat based on ONRC was non-inferior compared to fibrous haemostat based on ORC when used in accordance with its intended purpose, and was safe and efficient.

KEYWORDS

haemostasis; perioperative bleeding; oxidized cellulose; traumacel

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INTRODUCTION

As the age of the population grows and the results of oncological treatment improve, the number of patients in which a greater surgical resection procedure is necessary for the definitive success of the treatment increases. A large group of patients at risk of greater postoperative blood loss are patients with various types of cancer, indicated for radical surgery, especially patients with very large sometimes benign tumours where non-surgical treatment is not successful. Another group consists of patients indicated for surgical diagnostic intervention. A large group consists of patients after complicated inflammatory diseases such as the lungs and chest cavity, when it is necessary to perform decortication and pleurectomy, often with atypical lung resection. In all these groups of patients, a more demanding perioperative course can be predicted, and in the postoperative period it is necessary to anticipate greater blood losses from multiple non-surgical sources. Therefore, it is advantageous to use topical haemostatic agents and thus eliminate ongoing surgically untreatable bleeding. Various forms of haemostats are used as adjuncts to stop residual capillary bleeding persisting after the use of conventional methods to achieve haemostasis and to prevent postoperative blood loss. It allows the perioperative bleeding to stop, usually within a few minutes.

Topical haemostatic agents based on regenerated (ORC) or non-regenerated oxidized cellulose (ONRC) are available in various forms. Knitted gauze, powder and the newest form – fibrous felt, which is increasingly being used as of late. The fibrous felt allows better shaping and resizing, has better absorbency compared to the knitted gauze and copies the application site better.

Topical haemostats work by swelling into a jelly-like mass after soaking in blood, which helps to form a blood clot. This leads to local haemostasis and control of the bleeding. Unlike haemostatic patches, they do not contain fibrinogen or thrombin, parts of the coagulation cascade, that are associated with the risk of thrombosis (1). When used in adequate amounts, the haemostatic preparation is absorbed with virtually no tissue reaction and no residues. The secondary effect is antibacterial, based on low pH, and inhibits the growth and multiplication of micro-organisms (2, 7).

The vast majority of published works were performed with haemostats based on ORC (2–9). Only few papers describe the effect of ONRC haemostatic gauze (10–14) or felt (15–17) and only one published work compares the effect of ORC and ONRC knitted gauze in a larger group of patients (18). The works published so far show that ONRC has a similar or even superior effect (10, 18).

To date, no study has compared the effect of fibrous felt, the newest form, in a larger group of patients. Our comparative study focused on comparing the effect of the fibrous felt based on ORC and ONRC. In addition, the study included more surgical disciplines to compare the effect on different bleeding tissue types.

MATERIAL AND METHODS

OBJECTIVES

The main objective of the study was to compare the efficacy and safety of non-regenerated and regenerated oxidized cellulose based fibrous haemostat when used in accordance with their intended purpose.

The partial objectives were: to identify any previously unknown side-effects and the monitoring of known side-effects; to identify and analyse potentially newly emerging risks; to confirm the acceptability of the benefit-risk ratio; and to identify any systematic misuse of the device or off-label use of the device in order to verify the correctness of its intended purpose.

The primary endpoint was the successful result of a haemostatic agent: Successful haemostasis within 3 minutes of application and no need for surgical revision within 12 hours after the procedure for recurrent bleeding.

ETHICAL ISSUES

This study was conducted according to the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000) and approved by the Ethic Committee of the University Hospital Hradec Králové, Czech Republic. Written informed consent was obtained from every patient. All patients enrolled in the study had the option to withdraw from the study at any time.

PATIENTS

A total of 98 patients with diffuse soft tissue, vascular or parenchymal bleeding after conventional surgical haemostatic methods that did not work or are impractical (e.g., ligature, suture, compression, cauterization), were enrolled in the study from May 2020 until December 2020 at the University Hospital Hradec Králové, Czech Republic.

The choice of patients was not limited to a specific surgical procedure or diagnosis, nor to the age of the patients.

USED ORC AND ONRC HAEMOSTATS

Traumacel FAM Trium 5 × 10 cm (BIOSTER, a.s., Veverská Bítýška, Czech Republic) as ONRC based haemostat and Surgicel Fibrillar 5 × 10 cm (Ethicon, LLC, Puerto Rico) as ORC based haemostat were used in this study. ONRC is produced by oxidation of natural cotton, ORC is made by dissolution and extrusion and then oxidation. Under the microscope, the ORC fibres are smooth, while the ONRC fibres are porous and frayed.

The material of both is very soft and it is easy to divide into smaller pieces but at the same time it holds its shape well, so it can be sutured at the application site if needed and can also be easily used in endoscopic or robotic surgery.

OPERATIVE PROCEDURES AND DATA

The study took place in 4 centres: cardiosurgical, surgical, neurosurgical and urological. The centres were elected to cover the widest range of operational services. The clini-

cal study was designed to be prospective, controlled, and randomized.

The efficacy parameters monitored were the time required to achieve haemostasis, the rate of successful haemostasis within 2 minutes and within 3 minutes after administration. As safety parameters, complications during surgery, the necessity of surgical revision within 12 hours after the procedure for recurrent bleeding, and the occurrence of adverse events were chosen.

MEASURES TO MINIMIZE OR ELIMINATE BIAS

Blinding by the examiner cannot be achieved. Medical devices are recognizable by their physical properties. Randomization and objectivity were achieved by adding serial numbers to potential patients for the surgery and assigning which preparation would be administered to subjects with an odd serial number and which preparation would be administered to subjects with an even number was chosen in advance.

STATISTICS

The sample size was calculated based on the data from a previous clinical study that had a similar design. It was a non-inferiority test between two tested comparative haemostatic products based on ORC and ONRC. From this, the number of patients in one arm of the clinical study was calculated to be $n = 49$.

The clinical study was statistically designed as a test of non-inferiority of ONRC based haemostat compared to ORC based haemostat. The rate of successful haemostasis within 2 and 3 minutes was compared. The non-inferiority margin was set at 10%. The statistical method was an unpaired two-samples t-test of non-inferiority. Statistical differences were considered significant when $P < 0.05$.

RESULTS

There were 98 patients enrolled in the study, of whom 66% were men and 34% were women. The mean age of the patients was 62.5 years, the oldest patient was 85 years old and the youngest 20 years old. Baseline demographic characteristics are summarized in Table 1.

Tab. 1 Demographic Characteristics. SD, standard deviation; PHCCM, possible health complications, comorbidities and medications that may affect the outcome of treatment (for more information, see Table 2).

Characteristic	Traumacel FAM Trium (n = 49)	Surgical Fibrillar (n = 49)	Total (n = 98)	P-value
Age, mean (SD)	62.31 (14.40)	62.73 (13.69)	62.52 (14.05)	0.882
Sex, n (%)				
Male	31 (63)	34 (69)	65 (66)	0.669
Female	18 (37)	15 (31)	33 (34)	0.669
PHCCM, n (%)	29 (59)	23 (47)	52 (53)	0.312

In total 53% of patients had possible health complications, comorbidities and medications that may have affected the outcome of treatment. Differences between patient groups in this respect were not statistically significant. The overview of health complications, comorbidities and medications that may have affected the outcome of treatment is in Table 2.

Tab. 2 List of PHCCM and occurrence. PHCCM, possible health complications, comorbidities and medications that may affect the outcome of treatment.

	Occurrence
Comorbidities	Tumour (8), ischemic heart disease (5), chronic obstructive pulmonary disease (4), Crohn's disease (3), diabetes mellitus (2), atrial fibrillation (2), infection (2), aortic valve implantation (2), sepsis (1), polytrauma (1), cirrhosis (1), ATR syndrome (1), osteoporosis (1), hepatopathy (1), colostomy (1), phlegmona (1), heart failure (1)
Medications	Anopyrin (19), Godasal (9), Fraxiparin (6), Warfarin/Heparin (6), Tromboxan (2), Eliquis (2), Clexane (1), Brilique (1)
Other complications	Nicotine addiction (3), alcohol addiction (2), obesity (2)

The study covered various types of surgery. In addition to conventional surgery, laparoscopic and robotic procedures were included. The procedures performed in the study population were in the areas of thoracic surgery, vascular surgery, plastic surgery, abdominal surgery, neurosurgery and urology.

The differences in the relative proportions of bleeding from the target bleeding site (TBS) between groups were not significant. We can state that the worse bleeding status in neither of the ONRC or ORC groups could affect the primary endpoint. The proportion of bleeding rates was even in both groups. Most of the patients had mild or moderate bleeding. The list of operative procedures and degree of bleeding from the TBS are summarized in Table 3.

The expected dropout was 10–15% but, there was no dropout from the study. An overview of the number of patients monitored during the study is in Figure 1.

Successful haemostasis within 2 minutes was achieved in 43% and 33% in ONRC and ORC groups, respectively (confidence interval 99%; $p = 0.405$). There was a significant difference in the rate of successful haemostasis within 3 minutes that was achieved in 82% and 55% in the ONRC and ORC groups, respectively (confidence interval 99%; $p = 0.009$). Out of these clinical data it can be stated that the ONRC based haemostat is a non-inferior treatment method compared to the ORC based haemostat.

The mean time to achieve haemostasis (TTH) was 133.90 (SD = 54.95; median = 145.00), and 178.04 (SD = 82.33; median = 180.00) seconds in the ONRC, and ORC group, respectively (a normal distribution can be assumed). The shortest time to haemostasis was 30 seconds in both groups. The longest time to haemostasis was 245, and 350 seconds in the ONRC and ORC group, respectively. Mean TTH was shorter in the ONRC group with statistical significance $p = 0.002$.

Tab. 3 Operative Procedures and Data. SD, standard deviation; TBS, target bleeding site; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Variable	ONRC (n = 49)	ORC (n = 49)	P-value
Type of intervention, n (%)			
Classic	40 (82)	37 (76)	0.623
Laparoscopic	4 (8)	2 (4)	0.678
Robotic	3 (6)	5 (10)	0.715
Endoscopic	2 (4)	4 (8)	0.678
Area of surgery, n (%)			
Thoracic surgery	20 (40)	20 (40)	>0.999
General surgery	5 (10)	5 (10)	>0.999
Vascular surgery	7 (14)	7 (14)	>0.999
Plastic surgery	7 (14)	7 (14)	>0.999
Neurosurgery	5 (10)	5 (10)	>0.999
Urology	5 (10)	5 (10)	>0.999
Anatomic location of TBS, n			
Thoracic	21	18	0.680
Retroperitoneal / Abdominal	15	12	0.652
Pelvic	1	2	>0.999
Cutaneous / Subcutaneous	6	6	>0.999
Extremities	5	4	>0.999
Degree of bleeding, n			
1 = mild bleeding	24	25	>0.999
2 = moderate bleeding	21	20	>0.999
3 = severe bleeding	4	4	>0.999
4 = life-threatening bleeding	0	0	>0.999
Degree of bleeding, mean (SD)	1.59 (0.64)	1.57 (0.64)	0.878
Other methods used to stop bleeding from TBS, n			
Electrocoagulation	12	19	0.192
Mechanical methods	8	14	0.226
Pharmacological methods	1	0	>0.999
None	30	22	0.156

Revision surgery for re-bleeding was necessary in 0 (0%), and 1 (2%) of patients in the ONRC and ORC group, respectively.

In terms of primary endpoints, as the successful result of haemostatic agent use can be considered: a) successful haemostasis within 3 minutes of application, and b) no need for surgical revision within 12 hours after the procedure for recurrent bleeding. In these terms, a successful result was achieved in 40 (82%), and 27 (55%) patients in the ONRC and ORC group, respectively. Clinical outcomes are summarized in Table 4 and Figure 2.

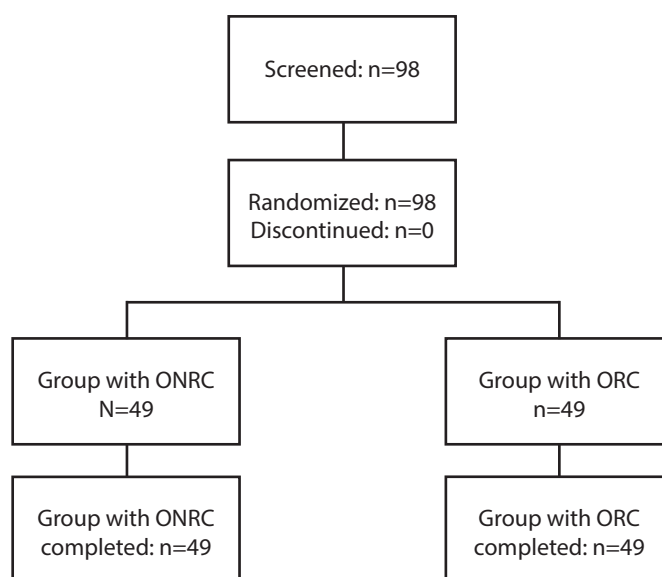


Fig. 1 An overview of the number of patients monitored during the study. ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Tab. 4 Clinical outcomes; SD, standard deviation; TTH, time to haemostasis; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Clinical parameter	ONRC (n = 49)	ORC (n = 49)	P-value
TTH, mean (SD)	133.90 (53.95)	178.04 (82.33)	0.002
TTH ≤ 120s, n (%)	21 (43)	16 (33)	0.405
TTH ≤ 180s, n (%)	40 (82)	27 (55)	0.009
Revision surgery for rebleeding, n (%)	0 (0)	1 (2)	>0.999

No adverse events (0% [0 of 98]) were reported for either study group both on the surgery day and at a 1-month follow-up. During the follow-up period, there was no reported unscheduled visit (0% [0 of 98]) of patients who underwent the surgery for medical problems, e.g., post-operative complications.

Among patients in the ONRC group, there were no intraoperative or early postoperative complications (0% [0 of 49]). Among patients in the ORC group there were two (4%) complications that were not related to the haemostatic agent. Safety data are summarized in Table 5.

Tab. 5 Safety data. AEs, adverse events; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Clinical parameter	ONRC (n = 49)	ORC (n = 49)	P-value
Complications, n (%)	0 (0)	2 (4)	0.495
AEs, n (%)	0 (0)	0 (0)	>0.999
AEs at 1-month follow-up, n (%)	0 (0)	0 (0)	>0.999
Unscheduled visits, n (%)	0 (0)	0 (0)	>0.999

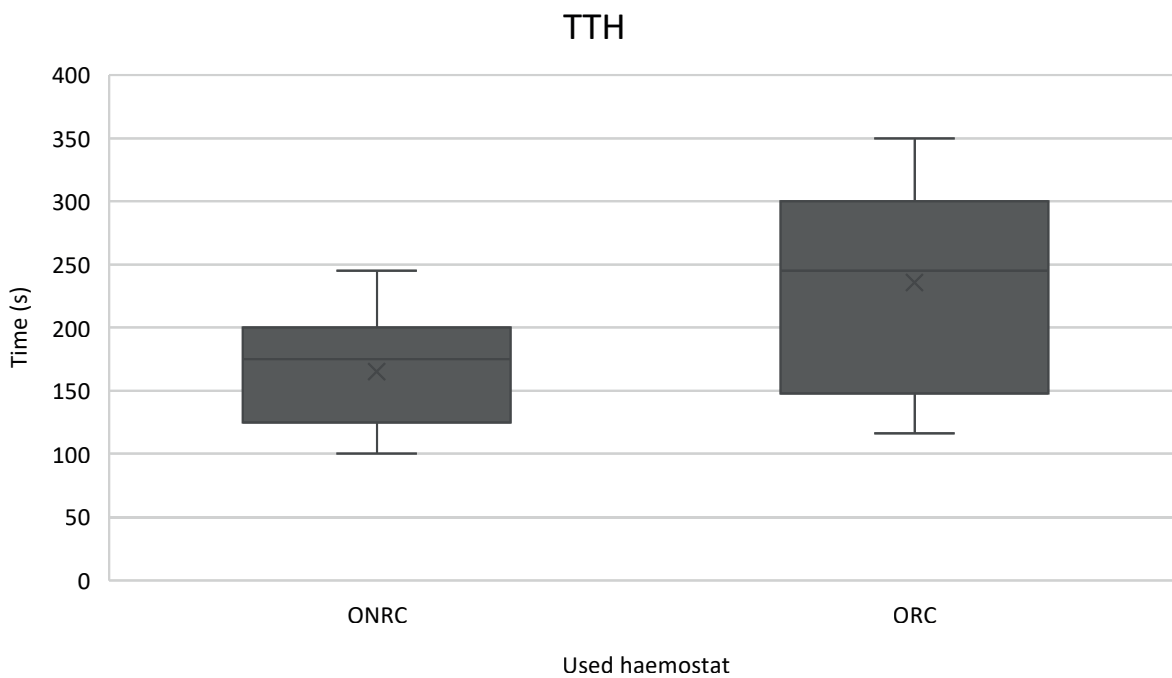


Fig. 2 Time to haemostasis between the ONRC and ORC groups. TTH, time to haemostasis; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

DISCUSSION

The use of local haemostats is becoming increasingly important in connection with the shift of surgical procedures towards more seriously ill patients. In patients with advanced cancer after neoadjuvant chemotherapy, the procedures are usually accompanied by a high number of different complications and a larger number of infectious complications. Decreased immunity of the patient may be involved. These operations have both higher morbidity and mortality.

The reduction of bleeding during the operation and in the postoperative period with the elimination of blood transfusions has a positive impact on patients in general, not only those with advanced oncological disease. In the postoperative period, waste of the thoracic drain does not only come from bleeding, but also lymphorrhea, for example after mediastinal or retroperitoneal lymphadenectomy. By applying a local haemostat based on cellulose, we can eliminate this lymph with a good effect. The spectrum of patients is shifting to a higher age group, and this is associated with greater comorbidity. Therefore, the effort to eliminate blood transfusions using local haemostats is playing an increasingly important role.

This study confirms the efficacy and safety of ONRC and ORC haemostats. There was a significant difference in TTH and in the rate of successful haemostasis within 3 minutes in favour of ONRC haemostats. However, this study did not address whether this difference, although significant, was of any clinical significance and therefore could have an impact on the surgeons' decision which haemostat they would use.

The study design also did not consider that the characteristics and severity of bleeding may differ in each type of the surgical procedure, and the efficiency parameters were not evaluated for the individual types of surgery,

because this would have required a considerably larger number of patients. This aspect was partially resolved by assessing the degree of bleeding. The numbers of patients with particular bleeding degrees in ONRC and ORC groups were even.

A favourable safety profile has been confirmed in our work thanks to the absence of side effects, dropouts and postoperative complications. Although the absence of dropouts was also due to the fact that all surgical procedures in the study population were planned. Not a single patient experienced an adverse event of any severity, and no haemostat-related complications were reported. From these findings, the high level of safety of both haemostats can be concluded.

However, even in these haemostats, complications may occur in exceptional cases. Several published works describe foreign body reactions with subsequent formation of a granuloma (7). The risk of these complications can be minimized by using the smallest necessary amount of the haemostat.

There have been some previous studies comparing other ONRC and ORC products. A study from 2013 compared the fibre structure, pH in solution, bactericidal effectiveness, and haemostatic effectiveness of an ONRC haemostat and an ORC haemostat. ORC pH was statistically more acidic than ONRC in a phosphate buffer solution, but equal in plasma. No difference in bactericidal effectiveness was observed. *In vivo*, ONRC provided superior time to haemostasis relative to ORC in the general surgery model; and superior haemostatic success relative to ORC at 30 (60% vs. 15%), 60 (85% vs. 37.5%), and 90 seconds (97.5% vs. 70.0%) in the peripheral vascular model (10). In 2021 one work was published involving the results of a clinical trial comparing the effectiveness of knitted forms of ORC and ONRC in patients undergoing hepatic resection. There was no significant difference between the ORC and ONRC

groups in time to haemostasis, and there were no differences in the rates of haemostatic success between the 2 groups at 120 seconds (18.4% vs. 24.3%) and 300 seconds (71.1% vs. 89.2%). However, the ONRC group was superior to the ORC group in haemostasis according to the survival analysis (log-rank test, $P = 0.044$). Moreover, there were also no significant differences between the 2 groups in postoperative drainage volume on the first 2 days and hospital stay (9). So far, all these published clinical data comparing the effectiveness of ORC and ONRC involved knitted haemostats (18).

Given the current trend of fibrous haemostats, which are produced by a technology different from knitted forms, it was good to compare the effectiveness of fibrous haemostats ORC and ONRC.

The new data documenting the use of fibrous ONRC and ORC haemostats gained in our study will be a beneficial contribution to existing knowledge in this area and confirm that ONRC haemostats are non-inferior to ORC haemostats when used according to their current intended use.

CONCLUSION

After a statistical assessment of the clinical data obtained from the study, it is evident that a fibrous haemostat based on ONRC was non-inferior compared to a fibrous haemostat based on ORC when used in accordance with its intended purpose, and that it is safe and efficient.

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ABBREVIATIONS

ONRC oxidized non-regenerated cellulose
ORC oxidized regenerated cellulose
TTH time to haemostasis

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An Investigation of the Accuracy and Reproducibility of 3D Printed Transparent Endodontic Blocks

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ABSTRACT

Due to a broad spectrum of endodontic rotary instruments on the market and no standardised protocol for comparing their mechanical properties, it can be challenging for clinician to choose proper instruments. In vitro studies using resin blocks with artificial canals can offer many valuable information because of their uniformity compared to studies performed on extracted teeth. To improve precision and reproducibility of artificial canals, 3D printing was used in this study to manufacture endodontic test block samples. 20 commercially available endodontic blocks Endo-Training-Bloc-J by Dentsply Sirona were tested. The mean values of the measured parameters were used for a 3D CAD model of their replicas. 20 copies of the endodontic training blocks were printed from acrylic resin (VeroClear-RGD810, Stratasys, Eden Prairie, USA) using the 3D printer Objet30 Pro (Stratasys, Eden Prairie, USA). The key dimensions of the commercial blocks and the 3D printed blocks were measured under and compared using t – test and Levene’s test for equality of variances. The profiles of the 3D printed artificial canals showed significantly lower dimensional variability when compared with the commercial blocks. 3D polyjet printing proved to be a precise and reproducible method for production of blocks for testing endodontic rotary instruments.

KEYWORDS

endodontic training block; 3D printing; additive manufacturing; artificial root canal; J shape resin block; PolyJet printing

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INTRODUCTION

Maintaining the original anatomy of a root canal during preparation is one of the goals of the root canal treatment. It is challenging especially in curved canals (1). To achieve this goal, NiTi (nickel-titanium) systems using the super-elastic properties of the nickel-titanium alloy have been introduced. NiTi rotary instruments are more flexible, and preparation is less time consuming when compared with stainless steel instruments (2). Probably the biggest disadvantage of this type of treatment is a risk of an abrupt separation of a tip of the instrument. This can prevent proper irrigation of a system of root canals and subsequently jeopardize the success of root canal treatment (3). Many NiTi endodontic systems came to the market during last decades and choosing proper system is essential for every clinical situation. Changing parameters, such as different cross section, conicity, surface treatment, can improve the performance of NiTi instruments (4, 5). Some procedures as heat treatment of alloy are proprietary (6).

There is no standardised protocol that compares properties of NiTi endodontic instruments. Some studies used extracted teeth to better simulate clinical situation but range of variations in the anatomy of root canals of teeth makes the study results difficult to interpret and reproduce (7, 8). Therefore, some other studies used artificial canals made of clear cast resin for their uniformity (9, 10). Transparent simulated root canal models also allow for overlapping pre- and post- instrumentation images to evaluate the preparation (11). However, the artificial root canals lack anatomical irregularities, three-dimensional curvatures, and other qualities of clinical situation. The market offers only few variations in the shape of a canal. Furthermore, the conventionally manufactured simulated root canal models have production-related deviations, so even these models are not sufficiently identical and lack standardization (12, 13). Nevertheless, the resin blocks are broadly used not only in theoretical studies but also for endodontic training, educational purposes, and laboratory assessment of qualities of endodontic instruments, where it is essential to have precise morphology of the artificial root canal. There are many classification systems describing root morphology. Cross-sectional shapes include round, oval, round oval, ribbon, irregular and C-shaped canals (14). Shape of root curvature can be classified as straight, J-shaped, entirely curved and S-shaped (15). For most purposes, the J-shaped artificial canals with round cross-section are the most relevant ones due to widely established test methodology (9, 11, 16). A commercially available endodontic block with J-shape round cross-section artificial canal with dimensions corresponding to the average physiological dimensions of the root canal is Endo-Training-Bloc-J by Dentsply Sirona.

The advance in the additive manufacturing makes it possible to create transparent endodontic blocks with artificial root canals of any conceivable shape with sufficient accuracy and reproducibility (17, 18). Current drop on drop 3D techniques allows for printing objects with resolution of 16 μm per layer. However, to this date, there is no study that has properly analysed the J-shaped endodontic training block and 3D printed its replica. The aim of this study was to investigate the possibilities of 3D printing

of endodontic blocks with artificial root canals using the 3D printer Object 30 by Stratasys Ltd. and to compare the accuracy and reproducibility of the 3D printed endodontic blocks (further referred to as the 3DP blocks) with the conventional commercially available endodontic blocks Endo-Training-Bloc-J by Dentsply Sirona (further referred to as the original resin blocks).

MATERIALS AND METHODS

A total of 20 ready-made transparent epoxy resin blocks – Plastic Practice Blocks .02 taper – Oblong for 15 file (Endo-Training-Bloc-J Dentsply Sirona, Ballaigues, Switzerland) were photographed under binocular microscope (DSZS 1112-300, Arsenal, Prague, Czech Republic). The key parameters of the artificial canals, i.e., the Canal profile, Canal thin, Canal thick, Cone length, Canal angle, Cone angle, and Pitch angle, shown in Figure 1, were measured with the help of NIS-Elements 3.20 (Nikon Instruments Inc., Melville NY, USA). The canal profile is defined by the perpendicular distances from the base line, measured at 100 to 1000 pixels positions with the help of the 100 \times 100-pixel grid. The base line is the line tangent to the output cylinder surface, starting at point where the thin tip of the canal intersects this surface (Figure 1).

The mean value of each parameter was used to design 3D drawings in CAD software (Cloud Powered 3D CAD/CAM Software for Product Design | Fusion 360, 2018, Autodesk, San Rafael, USA). Subsequently, 20 prototypes of endo blocks were printed from acrylic resin (VeroClear-RGD810, Stratasys, Eden Prairie, USA) using the 3D precision printer Objet30 Pro (Stratasys, Eden Prairie, USA). The Objet30 Pro uses the so called PolyJet or Drop on drop printing process where the object is built by selective spraying drops of a photopolymer in ultra-thin layers. Each photopolymer layer is cured with UV light after it is jetted, producing fully cured models that can be handled and used immediately, without post-curing (19).

High printing precision with the layer thickness of 16 μm was used. The printer used a soluble support material (SUP706B, Stratasys, Eden Prairie, USA), which should allow for hands-free, water-jet removal without damaging the delicate structures. A combined glossy, for transparent outer walls, and matte, for precise inner structures, printing technique was used. This should allow to observe the printed inner artificial canal structure through the transparent wall. To enhance optical properties of the transparent wall eliminating the undesirable light scattering on the still rough surface of the resin block, Evetric Bond (Ivoclar Vivadent AG, Schaan, Liechtenstein) with straight stainless steel dental matrix were used to create smooth surface and improve the transparency.

The printed prototypes were then instrumented using ISO 10 stainless steel K-file (Micro-Mega, Besançon, France) and ethanol 96% as irrigation to remove the soluble support material (SUP706B, Stratasys, Eden Prairie, USA).

The same procedure of measuring as for manufactured models was used for these prototypes. However, due to a small shift in the focal plane of the 3DP blocks relative to the original resin blocks, a difference in the micrograph

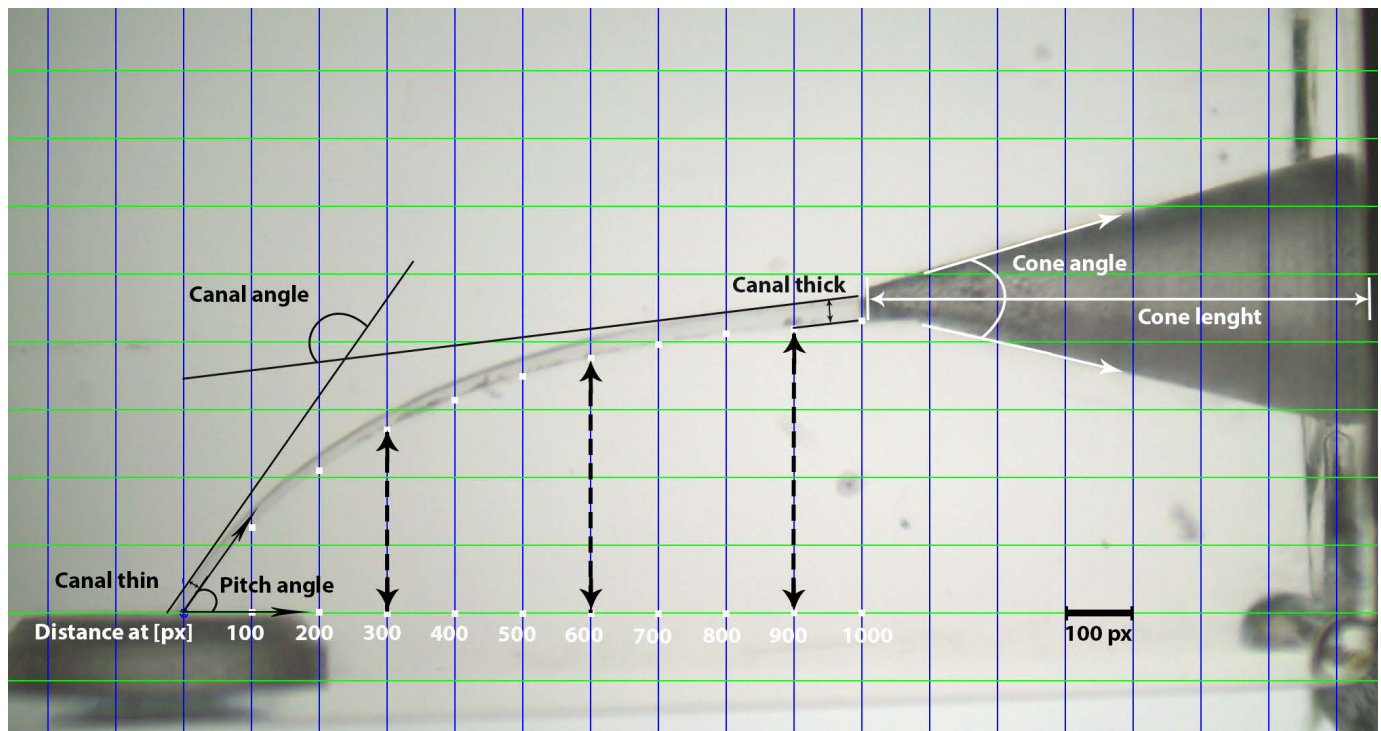


Fig. 1 3D printed block with highlighted measured parameters. 100 pixels correspond to a distance of 743.8 μm .

calibration occurred between the original and the 3DP block, i.e., 100 pixels in the micrographs of the original resin blocks corresponds to 852.2 μm while 100 pixels in the micrographs of the 3DP blocks corresponds to 743.8 μm . This mismatch led to a different “true positions”, at which the canal profile was measured, and need for fitting the original profile values with a polynomial function to calculate the profile values as if measured at the true positions in the 3DP micrographs. For this purpose, the profile data of the original blocks were fitted with a fourth-degree polynomial using the MS Excel 2016 (Microsoft Corp., Redmond WA, USA) polynomial trend line function. Nevertheless, as all the micrographs were calibrated using the same calibration slide, the measured distances were not affected.

The results were compared, processed, and statistically analysed using MS Excel 2016 (Microsoft Corp., Redmond WA, USA) and NCSS 10 statistical software (2015, NCSS, LLC., Kaysville, Utah, USA, ncss.com/software/ncss). Since all the data showed to be from normally distributed populations, we opted for using the mean and standard deviation of the sample (\pm SD) for the data description. We tested the printing accuracy by comparing the printed blocks' parameters with the values used in the 3D CAD design using 1-sample *t*-test. We compared the reproducibility of the commercially available endodontic blocks (Endo-Training-Bloc-J Dentsply Sirona, Ballaigues, Switzerland) with the printed blocks using Levene's test for equality of variances. In all the tests, a value of $p < 0.05$ was considered as significant.

RESULTS

Table 1 shows the measured key parameters of the original resin blocks and the corresponding rounded values used as

an input for the CAD model of the 3D printed blocks (available in the supplementary materials on the article web page). For the comparison purposes of the original resin blocks with the 3DP blocks, Table 1 also shows the corrected values of the original resin blocks obtained using the fitted fourth-degree polynomial function. The course of the function and its parameters are shown in Figure 2.

Table 2 shows the measured key parameters of the 3D printed blocks. When compared with the original resin blocks, the artificial canal profiles of the 3D printed blocks have significantly lower dimensional variability as shown by the results of the Levene's test (Table 3). The dimensional variability of the 3D printed blocks represented by coefficients of variation (Table 2) was 2 – 5 x lower than the variability of the original resin blocks (Table 3).

All the measured values of the canal profile of the 3D printed blocks were significantly different compared to the original resin blocks as proved by the *t* - test (one sample *t* - test, Table 3). The larger the measured profile value, the larger the observed difference. The maximum profile difference was observed at the “true” position of 7438 μm where the mean measured 3DP block profile value was by 8% smaller (Ratio of Means 3DP / Original, Table 3) than the corresponding profile value of the original resin block.

Apart from the Canal thin parameter, the other monitored parameters also differed significantly (one sample *t* - test, Table 3). Considering the data variability, the Canal thin, Canal thick Canal angle, and Pitch angle of the 3DP block did not differ significantly from the original resin block. Only in the case of the cone angle parameter, the variability of the measured data of the 3DP block was significantly larger, more than four times (Coefficient of Variation ratio 3DP / Original, Table 3), than that of the original resin block.

Tab. 1 Key parameters of the original epoxy resin block – Plastic Practice Blocks .02 taper – Oblong for 15 file (Endo-Training-Bloc-J Dentsply Sirona, Ballaigues, Switzerland) – ¹⁾ measured values, ²⁾ rounded mean values used as the input for the CAD model (available in the supplementary materials on the article web page), and ³⁾ corrected values used for comparison purposes.

dimension	(pixel)	true position (µm)	Original block ¹ (µm)	Coefficient of Variation ¹ (%)	Model input	
					Original ² (µm)	Corrected ³ (µm)
Canal profile	@ 100px	@ 852.1 µm	1208.0 ± 85.3	7.06	1208.0	1090.4
	@ 200px	@ 1704.3 µm	1954.3 ± 120.3	6.15	1954.3	1791.1
	@ 300px	@ 2556.5 µm	2467.8 ± 130.4	5.28	2467.8	2296.4
	@ 400px	@ 3408.6 µm	2820.9 ± 136.6	4.84	2820.9	2658.1
	@ 500px	@ 4260.8 µm	3065.1 ± 130.6	4.26	3065.1	2918.5
	@ 600px	@ 5112.9 µm	3249.4 ± 121.3	3.73	3249.4	3111.2
	@ 700px	@ 5965.0 µm	3381.4 ± 110.2	3.26	3381.4	3260.6
	@ 800px	@ 6817.2 µm	3481.8 ± 99.8	2.87	3481.8	3382.0
	@ 900px	@ 7669.3 µm	3590.8 ± 220.3	6.14	3590.8	3481.9
	@ 1000px	@ 8521.5 µm	3592.6 ± 82.2	2.29	3592.6	3557.4
Canal thin			136.9 ± 11.3	8.24	136.9	–
Canal thick			314.3 ± 15.2	4.84	314.3	–
Cone length			6033.4 ± 196.7	3.26	6033.4	–
			(deg)	(%)	(deg)	–
Canal angle			125.5 ± 2.8	2.22	125.5	–
Cone angle			29.4 ± 0.3	1.01	29.4	–
Pitch angle			58.2 ± 2.2	3.74	58.2	–

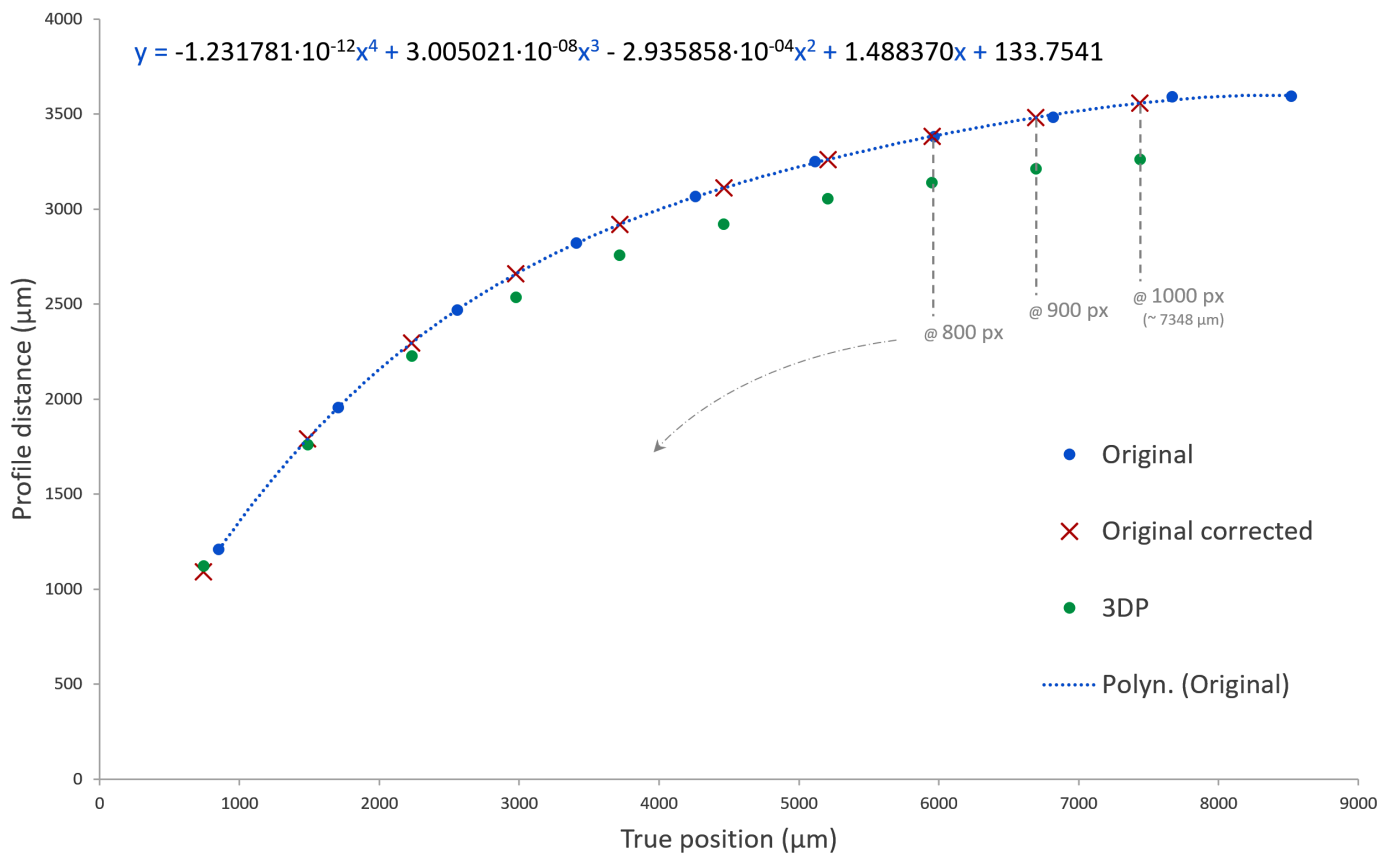


Fig. 2 Profile data of the artificial canals. The blue dots indicate the means of the measured profile data of the original blocks, the red crosses mark the corrected profile data of the original blocks as if measured at the same “true” positions as the 3DP blocks, the green dots indicate the means of the measured profile data of the 3DP blocks, and the blue dotted line depicts the fitted fourth-degree polynomial function. The formula represents the fourth-degree polynomial function fitted on the mean profile data of the original blocks with the resulting function parameters.

Tab. 2 Key parameters of the 3D printed endodontic blocks.

dimension		3DP block (μm)	Coefficient of Variation (%)	
	(pixel)			true position (μm)
Canal profile	@ 100px	@ 743.8 μm	1121.0 \pm 47.7	4.26
	@ 200px	@ 1487.6 μm	1759.3 \pm 41.1	2.34
	@ 300px	@ 2231.4 μm	2225.8 \pm 34.7	1.56
	@ 400px	@ 2975.2 μm	2535.9 \pm 30.7	1.21
	@ 500px	@ 3719.0 μm	2756.9 \pm 34.3	1.24
	@ 600px	@ 4462.8 μm	2921.0 \pm 32.5	1.11
	@ 700px	@ 5206.6 μm	3053.7 \pm 30.0	0.98
	@ 800px	@ 5950.4 μm	3138.0 \pm 35.3	1.13
	@ 900px	@ 6694.2 μm	3211.0 \pm 43.7	1.36
	@ 1000px	@ 7438.0 μm	3261.9 \pm 39.6	1.21
Canal thin			130.9 \pm 13.1	10.0
Canal thick			348.1 \pm 17.2	4.95
Cone length			5459.2 \pm 82.6	1.51
			(deg)	(%)
Canal angle			127.5 \pm 2.3	1.76
Cone angle			28.7 \pm 1.2	4.21
Pitch angle			54.2 \pm 2.3	4.23

Tab. 3 Comparison of the key parameters of original epoxy resin block – Plastic Practice Blocks .02 taper – Oblong for 15 file (Endo-Training-Bloc-J Dentsply Sirona, Ballaigues, Switzerland) with the 3D printed endodontic blocks. The asterisk (*) indicates insignificant differences of the respective parameters of the 3DP blocks in comparison with the original resin blocks.

dimension		Ratio of Means 3DP / Original (%)	one sample t - test		Coefficient of Variation ratio 3DP / Original (%)	Levene's test p - value
	true position (μm)		p - value	power		
Canal profile	@ 743.8 μm	103	= 0.010	0.777	56	= 0.018
	@ 1487.6 μm	98	= 0.003	0.907	34	> 0.001
	@ 2231.4 μm	97	> 0.001	1	27	> 0.001
	@ 2975.2 μm	95	> 0.001	1	22	> 0.001
	@ 3719.0 μm	94	> 0.001	1	26	> 0.001
	@ 4462.8 μm	94	> 0.001	1	27	> 0.001
	@ 5206.6 μm	94	> 0.001	1	27	> 0.001
	@ 5950.4 μm	93	> 0.001	1	35	= 0.003
	@ 6694.2 μm	92	> 0.001	1	20	= 0.037
	@ 7438.0 μm	92	> 0.001	1	48	= 0.027
Canal thin		96	= 0.055*	0.493	116	= 0.488*
Canal thick		111	> 0.001	1	113	= 0.272*
Cone length		90	> 0.001	1	42	= 0.050
		(%)			(%)	
Canal angle		102	> 0.001	0.958	81	= 0.392*
Cone angle		98	= 0.015	0.715	408	> 0.001
Pitch angle		93	> 0.001	1	105	= 0.876*

DISCUSSION

In our study, we fabricated 20 transparent endodontic blocks of the same design as the commercially available Plastic Practice Blocks .02 (Endo-Training-Bloc-J Dentsply Sirona, Ballaigues, Switzerland).

In previous studies (20–22), the endodontic resin blocks with a J-shaped artificial canal are described by the length, angle, and radius of curvature of the artificial canal. Nevertheless, especially in the case of determination of the canal angle, there are many different methods (according to Weine, Schneide, Luiten, etc.) (23) providing

significantly different results, even for the same tested resin block. Thus, these methods are not sufficiently accurate and reproducible. Therefore, we used a larger number of clearly defined parameters (Figure 1) to precisely measure, copy, and 3D print the endodontic blocks. We measured 20 original resin blocks and used the mean values of the selected parameters to design the new 3DP blocks.

Despite the printing resolution of 16 μm per layer, the resulting roughness of the block surface was relatively high, preventing direct observation of the artificial canal in the optical microscope. Polishing with different gums and pastes did not bring any improvement. The use of Evetric Bond (Ivoclar Vivadent AG, Schaan, Liechtenstein) with straight stainless steel dental matrix led to the formation of a smooth transparent layer that allowed observation of the internal structures of the printed block with a minimum distortion.

To observe the artificial canals, the newly printed blocks also required removal of the support material, which turned out to be quite difficult. We used high pressure water, which is the recommended method by the printer manufacturer. Nevertheless, this method did not remove the support material from the artificial canal. In many studies involving the investigation of the resin blocks, water (11, 24), isopropyl alcohol (25), or different types of alcohols were used as irrigation solutions. For us, 96% ethanol worked best as it helped to disrupt and remove the partially alcohol soluble support material. We found that ethanol was even a better irrigant than NaOCl or EDTA (17). Furthermore, in order to fill canal with irrigant and ensure patency, the canals were instrumented with stainless-steel files. It was necessary to prebend the stainless-steel instruments to protect the canals from alternating the design during their instrumentation.

We proved a high reproducibility of the 3D printing process of the endodontic training blocks printed from acrylic resin (VeroClear-RGD810, Stratasys, Eden Prairie, USA) using the 3D precision printer Objet30 Pro (Stratasys, Eden Prairie, USA). The dimensional variability of the 3DP blocks was significantly lower (3–5 times) for most of the tested parameters. It is the most important study output because only the blocks with a low dimensional variability allow for a consistent and reproducible results of the tests of endodontic instruments. The accuracy of the 3DP blocks was also sufficient. Although the measured dimensions of the 3DP blocks were statistically significantly different from the dimensions of the original resin blocks, the maximum difference was 11% and can be easily eliminated by modifying the CAD model (available in the supplementary materials on the article web page). A limitation of this study is the effect on the artificial canal profile by removing the support material. Even with the use of a fine and pre-bent ISO 10 stainless steel K-file, the canal was straightened, which is a typical problem when using rotary files (26) and is shown by a decrease in the pitch angle and a relative increase in the values of the canal profile measured at distances of 100, 200, 300 and 400 px. The use of a finer tools – e.g. ISO 06 and 08 – could not remove the support material from the artificial canal. Also, the proximal and distal diameters of the artificial canal of the 3DP blocks were affected. Alter-

native possibilities of the support material removal from the artificial canals should be further investigated.

Despite certain difficulties associated with the elimination of the support material, PolyJet printing is currently the only available 3DP method that can print such narrow (100 μm) curved cavities. For comparison, the SLA (stereolithography) method does not allow the printing of supports from different material that that of the object printed, the FFD (filament feeder) 3DP method does not allow such a fine resolution (usually not less than 50 μm per layer, e.g., TRILAB DeltiQ 2 by TRILAB Group s.r.o., Hradec Králové, Czech Republic) and is also limited by the minimum width of the printed line (usually not less than 250 μm , e.g., TRILAB DeltiQ 2 by TRILAB Group s.r.o., Hradec Králové, Czech Republic), the SLS (selective laser sintering) method is limited by the grain size of the sintered material (usually not less than 100 μm , e.g., Polyamid 12 PA 2200 by EOS GmbH, Krailling, Germany).

CONCLUSION

3D polyjet printing is a promising method of manufacturing endodontic test blocks. Its main advantages are high reproducibility of printing and the possibility of producing artificial root canals of any desired shape.

The profiles of the 3D printed artificial canals showed statistically significantly lower dimensional variability (2–5 times) when compared with the original resin blocks.

The disadvantage of the printing method used is the difficult support material removal negatively affecting the profile of the printed artificial canal. Alternative methods to remove the support material should be further investigated.

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Stressor Effects on Sex Ratios and Births in the Maltese Population during the First Half of the 20th Century

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ABSTRACT

Background: The sex ratio at birth (male/total = M/F) is expected to approximate 0.515. Stress is known to reduce livebirth M/F. In the first half of the 20th century, Malta was stressed by two World Wars.

Objectives: This study was carried out in order to analyse changes in reproductive performance and M/F of stillbirths and livebirths in Malta during this period.

Methods: Livebirth and stillbirth data (1910–1951) were obtained from official published Maltese government reports. Stillbirths were defined as any antenatal loss after 28 weeks of gestation.

Results: This analysis studied 347,562 live and 11,662 stillbirths. For 1919–1951, M/F at birth was 0.517, stillbirth M/F was 0.664, implying 28/40 M/F = 0.522. Assuming conceptional M/F = 0.5, estimated M/F for fetal wastage before 28 weeks was approximately 0.434. There was a decrease in the overall birth rate starting after 1911 to 1921, more marked for 1941–1943 followed by an overshoot in 1943–48. There was a statistically significant drop in M/F livebirths during the periods 1916–21 and 1934–45. Stillbirths decreased significantly after 1935 (M>F). A stillbirth M/F drop in 1937–45 and rise in 1946–51 were statistically significant.

Conclusions: Birth rate drops in both wars were ascribed to conscription, adverse living conditions and decreased fertility from nutritional restrictions. Both conflicts resulted in short post-war baby booms. The decrease in stillbirths is attributed to increase in antenatal attendances, hospital births and special food rations for pregnant women. The M/F observations suggest that the selective survival of both healthier female and male foetuses is favoured during times of stress.

KEYWORDS

birth rate/trends; sex ratio; Malta; infant, newborn; starvation

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INTRODUCTION

The sex ratio at birth (M/F) is expected to approximate 0.515 (1). It is estimated that circa a quarter of conceptions are lost (2, 3), and the greater preponderance of male livebirths suggests that there is some form of mechanism whereby proportionately more female than male fetuses are lost during pregnancy (4). The exact nature of this mechanism is undetermined. Stress is known to reduce livebirth M/F but the ratio still favours male births suggesting that proportionately more male fetuses are lost during times of stress (5). This accords with the Trivers-Willard hypothesis (TWH) which avers that evolution has favoured parents who are able to bias M/F according to the circumstances encountered during pregnancy (6). TWH postulates that in a polygynous species, wherein males have multiple mating opportunities and thus a greater ability to pass on parental genes, a healthy mother should bias M/F towards male births. On the other hand, mothers in a poor state of health would have a greater propensity to abort male pregnancies since these are less likely to survive to term, and should they do so, are more likely to be frail and not survive childhood. If they do survive to adulthood, they would compete poorly for mating opportunities against more robust males. On the other hand, the female foetus is more likely to survive pregnancy under poor conditions and on reaching adulthood, will almost certainly be fertilised. Spontaneous miscarriage of a male fetus during a stressful pregnancy may therefore result in a greater proportion of females encountering males who may be more successful at reproducing the species (6). The antenatal timing for the disproportionate loss of male fetuses during times of stress has however not been fully elucidated (4, 7).

During the first half of the twentieth century, the Maltese population was subject to periods of marked physical and mental stress. The second decade included the First World War (June 1914 – November 1918) and this was very quickly followed by the Spanish Flu epidemic. During the war, Malta was a British base and was only indirectly affected. However, a significant number of men joined the British Services while the country experienced an economic depression. The end of that conflict coincided with the onset of H1N1 influenza pandemic which affected the Maltese population in three major waves that ended in 1925 (8).

The 1940s were characterised by Italian expansionism led by the Italian dictator Benito Mussolini. The Maltese Islands located just south of Sicily, still under British dominion, viewed these expansionist activities with anxiety. The first concern related to the Abyssinia Crisis of 1935 involving the Kingdom of Italy and the Empire of Ethiopia leading to the Second Italo-Ethiopian War (1935–1937). The fear of being involved in this conflict was sufficient to drive the Maltese health authorities to draw up an emergency war scheme and provide for medical equipment and medications in case of a prolonged siege. The onset of direct hostilities in the Second World War involving the Maltese population occurred in June 1940 initiating the Siege of Malta which lasted until November 1942 (8). During the siege, Axis forces attempted to capture Malta due

to its strategic location. The constant bombing resulted in hardship, privation and hunger for the Maltese until the Axis lost the Second Battle of El Alamein and Allied forces landed in Morocco and Algeria in 1942 (8, 9). The adverse effects of the Siege of Malta persisted in the subsequent years until social conditions returned to normality. This conflict had significant effect on the reproductive performance of the Maltese population with a significant drop in birth rate during the period (10, 11).

This study was carried out to determine whether the observed changes in reproductive performance in the period before, during and after these conflicts affected the male-to-female ratios of stillbirths and livebirths in Malta.

METHODS

Malta's population currently approximates half a million. The total number of livebirths and livebirth rate data (1910–1951) were obtained from the published Maltese Department of Health annual reports for the period. Sex identified data was only available for the period 1916–1951 allowing for the calculation of the annual sex-differentiated birth rates and the M/F ratios (11). Stillbirth data was obtained by compiling the fortnightly mortality data published by the Department of Health for the period. During the period under review, stillbirths were defined as any antenatal loss after 28 weeks of gestation. Stillbirth data was unavailable for the period 1910–1918 (12).

The quadratic equations of Fleiss were used for the calculation of 95% confidence intervals for ratios (13). Statistical analysis was performed using bespoke Excel spreadsheets, namely Pearson correlation (14). A p value ≤ 0.05 was taken to represent a statistically significant result.

RESULTS

This analysis studied 347,562 live births and 11,662 stillbirths. For the period when sex data for both livebirths and stillbirths was available (1919–1951), the M/F ratio at birth was 0.517, while the M/F ratio for stillbirths was 0.664, implying that at 28 weeks gestation, M/F ratio stood at 0.522 (Table 1). Assuming a < 28 week miscarriage rate of about 25% of total conceptions, the total conceptions in Malta during the period 1919–1951 approximated 396,052. If the primary sex ratio at conception is 0.500, then equal numbers of males and females are conceived. The estimated M/F ratio for fetal wastage before 28 weeks of pregnancy would therefore approximate 0.434 (Table 1).

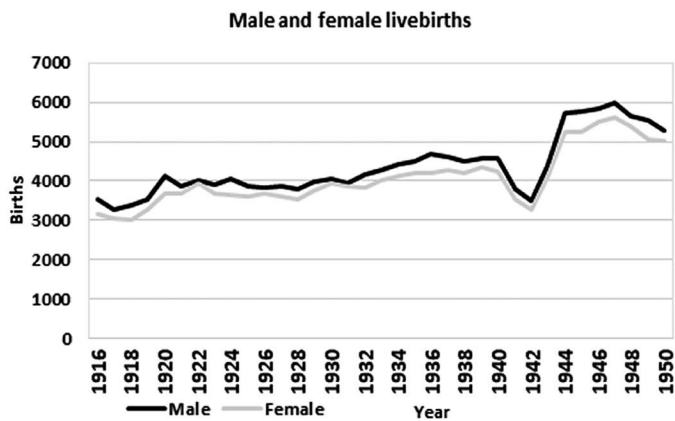
LIVE BIRTHS

Births for both sexes increased throughout the period studied except for a dip that coincided with WW2 (Figure 1). There was a decrease in the overall birth rate starting after 1911 and continuing through the WW1 period extending to around 1921. A more marked drop in overall

Tab. 1 Actual and estimated fetal wastage by sex >28 and <28 weeks gestation.

	Male	Female	M/F ratio	Proportionate conceptional fetal loss
Livebirths	147,359	138,018	0.516	
Observed fetal wastage >28 weeks	7,749	3,913	0.664	3rd tri: 11,662-- 2.9%
At 28 weeks gestation	155,108	141,931	0.522	
Assumed fetal wastage <28 weeks*	42,918	56,095	0.434	1/2nd tri: 99,013 – 25.0%
Estimated conceptions	198,026	198,026	0.500	

* assumed at 25% of conceptions

**Fig. 1** Absolute number of male and female livebirths and stillbirths in Malta, 1910–1951.

birth rates is evident during the WW2 period starting in 1941 and extending to 1943 followed by an overshoot in birth rate during 1943–48 period. The observed changes in overall birth rates is very closely mirrored in the rates for both sexes (Figure 2). There was a statistically significant gradual increase in births of both sexes from 1916–1951 (Pearson correlation, males $r = 0.8$, $p < 0.0001$, females $r = 0.82$, $p < 0.0001$).

After visual inspection, grouped data analysis suggest statistically significant changes during different periods with a rise in M/F ratios during the period 1916–21 and 1934–45 (Table 2).

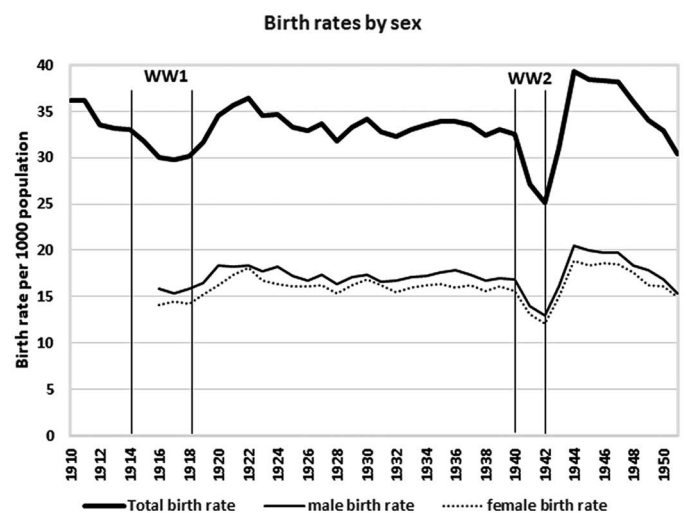
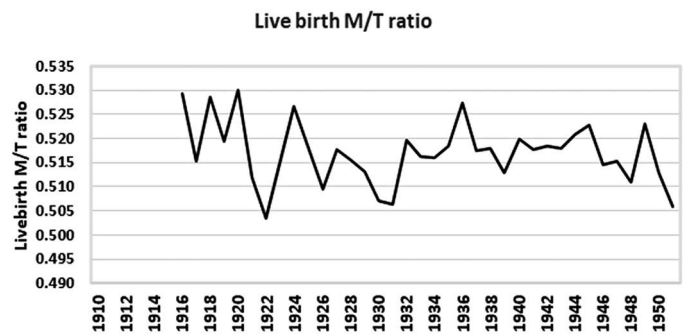
Tab. 2 M/F and 95% confidence intervals for livebirths by sex for the period 1916–1951.

	1916–21	1922–33	1934–45	1946–51
M	21,725	47,765	55,011	33,058
F	19,858	45,173	50,963	31,269
Total	41,583	92,938	10,5974	64,327
UCI	0.5273	0.5172	0.5221	0.5178
M/F ratio	0.5224	0.5139	0.5191	0.5139
LCI	0.5176	0.5107	0.5161	0.5100
p	0.004		0.023	0.992

p-value comparisons with 1922–33

STILLBIRTHS

Absolute number of male stillbirths increased overall throughout the period studied but absolute female still-

**Fig. 2** Male and female livebirths and M/F ratio in Malta, 1910–1951.

births dropped after WW2 (Figure 1). The annual still-birth rate shows a marked decrease in rate after 1935 maintaining a steady downward trend in the subsequent years. There appeared to be a disproportionately greater increase in male losses throughout the period (Figure 3). The M/F ratio appears to have taken a downward trend after 1936 maintained to 1947, after which a marked rise in M/F ratio is again exhibited. For the period 1919–1947, there was a highly significant correlation between male and female stillbirths (Pearson $r^2 = 0.73$, $p < 0.0001$). The drop from 1919 to 1951 was significant for both sexes albeit with a poorer fit than the live births presented in the previous section, and with female fit better than male fit (Table 3). Grouped data analysis suggest statistically significant changes during different periods with a fall in M/F ratios during the period 1937–45 and rise in the period 1946–51 (Table 3).

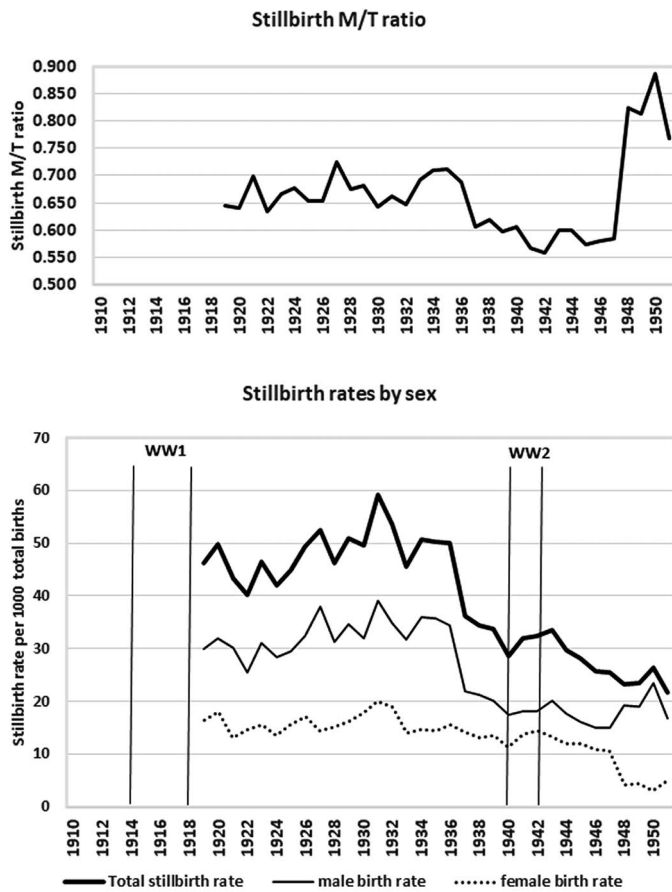


Fig. 3 Male and female stillbirths and M/F ratio in Malta, 1910–1950.

Tab. 3 M/F and 95% confidence intervals for stillbirths by sex for the period 1919–1951.

	1919–24	1925–36	1937–45	1946–51
M	1,367	3,666	1,552	1,164
F	702	1,728	1,062	421
Total	2,069	5,394	2,614	1,585
UCI	0.6810	0.6921	0.6126	0.7558
M/F ratio	0.6607	0.6796	0.5937	0.7344
LCI	0.6398	0.6670	0.5746	0.7118
p		0.133	<0.0001	<0.0001

p-value comparisons with 1919–24

DISCUSSION

The two World Wars led to a significant drop in the overall birth rate of the Maltese population. This has been ascribed to various causes including the calling up of males for military service and, especially during the second conflict when the islands were directly affected, the adverse living environment and decreased biological fertility from nutritional restrictions. Both conflicts were followed by ‘post-war baby booms’ with a short-lived rise in birth rates (10, 15). Similar observations were made for most European countries including the United Kingdom where the birth rate dropped to its lowest level during the 1940–41 period rising sharply to peak in 1947 (16). Indeed, a dip

in fertility (and hence births) has been observed during times of biological stress in several other studies (17–19).

In contrast, the stillbirth rate in the Maltese Islands had started to decrease in the latter half of the third decade of the 20th century, a decrease that was maintained right through the conflict years after. The continued decline in stillbirth rate during the war years has been attributed to the increase in antenatal attendances and hospital births noted during the conflict years and to special rations allocated to expectant women (10, 15). Similar observations were made in the United Kingdom and the Netherlands (20, 21).

While M/F almost invariably demonstrates a male excess, it is known that male fetuses are more likely to be lost during the third trimester of pregnancy than female fetuses (20). The British Perinatal Mortality Study carried out in 1958 reported that the sex distribution of both antepartum and intrapartum stillbirths with a gestational age >28 weeks showed a preponderance of male deaths – calculated M/F ratio of 0.549 and 0.524 respectively. A similar male predominance of early neonatal deaths (M/F of 0.585) was reported (20). Some studies also noted a dip in male births that exceeded female births in accordance with the Trivers-Willard hypothesis, skewing M/F toward females during times of biological and psychological stress (22). Arguably the most notable such study described the Great Leap Forward in China (11/1957–1/1961) (23) with an estimated loss of 18,286,000 births in 1959–61 with a further additional male deficit of 3.2 per 1000 births (24).

This study confirms that at 28 weeks gestation, the sex ratio was similar to that reported for livebirths favouring male offspring. Assuming that at conception, M/F approximates to 0.500 (4), it appears that a proportionate greater female wastage occurs during the first two trimesters of pregnancy (25). A study involving 750 spontaneous miscarriages occurring between the 5–25th week of pregnancy reported a predominance of female pregnancy wastage whether the fetuses were noted to have a normal or a trisomy karyotype (calculated M/F ratio of 0.416 and 0.487 respectively) (25).

With a reported miscarriage rate of approximately 25% and the larger majority occurring in the first trimester (26), the disproportionate loss of female fetuses results in a significant deficit that persists right through the perinatal period even though proportionately more male fetuses are lost during the third trimester and neonatal period. The reasons for the proportionately excessive female wastage in the first trimester have not been completely elucidated (27). However, its evolutionary purpose may be to ensure that the healthiest females survive to ensure effective reproductive capabilities. In times of stress, where the livebirth M/F ratio is reduced, the mechanism may involve either reduced female wastage or increased male wastage during the first trimester (28). Physical or psychological stressor situations have been associated with an increased risk of miscarriages (29), suggesting that the most likely mechanism in play is more likely to be an increase in first trimester male wastage rather than a protective mechanism to reduce female wastage and the mechanism for this may be the observed raised progesterone and cortisol

during times of stress (30). Indeed, even X and Y bearing sperm have different susceptibility to stress (31, 32).

Human evolution may have developed mechanisms whereby the less healthy members of the female species are excluded from the reproductive equation by ensuring a higher female fetal wastage in the first trimester of pregnancy. Since the female of the species bears the main brunt of the reproductive process, this mechanism ensures that more reproductive-capable females are available to propagate the species. The male of the species has a limited role in the reproductive process and less healthy members can still effectively contribute to species survival. In times of biological stress, evolution appears to have favoured the survival, not only of healthier female fetuses, but also healthier males with an apparent increase in first trimester male fetal wastage (33).

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Necrotizing Fasciitis in the Immediate Post-Operative Period Following Resection and Free Flap Reconstruction for Oral Cancer

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ABSTRACT

Necrotising fasciitis (NF) is a rapidly spreading bacterial infection of the fascial planes and can be fatal if is not treated urgently. Here, we present the case of a 65-year-old female, with oral squamous cell carcinoma, treated surgically with curative intent. On the second post-operative day from a mandibulectomy, selective neck dissection and reconstruction with a fibula free flap, she developed rapidly progressing NF, at the surgical site.

KEYWORDS

necrotizing fasciitis; oral cancer; reconstruction; complications

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INTRODUCTION/BACKGROUND

NF is a bacterial infection, often polymicrobial, that can be destructive, rapidly progressing and potentially fatal. The overall reported mortality rate can be as high as 29.7% (1, 2). It is an infection of the soft tissues and moves along the fascial planes. The term was first used by Wilson (1952) and mainstays of treatment include urgent surgical debridement and antimicrobial therapy. Early intervention is essential when treating this condition to prevent serious morbidity or mortality (3).

Many different microorganisms, both aerobic and anaerobic, have been implicated in the different classifications of NF and can commonly include group A streptococcus, Methicillin-resistant staphylococcus aureus (MRSA), *Streptococcus pyogenes* as well as gram-negative organisms, as seen in this case. However, due to the variation, many bacteria cannot be ruled out with rare cases of *Pseudomonas aeruginosa* demonstrating this (3, 4). NF is rare in the head and neck region with most cases linked to cervicofacial infections (1). And even fewer cases have been linked to patients with head and neck cancer (5). Here we present the case of a patient with oral squamous cell carcinoma who developed NF following resection and reconstruction with a fibula free flap.

CASE DESCRIPTION

A 65-year-old woman presented to the extraction clinic at Leeds Teaching Hospitals in June 2020 for dental extractions following a referral from their dentist. Abnormal gingival hyperplasia was noticed around the lower left first molar socket and a biopsy was taken that confirmed moderate differentiated squamous cell carcinoma (SCC). The staging scans included a head and neck MRI and a high-resolution CT thorax. The MRI detected ipsilateral abnormal level IB and II lymph nodes with a staging of T4 N2b M0. The treatment plan, as verified by the tumour board, included resection with reconstruction followed by adjuvant radiotherapy.

The patient's medical history included longstanding insulin-treated type 2 diabetes, coronary artery disease treated with a coronary artery bypass in May 2019, hypertension, hypercholesterolaemia and acid reflux. She was a former smoker having quit around 7 years previously and did not drink alcohol. The patient's allergies included amoxicillin and metronidazole. Their initial operation was completed in August 2020. A mandibulectomy, selective neck dissection and reconstruction with fibula free flap were completed and three vacuum drains were used as per current practice. One intraoperative and two post-operative doses of gentamicin were given for prophylaxis.

There were no surgical complications, and they were discharged from the intensive care unit 24 hours later needing no cardiovascular support and self-ventilating through the tracheostomy placed in the operating theatre.

As is normal practice within this unit, hourly flap observations were completed during the first 48 hours post operation. These were documented as normal until the patient was 2 days post-operative when suddenly there was

no capillary refill detected from the flap, no clear sounds were detected on the doppler, no bleeding occurred when the flap was scratched with a needle and an oral odour was noted.

The patient returned to theatre immediately for surgical exploration. Findings during theatre included (Figure 1) necrotic skin edges, necrotic muscles including the platysma, strap muscles, sternocleidomastoid and anterior belly of digastric. There was necrosis of the free flap pedicle and the muscle component of the free flap, with on evidence of mechanical obstruction at the anastomosis. Suppuration, foul smell and green colouration were all noted. A potential diagnosis of NF was first raised at this point. She received extensive debridement and a pedicle flap (*Pectoralis major*) was used to cover the major vessels of the neck. The initial drains were replaced with new ones.

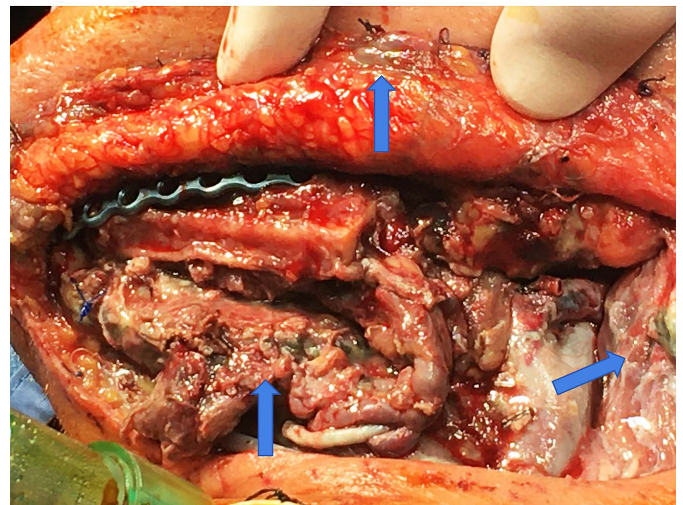


Fig. 1 Arrows indicating green appearance with necrosis of the platysma, sternomastoid and digastric muscles.

Samples were sent for histopathology, and microbiology and the patient was admitted to the intensive care unit with empirical IV teicoplanin, clindamycin, aztreonam and gentamicin antibiotics. After a microbiology review the same day, the gentamicin and aztreonam were stopped and ciprofloxacin added, following the trust's NF guidelines.

Cultures were positive for gram negative anaerobes, including *veillonella parvula*, susceptible to clindamycin. There was some *pseudomonas aeruginosa* growth as well along with respiratory flora. Teicoplanin was stopped after a 5-day course, but clindamycin and ciprofloxacin were continued for 20 days.

Histology results were received 7 days after the return to surgery. Results showed a chronic inflammatory infiltrate in both the platysma and left parotid lymph node samples. The platysma showed necrosis of fibrocollagenous tissue, and the lymph node also had evidence of necrosis (Figure 2). Both samples were consistent with a diagnosis of necrotising fasciitis.

No further evidence of necrotising fasciitis was identified after the initial return to theatre despite complications with flap healing. A small neck dehiscence noted 24 hours later. A fistula also formed in the submental region causing a saliva leak, that was persistent. The skin layer of

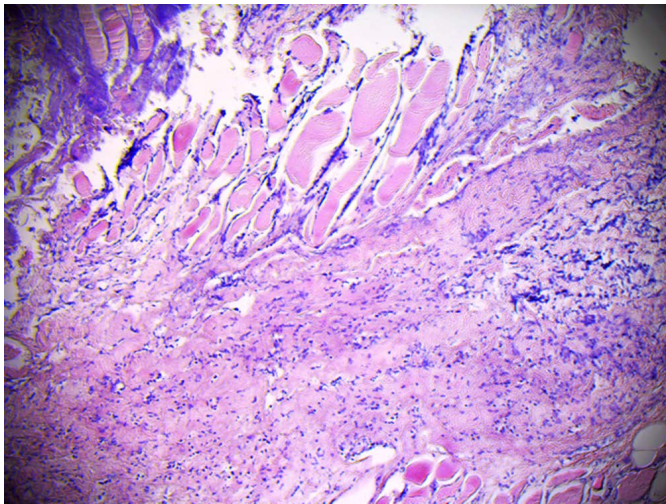


Fig. 2 Necrotic fibrocollagenous tissue, mixed inflammation spreading across fibrocollagenous tissue and skeletal muscle.

the pedicle flap became non-viable despite muscle granulation and needed debriding twice more prior to discharge. Dressings were changed frequently and included intraoral iodine-based packs.

This patient was discharged 28 days after their initial admission for the primary cancer resection. Despite clear margins at her initial operation two weeks after her discharge she developed a rapidly growing retromolar mass. The biopsy showed a new area of moderately differentiated squamous cell carcinoma. New CT imaging showed spread to the right mandible and pulmonary metastases that developed two months after the initial staging scans. She went to end of life care and passed away 9 weeks after the initial surgery, from widespread metastatic disease.

CONCLUSION

This is a unique case of a patient developing NF following the resection and reconstruction with a free flap. Early diagnosis of NF is mandatory, and any delay could prove fatal, given its association with more extensive surgery

and higher mortality rates. In specific patient groups (e.g., elderly patients with diabetics) knowing that this is a potential risk factor, may allow early intervention. Diabetes has been established as the most frequent risk factor for NF (2). This patient had moderately controlled type 2 diabetes (pre-operative HbA1c 68 mmol/mol) which was being treated with insulin and metformin. This could have increased this patient's susceptibility to developing this infection. Other common co-morbidities include liver cirrhosis, chronic heart failure, obesity, alcohol abuse, immunodeficiency, hypertension, and peripheral vascular disease (2). Risk assessment before major head and neck operations is essential combine with close post-operative monitoring. Some high-risk patients may benefit from pre-operative antibiotics followed by a longer postoperative course, rather than the 3 doses in total, of our current protocol. Such an approach, in this case presented, allowed for the changes to patient status and the free flap, caused by NF, to be quickly identified, escalated and managed with the patient rapidly returning to theatre. Surgical intervention is lifesaving and must be performed as early as possible, since a delay in treatment beyond 12h can prove fatal.

CONFLICT OF INTEREST

The authors have no conflict of interest to report

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